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# Association Between Hepatitis C Virus and Chronic Kidney Disease: A Systematic Review and Meta-Analysis

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## ABSTRACT

**Introduction and aim.** The role of hepatitis C virus infection as a risk factor for the development and progression of chronic kidney disease in the general population remains unclear. **Material and methods.** A systematic review of the published medical literature was performed to assess whether positive anti-HCV serologic status is associated with higher frequency of chronic kidney disease in the adult general population. We used a random-effects model to generate a summary estimate of the relative risk of chronic kidney disease (defined by lowered glomerular filtration rate or detectable proteinuria) with HCV across the published studies. Meta-regression and stratified analysis were also carried out. **Results.** Forty studies were eligible (n = 4,072,867 patients), and separate meta-analyses were conducted according to the outcome. Pooling results of longitudinal studies (n = 15 studies, n = 2,299,134 unique patients) demonstrated an association between positive anti-HCV serologic status and increased incidence of CKD, the summary estimate for adjusted HR with HCV across the surveys, 1.54 (95% CI, 1.26; 1.87) (P < 0.001). Between-study heterogeneity was observed (Q value by Chi-squared [$\chi^2$] test 500.3, P < 0.0001). The risk of chronic kidney disease related to HCV, in the subset of surveys from Asia was 1.45 (1.27; 1.65) (P < 0.001) (no heterogeneity). According to our meta-regression, ageing (P < 0.0001) and duration of follow-up (P < 0.0001) increased the risk of chronic kidney disease among HCV-positive subjects. We observed a relationship between anti-HCV positive serologic status and frequency of proteinuria, adjusted effect estimate of proteinuria with HCV among surveys was 1.633 (95% CI, 1,29; 2.05) (P < 0.001) (n = 10 studies; 315,404 unique patients). However, between-studies heterogeneity was noted (P value by Q test < 0.0001). **Conclusion.** An association between HCV infection and increased risk of chronic kidney disease in the general population exists. The mechanisms underlying such association are currently under active investigation.

**Key words.** Chronic renal insufficiency. Hepatitis C. Interferons. Meta-Analysis. Renal dialysis.

## INTRODUCTION

Hepatitis C virus infection is an important cause of liver disease worldwide.[1] Recent evidence has been accumulated showing that chronic hepatitis C virus infection plays significant activity in various organs and tissues other than the liver.[1] Increasing information exists on the activity of HCV on kidneys and a relationship between chronic hepatitis C virus infection and chronic kidney disease has been mentioned.[2] HCV and CKD are major public health issues all over the world; globally, in 2015, an estimated 71 million people were living with chronic HCV infection.[3] A novel systematic review reported that the global mean prevalence of CKD in general population was 13.4% in stages 1 to 5 and 10.6% in stages 3 to 5.[4]

Conventional risk factors for developing chronic renal disease do not fully explain the current frequency of chronic kidney disease in the adult general population of developed world. Various authors have evaluated the impact of HCV on the development of chronic kidney disease in general population;[5-7] our meta-analysis of clinical observational studies (n = 9; 1,947,034 unique patients) had demonstrated a relationship between positive anti-HCV serologic status and increased incidence of chronic kidney disease; the summary estimate for adjusted hazard ratio was 1.43 (95% Confidence Interval, 1.23; 1.63,

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P = 0.0001).[6] However, between-studies heterogeneity was noted (P value by Q test < 0.0001) and this precluded more definitive results.

Several biological mechanisms have been advocated to explain the increased risk of CKD in HCV-infected individuals. There is an association between HCV infection and glomerular disease in native kidneys and after solid organ transplant.[8] Renal injury in HCV-positive patients can also be given by endothelial dysfunction which is in turn promoted by enhanced oxidative stress, pro-inflammatory cytokines, insulin resistance, or non-alcoholic steato-hepatitis (NASH).[9-11]

The recent publication of additional and large studies on this topic has led us to summarize again the scientific evidence on the connection between chronic kidney disease and exposure to HCV infection. We have again reviewed the available evidence on the relationship between HCV infection and the development of chronic kidney disease in the adult general population by performing a systematic review of the literature with a meta-analysis of clinical observational studies.

## MATERIAL AND METHODS

This work is in agreement with the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement (Annex 1).[12]

### Search strategy and data extraction

English-language citations from the national Library of Medicine's Medline database from 1989 through December 1, 2017 were reviewed by two authors (F.F., and F.M.D.). The first assay for HCV was manufactured in 1989 and data on HCV status are therefore not available for the time before 1989. Our search was conducted by four Medline databases engines (Embase, Grateful Med, Ovid, and PubMed), and was limited to human studies.

The following algorithm in medical subject heading and in free text words was applied: ("HCV" or "HCV Antibody Positive Serologic Status" or "Hepatitis C" or "Hepatitis C Virus Infection") and ("CKD" or "Chronic Kidney Disease" or "End-Stage Renal Disease" or "ESRD" or "Glomerulonephritis" or "Low Glomerular Filtration Rate" or "kidney Failure" or "Kidney Impairment" or "Kidney Insufficiency" or "Renal Failure" or "Renal Impairment" or "Renal Insufficiency") and ("Interferon" or "IFN" or "pegylated Interferon" or "peg-IFN" or "Ribavirin") and ("DAAs") and ("Sustained Virological Response" or "Sustained Viral Response" or "Cure") and ("Hazard Ratio" or "HR"). We performed an additional search with electronic searches of the Cochrane Library; manual searches of selected specialty journals were done to identify all pertinent literature. We also searched reference lists from qualitative topic reviews and published clinical studies. It was previously demonstrated that a Medline search alone might not be sensitive enough.[13] Data on study design, study period, patient characteristics, HCV prevalence, antiviral therapy towards HCV, and kidney disease outcomes were abstracted. Authors of selected papers were contacted to obtain missing data and only data from individuals with known HCV status were included in the meta-analysis. We achieved consensus for all data. We compared studies to eliminate duplicate reports for the same patients, which included contact with investigators when necessary. We pre-specified eligibility and exclusion criteria. Our search was limited to human studies that were published in the English literature.

### Inclusion criteria

We enrolled studies if they met the following inclusion criteria:

- They presented original data from cohort and longitudinal studies;
- The outcome of interest was clearly defined as frequency of chronic kidney disease, i.e., reduced glomerular filtration rate and/or detectable proteinuria in the adult general population according to anti-HCV serologic status; and
- They provided adjusted risk estimates and their confidence intervals. Both case-control studies and cohort studies were considered as eligible for inclusion in the analysis.

If data on the same population were duplicated in more than one study, we included the most recent study in the analysis. Information of HCV serologic status was recorded at the time of enrollment. We enrolled studies were the diagnosis of HCV infection was performed by testing for anti-HCV antibody in serum and/or HCV RNA detection by nucleic acid testing. Surveys based on administrative codes (ICD-9) were also evaluated.

### Ineligible studies

We have excluded studies if they reported inadequate data on the association between chronic kidney disease and anti-HCV positive serologic status (e.g., incomplete information on HCV status or renal outcomes). We have excluded unpublished studies, studies that were only published in abstract form or as interim reports; we have not considered letters and review articles for this systematic review.

### Quality assessment

The quality of the 40 studies was appraised using a scale adapted from the 'Newcastle/Ottawa Scale (NOS)'.[14] The Newcastle-Ottawa scale is a scoring system that assesses every aspect of an observational epidemiologic study from a methodological point of view. When a study included relevant information that could be associated with the NOS, one point was added. Seven items in cross-sectional studies and eight items in cohort and case-control studies that could be related to the NOS were identified. Therefore, cross-sectional studies assigned 8-10, 6-7, 4-5, or 0-3 points (stars) were evaluated as very good, good, satisfactory or unsatisfactory studies, respectively. Similarly, cohort/case-control studies with 7-9, 5-6, 4 and 0-3 points (stars) were identified as very good, good, satisfactory or unsatisfactory, respectively. We carried out subgroup analyses based on those studies provided with very good quality. Data extraction and quality scoring were performed independently by two reviewers (F.F. and F.M. D.) and the results were merged by consensus. The complete protocol for quality scoring is available on-line (Annex 2A).

### Outcomes measures

We made separate meta-analyses according to the outcome. One meta-analysis included longitudinal studies evaluating the incidence of chronic kidney disease, another enrolled cross-sectional studies addressing the prevalence of chronic kidney disease. An additional meta-analysis regarded the frequency of proteinuria (or glomerular disease). Staging of chronic kidney disease was categorized according to the Kidney Disease Outcomes Quality Initiative (K/DOQI) definition, and estimated glomerular filtration rate was calculated using the four-variable MDRD equation.[15]

The primary end point was to provide adjusted estimates of the risk (and 95% CIs) of incidence (or prevalence) of chronic kidney disease in the adult general population according to anti-HCV serologic status. Multivariate analysis was carried out to evaluate the independent effect of anti-HCV positive status on the frequency of chronic kidney disease after adjustment for potential confounders (covariates) (e.g., age, gender, race/ethnicity, diabetes mellitus, and others). Cox proportional hazard regression analysis and logistic regression analysis were carried out in longitudinal and cross-sectional studies, respectively. An additional end-point was the adjusted estimate of the risk (and 95% CIs) of frequency of proteinuria (or glomerular disease) in the adult general population according to anti-HCV serologic status.

### Data synthesis and analysis

We weighted the study-specific log hazard ratios by the inverse of their variance to obtain a pooled effect estimate and its 95% confidence intervals. For each study, we used the estimate of the effect measure that was adjusted for the largest number of confounders. We present both fixed-effects and random-effects pooled estimates but use and report the latter when heterogeneity was present. We used the random-effects approach, as described by DerSimonian and Laird,[16] Cochrane Q-test was used for quantifying the heterogeneity.[17] The $I^2$ statistic, which is the percentage of total variation across studies due to heterogeneity rather than chance, was also calculated.[18] The null hypothesis of this test is the presence of homogeneity (absence of heterogeneity). We explored the origin of heterogeneity by restricting the analysis to subgroups of studies defined by study characteristics such as country of origin, response to antiviral therapy, and others. Heterogeneity was also evaluated by meta-regression in order to look at the effect of potential and continuous covariates on the outcome of interest. Subgroup or stratified analyses and meta-regression were pre-specified. We performed random-effects meta-regression using the method of moments or maximum likelihood approaches where appropriate, a single predictor is allowed in each model (simple meta-regression). Publication bias was assessed by the Egger test for funnel-plot asymmetry. All analyses were done with the statistical package Comprehensive Meta-Analysis (CMA), version 2.0 (Biostat Inc., USA, 2005). The 5% significance level was adopted for $\alpha$ risk. Every estimate was given with its 95% Confidence Intervals.

## RESULTS

### Literature review

As shown in figure 1, we retrieved 4,533 articles and 230 full-text papers were assessed for eligibility. The list of the 230 full-text papers is reported in the Annex 3. Forty studies met our inclusion criteria and were published in 29 papers (Figure 1) and carried out in 3 continents (n = 4,072,867 patients).[19-47] Thus, some studies contributed data on more than one kidney disease outcome, but each cohort was represented once in any meta-analysis. There was a 100% concordance between reviewers with respect to final inclusion and exclusion of studies reviewed based on the predefined inclusion and exclusion criteria.

Information on HCV serological status was collected at the time of enrollment. We included studies where the diagnosis of HCV infection and chronic kidney disease were done by administrative data (ICD-9-CM codes).[24-27,30,33,45]

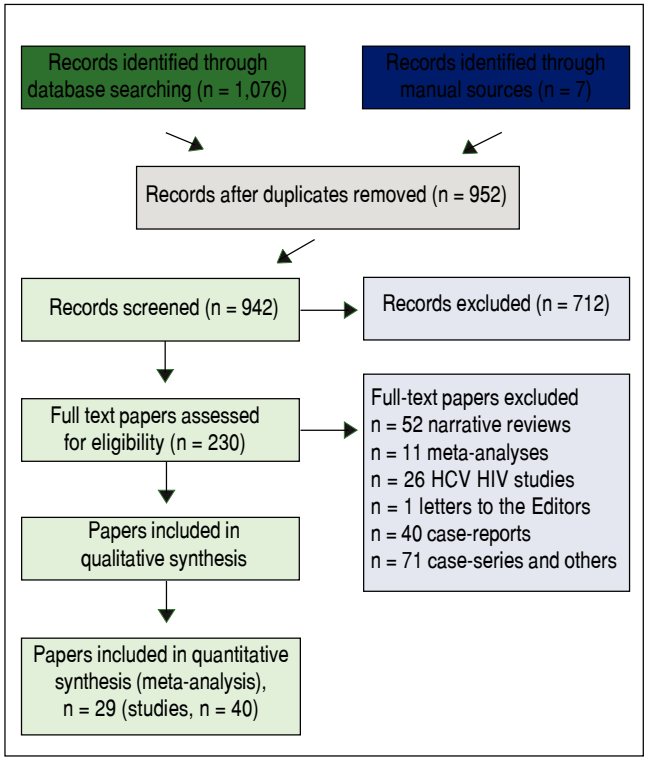


***Figure 1.*** *Flow diagram of study selection.*

In one report the diagnosis of HCV was recorded by historical collection of hepatitis C history (individual interviews).[44] Anti-HCV serologic status and occurrence of CKD were detected in the remaining surveys by laboratory tests.[19-23,28,29,31,32,34-43]

The relationship between HCV infection, as detected by positive HCV RNA in serum, and chronic kidney disease was addressed in three reports only. Two studies evaluated the link between positive HCV RNA status and incidence of ESRD;[29,45] one evaluated the prevalence of CKD according to HCV RNA status.[32]

## Patient characteristics

Supplemental tables 1-8 report some salient demographic and clinical characteristics of subjects enrolled in the included studies. The mean age of subject cohorts ranged from 37.6 to 61.9 ± 14 years. The gender distribution ranged from 31.2% to 95.7% male. Eighteen studies were from the US, thirteen were from Taiwan, and three from Europe. There were two reports from Japan, China and Quatar, respectively. The average follow-up ranged between 1.6 ± 0.2 to 16.8 years among longitudinal studies. The quality scores ranged between 4 and 7 (longitudinal studies) (Annex 2B), and 5 and 7 (cross-sectional studies) (data not shown).

## Summary estimate of outcome: Incidence of CKD (reduced eGFR)

Fifteen longitudinal studies (n = 2,299,134 unique patients; 295,773 HCV-positive and 2,003,361 HCV-negative patients) gave information on the incidence of CKD among HCV-positive subjects.[19-33] We found a significant association between positive anti-HCV serologic status and increased incidence of CKD, adjusted HR with HCV across the surveys, 1.54 (95% CI, 1.26; 1.87) (P < 0.001). Test for homogeneity of the aHR across the fifteen studies gave a Q value (by Chi-squared [$\chi^2$] test) of 500.3, $I^2$ = 97.2% (P = 0.0001); that is, the homogeneity assumption was rejected (Table 1). The funnel plot concerning the publication bias is reported in figure 2. The Egger test demonstrated no publication bias (P = 0.2). Figure 3 reports the aHR and 95% confidence intervals for each study.

## Summary estimate of outcome: Prevalence of CKD (reduced eGFR)

Fifteen studies (n = 865,494 unique patients; 81,054 HCV-positive and 784,175 HCV-negative patients) evaluated the prevalence of CKD in HCV-infected patients.[20-22,34-45] We found no association between positive anti-HCV serologic status and increased prevalence of CKD, adjusted OR with HCV across the studies, 1.04 (95% CI, 0.91; 1.31) (P = 0.33). Tests for homogeneity of the aOR across the fifteen studies gave a Q value (by $\chi^2$ test) of 96.2 ($I^2$ = 85.4) (P = 0.0001); in other words, the homogeneity assumption was rejected (Table 1). The Egger test demonstrated no publication bias (P = 0.12). Figure 4 reports the aOR and 95% confidence intervals for each study.

The adjusted effect estimate of the occurrence of CKD among HCV RNA positive patients was 1.64 (95% CI, 1.32; 2.048) (P = 0.0001). Heterogeneity statistics, Q value (by $\chi^2$ test) = 1.23 (P-value = 0.54).

## Summary estimate of outcome: Frequency of proteinuria

Ten studies (n = 378,769 unique patients; 63,365 HCV-positive and 315,404 HCV-negative patients) evaluated the frequency of proteinuria according to anti-HCV positive serologic status.[33,34,36-39,42,43,46,47] We found a significant association between positive anti-HCV serologic status and increased frequency of proteinuria, adjusted risk of proteinuria associated with HCV across the surveys, 1.633 (95% CI, 1,29; 2.05) (P < 0.001). Test for homogeneity of the adjusted risk or proteinuria across the ten studies gave a Q value (by $\chi^2$ test) of 37.47 ($I^2$ = 75.9%) (P = 0.0001); that is, the homogeneity assumption was rejected (Table 2).

**Supplemental Table 1.** Longitudinal studies included in the meta-analysis (outcome: incidence of chronic kidney disease) (I).

| Authors | Crook E | Tsui J | Moe S | Asrani S | Butt A |
|---|---|---|---|---|---|
| Reference year | 2005 | 2007 | 2008 | 2010 | 2011 |
| Country | USA | USA | USA | USA | USA |
| Patients, n | 312 | 474,369 | 7,038 | 88,822 | 43,139 |
| Follow-up, years | 1.6± 0.2/2.1 ± 0.1 | 3.6 | 3.46 | 2.1 ±1.05 | 3.1± 1.4/3 ± 1.3 |
| Anti-HCV positive patients, n | 26 (8.3%) | 52,874 (11.1%) | 2,243 (31.8%) | 8,063 (9.1%) | 18,002 (41.7%) |
| Age, years | 55.6 ± 2/60.5 ± 0.78 | 52 ± 9/59 ± 13 | 42.2 ± 11 | 48.7 ± 8/43.2 ± 11 | 51.9 ± 7/52.8 + 7 |
| Male, n | 110 (35%) | 447,494 (94.3%) | 3,481 (49.5%) | 37,724 (42.4%) | 41,974 (97.3%) |
| Caucasian, n | 49 (15.7%) | 318,854 (67%) | 3,556 (50.5%) | NA | 24,347 (56%) |
| Diabetes mellitus, n | 312 (100%) | 120,692 (25%) | 1,319 (18.7%) | 9,317 (10.4%) | 10,809 (25%) |
| Outcome | ESRD | ESRD | CKD stages 3-5 | CKD stages 3-5 | CKD stages 3-5 |
| Adjusted HR (95% CI) | 3.49 (1.27; 9.57) | 2.8 (2.43, 3.23) | 0.89 (0.79; 1.015) | 0.92 (0.79; 1.08) | 1.3 (1.23; 1.37) |

**Supplemental Table 2.** Longitudinal studies included in the meta-analysis (outcome: incidence of chronic kidney disease) (II).

| Authors | Hofmann J | Su F | Chen Y | Chen Y | Lee J |
|---|---|---|---|---|---|
| Reference year | 2011 | 2012 | 2013 | 2014 | 2014 |
| Country | Sweden | Taiwan | Taiwan | Taiwan | Taiwan |
| Patients, n | 222,536 | 37,746 | 15,910 | 47,150 | 4,185 |
| Follow-up, years | 9.3 | 5.58 ± 2.04 | 5.8/5.92 | 7.1/7.43 | 2.2 ± 1.6 |
| Anti-HCV positive patients, n | 25,412 (11.4%) | 6,291 (16.6%) | 3,182 (20%) | 9,430 (20%) | 317 (7.6%) |
| Age, years | 37.6/NA | NA | NA | NA | 61.9 ± 14 |
| Male, n | 69.1%/NA | 19,074 (50.5%) | 8,095 (50.8%) | 23,365 (49.5%) | 2,447 (58.5%) |
| Caucasian, n | 89.2%/NA | NA | NA | NA | NA |
| Diabetes mellitus, n | 3.7%/NA | NA | 981 (6.2%) | 7,792 (16.5%) | 1,504 (36.2%) |
| Outcome | CKD stages 1-5 | ESRD | CKD stages 1-5 | CKD Stages 1-5 | ESRD |
| Adjusted HR (95% CI) | 3.9 (3.2; 4.8) | 1.53 (1.17; 2.01) | 1.75 (1.25; 2.43) | 1.28 (1.12; 1.46) | 1.32(1.07; 1.62) |

**Supplemental Table 3.** Longitudinal studies included in the meta-analysis (outcome: incidence of chronic kidney disease) (III).

| Authors | Molnar M | Hwang J | Rogal S | Lai T | Park H |
|---|---|---|---|---|---|
| Reference year | 2015 | 2016 | 2016 | 2017 | 2017 |
| Country | USA | Taiwan | USA | Taiwan | USA |
| Patients, n | 1,021,049 | 19,574 | 71,528 | 19,984 | 225,792 |
| Follow-up, years | 8.0 | 12 | 4.9±2/5.9 ± 2.8 | 16.8 | 1.75 |
| Anti-HCV positive patients, n | 100,518 (9.8%) | 9,787 (50%) | 2,589 (3.6%) | 591 (2.9%) | 56,448 (25%) |
| Age, years | 54.5 ± 13 | 55.7 ± 12.1 | 51 (43; 57)/55 (51; 59) | 47.3 ± 10 | NA |
| Male, n | 939,365 (92%) | 10,044 (51.3%) | 68,463 (95.7%) | 9,804 (49.1%) | 137,231 (60.7%) |
| Caucasian, n | 705,537 (69%) | NA | 40,647 (56.8%) | NA | NA |
| Diabetes mellitus, n | 216,933 (21.2%) | 19,574 (100%) | 17,593 (24%) | 1,616 (8.1%) | 36,739 (16.3%) |
| Outcome | ESRD | ESRD | CKD stages 3-5 | ESRD | CKD stages 3-5 |
| Adjusted HR (95% CI) | 1.98 (1.81; 2.16) | 1.47 (1.1; 1.93) | 0.86 (0.79; 0.92) | 2.33 (1.40; 3.89) | 1.27 (1.18; 1.37) |

**Supplemental Table 4.** Cross-sectional studies included in the meta-analysis: prevalence of chronic kidney disease (I).

| Authors | Tsui J | Tsui J | Dalrymple L | Ishizaka N | Moe S |
|---|---|---|---|---|---|
| Reference year | 2006 | 2007 | 2007 | 2008 | 2008 |
| Country | USA | USA | USA | Japan | USA |
| Patients, n | 15,029 | 474,369 | 25,782 | 12,535 | 13,139 |
| Anti-HCV positive patients, n | 366 (2.4%) | 52,874 (11.1%) | 1,928 (7.5%) | 72 (0,6%) | 3,938 (30%) |
| Age, years | NA | 52+9/59 ± 13 | 53 ± 9/58 ± 14 | 59.2 ± 10/53.1 ± 10 | 41.9 ± 12.7 |
| Male, n | 7,136 (47%) | 447,492 (94%) | 23,462 (91%) | 8,054 (64.2%) | 6,434 (48.9%) |
| Caucasian, n | 11,367 (75.6%) | 318,854 (67%) | 14,580 (56%) | NA | 6,858 (52%) |
| Diabetes mellitus, n | 751 (5%) | 120,691 (25.4%) | 5,533 (21.5%) | NA | 2,996 (22.8%) |
| Study design | CS | CS | CS | CS | CS |
| Outcome | Low eGFR, < 60mL/min per 1.73 $m^2$ | Low eGFR, < 60 mL/min per 1.73 $m^2$ | Renal insufficiency, serum creatinine > 1.5 mg/dL | Low eGFR, < 60 mL/min per 1.73 $m^2$ | Low eGFR, < 60 mL/min per 1.73 $m^2$ |
| Adjusted OR (95% CI) | 0.89 (0.49; 1.62) | 0.91 0.88; 0.95 | 1.4 (1.11; 1.76) | 1.63 0.95; 2.8 | 0.69 (0.62; 0.77) |

**Supplemental Table 5.** Cross-sectional studies included in the meta-analysis: prevalence of chronic kidney disease (II).

| Authors | Asrani S. | Lee J. | Derbala M. | Aoufi Rabih S. | Lin M. |
|---|---|---|---|---|---|
| Reference year | 2010 | 2010 | 2010 | 2012 | 2013 |
| Country | USA | Taiwan | Quatar | Spain | Taiwan |
| Patients, *n* | 167,569 | 54,966 | 300 | 265 | 3,352 |
| Anti-HCV positive patients, *n* | 13,384 (7.9%) | 5,189 (9.4%) | 233 (77.7%) | 120 (72.7%) | 187 (5.6%) |
| Age, years | 47.8 ± 8.6 / 40.4 ± 11.8 | 60.8 ± 11.5 | 46 (41; 53) | 56 ± 16.6 / 55.3 ± 15.7 | 47.5 ± 17.4 |
| Male, *n* | 75,577 (45%) | 17,168 (31.2%) | 239 (79.7%) | 140 (53%) | 1,629 (48.6%) |
| Caucasian, *n* | NA | NA | 0 | NA | 0 |
| Diabetes mellitus, *n* | 11,614 (6.9%) | 5,302 (9.6%) | 138 (46%) | 25 (9%) | 191 (5.6%) |
| Study design | CS | CS | CS | CS | CS |
| Outcome | Low eGFR, < 60 mL/min per 1.73 $m^2$ | Low eGFR, < 60 mL/min per 1.73$m^2$ | Low eGFR, < 60 mL/min per 1.73$m^2$ | Low eGFR, < 60 mL/min per 1.73$m^2$ | CKD |
| Adjusted OR (95% CI) | 0.90 (0.36; 2.27) | 1.3 (1.2; 1.42) | 1.12 (0.5; 1.5) | 18.3 (2.3; 143) | 0.65 (0.45; 0.94) |

**Supplemental Table 6.** Cross-sectional studies included in the meta-analysis: prevalence of chronic kidney disease (III).

| Authors | Li W. | Zeng Q. | Kurbanova N. | Su S. | Lai T. |
|---|---|---|---|---|---|
| Reference year | 2014 | 2014 | 2015 | 2015 | 2017 |
| Country | Taiwan | China | USA | Taiwan | Taiwan |
| Patients, *n* | 24,642 | 15,549 | 33,729 | 10,463 | 13,805 |
| Anti-HCV positive patients, *n* | 1,699 (6.9%) | 94 (0.6%) | 659 (1.9%) | NA | 431 (3.1%) |
| Age, years | 42.9 ± 14.5 | 49.2 + 9.3 | 49.8 | 54 + 15.1 | 47.5 ± 10 |
| Male, *n* | 12,827 (52.1%) | 10,909 (67.5%) | 16,284 (48%) | 5,218 (49.8%) | 6,601 (47.8%) |
| Caucasian, *n* | 0 | NA | 16,147 (47.9%) | 0 | 0 |
| Diabetes mellitus, *n* | NA | 1,508 (9.7%) | 4,143 (12.2%) | 3,182 (30.4%) | 335 (0.02%) |
| Study design | CS | CS | CS | CCS | CS |
| Outcome | CKD | CKD | CKD | CKD | CKD |
| Adjusted OR (95% CI) | 1.24 (1.05; 1.48) | 0.74 (0.18; 3.04) | 0.88 (0.57; 1.37) | 1.22 (0.85; 1.74) | 1.91 (1.27; 2.88) |

**Supplemental Table 7.** Studies included in the meta-analysis: frequency of proteinuria (or glomerular disease) (I).

| Authors | Liangpunsakul S. | Tsui J. | Huang J. | Ishizaka N. | Derbala M. |
|---|---|---|---|---|---|
| Reference year | 2005 | 2006 | 2006 | 2008 | 2010 |
| Country | USA | USA | Taiwan | Japan | Quatar |
| Patients, *n* | 13,990 | 15,029 | 9,934 | 12,535 | 300 |
| Anti-HCV positive patients, *n* | 368 (2.6%) | 366 (2.4%) | 646 (6.5%) | 72 (0.6%) | 233 (77.7%) |
| Age, years | 47.6 ± 19 | NA | 55.2 ± 6 | 53.1 ± 10.6 | 46 (41; 53) |
| Male, *n* | 7,192 (46.9%) | 7,136 (47.5%) | 4,291 (43.1%) | 8,054 1(64.2%) | 239 (79.9%) |
| Caucasian, *n* | 10,505 (68.5%) | 11,367 (75.6%) | 0 | 0 | NA |
| Diabetes mellitus, *n* | 1,349 (8.8%) | 751 (5%) | 1,241 (12.5%) | NA | 138 (46%) |
| Study type | Nested case-control | CS | CS | CS | CS |
| Outcome | Urine albumin excretion/ creatinine ratio, ≥ 30 mcg/mg | Spot urine albumin/ creatinine ratio, > 17 mcg/mg | Urine protein ≥ 1+ | Urine albumin excretion ratio (UAER), > 30 mg/g | Albumin Creatinine ratio, > 2.2 mg/mmol |
| Adjusted OR (95% CI) | 1.99 (1.38; 2.85) | 1.38 (0.91; 2.07) | 1.648 (1.246; 2.17) | 1.59 (0.83; 3.02) | 1.4 (0.8; 2.3) |

**Supplemental Table 8.** Studies included in the meta-analysis: frequency of proteinuria (or glomerular disease) (II).

| Authors | Lee J. | Aoufi Rabih S. | Zeng Q. | Kurbanova N. | Park H. |
|---|---|---|---|---|---|
| Reference year | 2010 | 2012 | 2014 | 2015 | 2017 |
| Country | Taiwan | Spain | China | USA | USA |
| Patients, *n* | 54,966 | 265 | 15,549 | 33,729 | 222,472 |
| Anti-HCV positive patients, *n* | 5,189 (9.4%) | 120 (72.7%) | 94 (0.6%) | 659 (1.9%) | 55,618 (25%) |
| Age, years | 60.8 ± 11.5 | 56 + 16/ 55.3 ± 15 | 49.2 ± 9.3 | 49.8 ± 18.7 | NA |
| Male, *n* | 17,168 (31.2%) | 140 (52.8%) | 10,509 (67.5%) | 16,284 (48.2%) | 137,231 (60.7%) |
| Caucasian, *n* | NA | NA | 0 | 16,147 (47.9%) | NA |
| Diabetes mellitus,*n* | 5,302 (9.6%) | 25 (9%) | 1,508 (9.7%) | 4,143 (12.2%) | 36,739 (16.3%) |
| Study type | CS | CS | CS | CS | Longitudinal |
| Outcome | Urine protein, > 1 + | Microalbuminuria/ creatinine, > 30 mcg/L | Albumin Excretion ratio, > 30 mg/g | Urine albumin creatinine ratio, > 30 mg/g | MPGN |
| Adjusted effect estimate (95% CI) | 1.14 (1.0; 1.3) | 2.05 (0.98; 4.29) | 1.3 (0.32; 5.32) | 1.95 (1.11; 3.41) | 2.23 (1.84; 2.71) |
| Estimate | OR | OR | OR | OR | HR |

**Table 1.** Summary measure for adjusted effect estimate of CKD according to anti-HCV serologic status among various groups of interest.

| | N | Adjusted effect estimate (random-effects model) | Q value (by $\chi^2$ test) | $I^2$ |
|---|---|---|---|---|
| Outcome: incidence of chronic kidney disease (aHR) | | | | |
| Longitudinal studies (All) | 15 | 1.54 (1.26; 1.87) | 500.3 (P < 0.0001) | 97.2% |
| Longitudinal studies (from US) | 8 | 1.36 (1.05; 1.75) | 356.0 (P < 0.0001) | 98.1% |
| Longitudinal studies (from Asia) | 6 | 1.45 (1.27; 1.65) | 8.1 (P = 0.1) | 38.4% |
| Longitudinal studies (ESRD only) | 7 | 1.88 (1.48; 2.37) | 48.8 (P = 0.001) | 87.2% |
| Longitudinal studies (CKD only) | 8 | 1.31 (1.05; 1.63) | 244 .2 (P = 0.0001) | 97.1% |
| Quality score ≥ 7 | 7 | 1.28 (1.04; 1.58) | 45.7 (P = 0.0001) | 86.9% |
| Quality score < 7 | 8 | 1.77 (1.32; 2.37) | 427.8 (P = 0.0001) | 98.3% |
| Outcome: prevalence of chronic kidney disease (aOR) | | | | |
| Cross-sectional studies (All) | 15 | 1.04 (0.91; 1.31) | 96.2 (P < 0.0001) | 85.4% |
| Cross-sectional studies (from USA) | 6 | 0.9 (0.71; 1.17) | 32.4 (P = 0.0001) | 84.5% |
| Cross-sectional studies (from Asia) | 8 | 1.2 (1.01; 1.42) | 18.1 (P = 0.01) | 61.5% |

- Crook, *et al.*:[18] HR adjusted for renal function at baseline, urine protein excretion, blood pressure, gender, race, presence of diabetic nephropathy, age, duration of diabetes, and renin angiotensin system inhibitors at baseline.
- Tsui, *et al.*:[19] HR adjusted for age, gender, race/ethnicity, educational status, smoking status, comorbidities.
- Moe, *et al.*:[20] HR adjusted for age, gender, race, baseline GFR, diabetes, hypertension, AST, HIV.
- Asrani, *et al.*:[21] HR adjusted for age, gender, baseline GFR, comorbidities (cirrhosis, diabetes, hypertension, heart failure, peripheral vascular disease, coronary artery disease, chronic obstructive pulmonary disease, diabetes, HIV), drug abuse, alcohol abuse, depression, diuretics, inhibitors of the renin-angiotensin system.
- Butt, *et al.*:[22] HR adjusted for age, gender, race, baseline eGFR, hypertension, smoking, chronic obstructive pulmonary disease, diabetes, dyslipidemia, anemia, alcohol abuse, drug abuse, ACEi/ARB use, decompensated liver disease.
- Hofmann, *et al.*:[23] HR adjusted for age, gender.
- Su, *et al.*:[24] HR adjusted for gender, age, occupation, urbanization level, CCI.
- Chen, *et al.*:[25] HR adjusted for age, gender, diabetes, hypertension, coronary artery disease, hyperlipidemia, liver cirrhosis, geographic region, urbanization level, enrolee category, number of healthcare visits in 1 year before study entry.
- Chen, *et al.*:[26] HR adjusted for gender, age, diabetes, hypertension, coronary artery disease, hyperlipidemia, cirrhosis, geographic region, urbanization level, enrolee category, number of medical visits in 1 year before study entry.
- Lee, *et al.*:[27] HR adjusted for gender, marital status, educational status, herb use, HBV infection, comorbidity (diabetes mellitus, hypertension, mild liver disease, severe liver disease, cardiovascular disease), body mass index, haemoglobin, platelets, ALT, cholesterol, uric acid, glucose, CKD stage, urine protein/creatinine ratio.
- Molnar, *et al.*:[28] HR adjusted for age, gender, ethnicity, baseline eGFR, comorbidities (diabetes, hypertension, cardiovascular disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, lung disease, dementia, rheumatic disease, malignancy, HIV, depression), body mass index, systolic blood pressure, diastolic blood pressure, socioeconomic parameters (income, marital status, service connection), adherence to medical interventions, medical adherence, number of healthcare encounters during the follow-up, number of prescribed antihypertensive medications and ACEi/ARB usage throughout follow-up.
- Hwang, *et al.*:[29] HR adjusted for age, gender, comorbidity (hypertension, coronary artery disease, hyperlipidemia, gout, liver cirrhosis, HBV).
- Rogal, *et al.*:[30] HR adjusted for age, race, gender, body mass index, diabetes, hypertension, cirrhosis, alcohol abuse or dependence, drug abuse or dependence, ACEi/ARB use at baseline.
- Lai, *et al.*:[31] HR adjusted for age, gender, diabetes, hypertension, baseline chronic kidney disease, serum cholesterol, triglycerides, uric acid, urinary protein excretion.
- Park, *et al.*:[32] HR adjusted for age, gender, cirrhosis, diabetes, comorbidities (hypertension, diabetes, dyslipidemia, alcohol use, drug abuse, chronic obstructive pulmonary disease, heart failure, peripheral vascular disease, cerebrovascular disease, coronary artery disease, hepatitis A, hepatitis B, HIV, cirrhosis, hepatocellular carcinoma), ACEi/ARB, change of comorbidities, change of medication use.
- Tsui, *et al.*:[19] OR adjusted for age, gender, race/ethnicity, educational status, smoking status, diabetes, arterial hypertension.
- Tsui, *et al.*:[33] OR adjusted for age, gender, race/ethnicity, comorbidities (diabetes, hypertension, chronic obstructive pulmonary disease, congestive heart failure, coronary artery disease, HIV, substance abuse).
- Dalrymple, *et al.*:[34] OR adjusted for age, gender, race, diabetes, hypertension.
- Ishizaka, *et al.*:[35] OR adjusted for age, gender, systolic blood pressure, HBsAg, and fasting plasma glucose.
- Moe, *et al.*:[20] OR adjusted for age, gender, diabetes, hypertension, AST, HIV status, laboratory values (rheumatoid factor, cryoglobulins).
- Asrani, *et al.*:[21] OR adjusted for age, gender, comorbidities (cirrhosis, diabetes, hypertension, coronary artery disease, chronic obstructive pulmonary disease, peripheral vascular disease, heart failure, and HIV), drug or alcohol abuse, diuretics, inhibitors of the renin-angiotensin system.

- Lee, *et al.*[36] OR adjusted for age, gender, educational status, BMI, albumin level, cholesterol level, uric acid level, hypertension, diabetes mellitus.
- Derbala, *et al.*:[37] OR adjusted for age, gender.
- Aoufi Rabih, *et al.*:[38] OR adjusted for age, gender, diabetes, hypertension, obesity, rheumatic disease.
- Lin, *et al.*:[39] OR adjusted for age, gender, years of education, annual income, medical history (hypertension, diabetes mellitus, cardiovascular disease, stroke, gout, liver disease, urinary tract disease, cancer), health-related behaviors (oral and intravenous analgesic use, cigarette smoking, alcohol drinking, health supplements, Chinese herbs use, betel-nut chewing, Long Dan Xie Gan Tang).
- Li, *et al.*:[40] OR adjusted for age, gender, alcohol drinking status, hypertension, serum creatinine, BMI, waist-to-height ration, fasting glucose, cholesterol, triglycerides, uric acid.
- Zheng, *et al.*:[41] OR adjusted for age, gender, HBV, hypertension, diabetes mellitus, BMI, albumin, high-density cholesterol low-density cholesterol, triglycerides, total cholesterol, uric acid.
- Kurbanova, *et al.*:[42] OR adjusted for age, gender, race, hypertension, diabetes, BMI.
- Su, *et al.*:[43] OR adjusted for gender, age, obesity, income, HBV status, uric acid levels, anaemia, hyperlipidemia, smoking status, alcoholic status, betel nut chewing, exercise habits, groundwater use.
- Lai, *et al.*:[44] OR adjusted for age, male, literate status, cigarette smoking, alcohol consumption, diabetes, hypertension, heart disease, HBsAg status, uric acid levels, serum cholesterol, serum triglycerides.

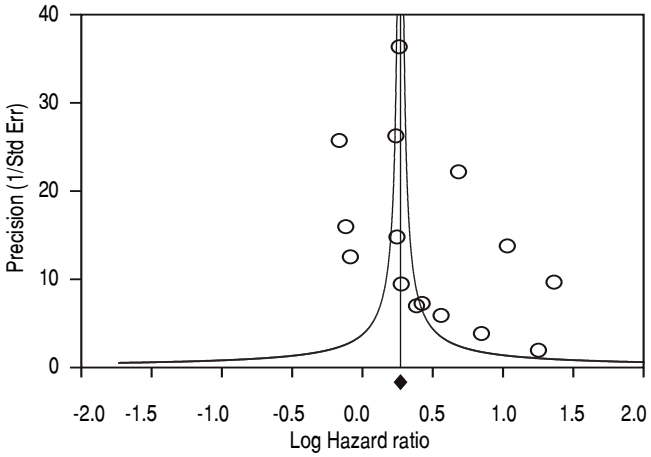


***Figure 2.*** *Funnel plot of precision by Log Hazard Ratio (n = 15 longitudinal studies; n = 2,299,134 unique patients) (Outcome: incidence of CKD).*

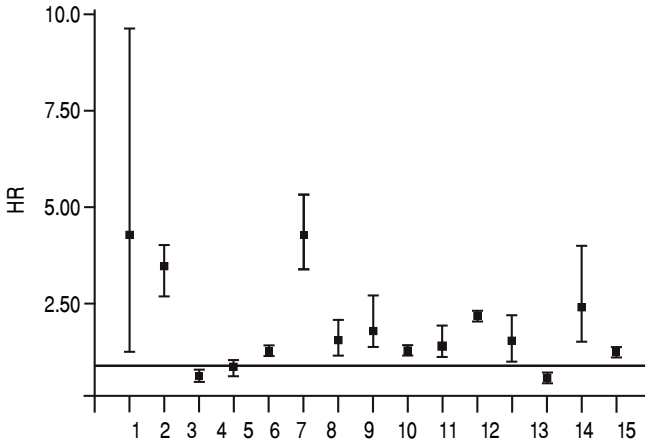


***Figure 3.*** *aHR and 95% confidence intervals for each study (n = 15 longitudinal studies; n = 2,299,134 unique patients) (Outcome: incidence of CKD). aHR of CKD associated with HCV (longitudinal surveys), 1.54 (95% CI, 1,26; 1.87) (P < 0.001). Q value by $\chi^2$ test, 500.3 (P = 0.0001), $I^2$ = 97.2%*

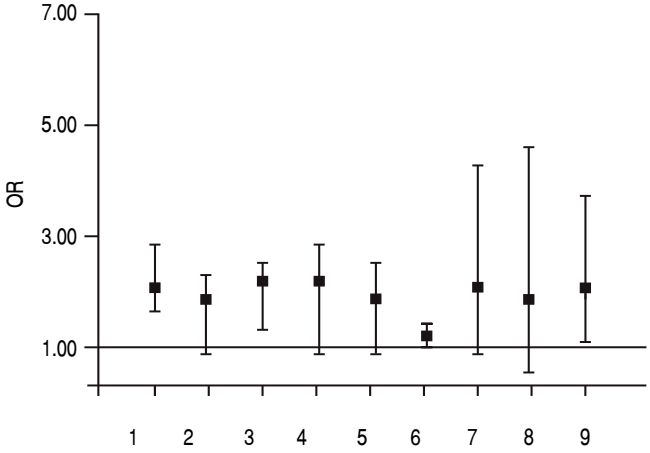


***Figure 4.*** *aOR and 95% confidence intervals for each study (n = 9 cross-sectional studies; n = 156,297 unique patients) (Outcome: prevalence of proteinuria). aOR of proteinuria associated with HCV (cross-sectional surveys), 1.51 (95% CI, 1,25; 1.82) (P < 0.001). Q value by $\chi^2$ test, 15.5 (P = 0.049), $I^2$ = 48.7%.*

The Egger test demonstrated no publication bias (P = 0.33). Figure 4 reports the aOR and 95% confidence intervals for each cross-sectional study.

## Stratified analysis and meta-regression

As shown in tables 1 and 2, our stratified analysis showed some substantial differences in pooled aHR across various subgroups. There was a significant association between anti-HCV positive serologic status and prevalence of chronic kidney disease among studies coming from Asia, 1.2 (1.01; 1.42) (P < 0.01) (Table 1); heterogeneity persisted, Q value (by $\chi^2$ test) of 32.4 (P = 0.0001). Tables 1 and 2 report that the homogeneity assumption was rejected in numerous subsets.

**Table 2.** Summary measure for adjusted effect estimate (outcome: frequency of proteinuria or glomerular disease) according to anti-HCV serologic status among various groups of interest.

| | N | Adjusted effect estimate (random-effects model) | Q value (by $\chi^2$ test) | $I^2$ |
|---|---|---|---|---|
| Outcome: proteinuria (frequency) | | | | |
| All studies | 10 | 1.63 (1.29; 2.05) | 37.4 (P = 0.000) | 75.9% |
| US studies | 4 | 1.95 (1.58; 2.39) | 4.3 (P = 0.22) | 30.6% |
| Asian studies | 5 | 1.33 (1.09; 1.62) | 6.1 (P = 0.18) | 34.88% |
| Studies based on dipstick analysis | 2 | 1.33 (0.93; 1.90) | 5.35 (P = 0.02) | 81% |
| Studies based on spot urine albumin/creatinine ratio | 7 | 1.66 (1.36; 2.01) | 3.1 (P = 0.7) | 0.0 |
| Cross-sectional studies<br>Outcome: proteinuria (prevalence) aOR | 8 | 1.41 (1.18; 1.67) | 10.3 (P = 0.1) | 32.2% |
| Cross-sectional and nested case-control studies<br>Outcome: proteimuria (prevalence) aOR | 9 | 1.51 (1.25; 1.82) | 15.5 (P = 0.049) | 48.7% |

- Liangpunsakul, *et al.*:[45] OR adjusted for age, race, hypertension, gender, body mass index.
- Tsui, *et al.*:[33] OR adjusted for age, gender, race/ethnicity, educational status, smoking status, diabetes, hypertension.
- Huang, *et al.*:[46] OR adjusted for diabetes, hypertension, BMI, age, triglycerides, gender, ALT, total cholesterol, triglycerides, HBsAg status.
- Ishizaka, *et al.*:[35] OR adjusted for age, gender, systolic blood pressure, fasting plasma glucose, ALT, HBsAg status.
- Lee, *et al.*:[36] OR adjusted for age, gender, educational status, BMI, hemoglobin level, albumin level, cholesterol level, uric acid level, hypertension, diabetes mellitus.
- Derbala, *et al.*:[37] OR adjusted for diabetes, age, gender, cryoglobulinemia, creatinine.
- Aoufi Rabih, *et al.*:[38] OR adjusted age, gender, hypertension, diabetes, obesity, rheumatic disease.
- Zeng, *et al.*: [41] OR adjusted for age, gender, BMI, albumin, hypertension, diabetes, total cholesterol, triglycerides, low-density lipoprotein cholesterol.
- Kurbanova, *et al.*: [42] OR adjusted for age, gender, race, hypertension, diabetes, BMI.
- Park, *et al.*:[32] HR adjusted for age, gender, calendar year, comorbidities (hypertension, dyslipidemia, diabetes, chronic obstructive pulmonary disease, heart failure, peripheral vascular disease, cerebrovascular disease, coronary artery disease, HIV, HAV, HBV, cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, alcohol abuse, drug abuse).

**Table 3.** Meta-regression: Impact of continuous variables on aHR (n = 15 studies, n = 2,299,134 unique patients) (incidence of CKD).

| | Regression coefficient | Standard error | 95% CI | Z value | P value |
|---|---|---|---|---|---|
| Reference year | -0.030 | 0.033 | -0.09; 0.03 | -0.90 | 0.36 |
| Size | 0.00 | 0.000 | -0.00; +0.00 | 1.50 | 0.13 |
| Age | 0.034 | 0.003 | 0.026; 0.04 | 8.70 | 0.000 |
| Follow-up | 0.041 | 0.006 | 0.031; 0.055 | 6.96 | 0.000 |
| Diabetics | 0.003 | 0.003 | -0.004; 0.010 | 0.803 | 0.421 |
| Males | 0.002 | 0.004 | -0.007; 0.01 | 0.48 | 0.62 |
| HIV | -0.04 | 0.04 | -0.131; 0.039 | -1.06 | 0.286 |
| HBsAg | 0.034 | 0.017 | 0.00; 0.06 | 2.01 | 0.06 |
| HCV rate | -0.004 | 0.007 | -0.019; 0.009 | -0.66 | 0.50 |
| Hypertension | 0.00 | 0.05 | -0.01; 0.01 | 0.066 | 0.99 |

**Table 4.** Meta-regression: Impact of continuous variables on adjusted effect estimate (n = 10 studies, n = 315,404 unique patients) (frequency of proteinuria).

| | Regression coefficient | Standard error | 95% CI | Z value | P value |
|---|---|---|---|---|---|
| Reference year | 0.02 | 0.02 | -0.017; 0.06 | 1.10 | 0.26 |
| Size | 0.000 | 0.000 | -0.000; 0.000 | 1.43 | 0.151 |
| Age | -0.034 | 0.010 | -0.054; -0.013 | -3.25 | 0.001 |
| Diabetics | -0.001 | 0.008 | -0.018; 0.016 | -0.117 | 0.90 |
| Males | 0.008 | 0.005 | -0.002; 0.019 | 1.5 | 0.132 |
| HBsAg | -0.03 | 0.01 | -0.067; -0.005 | -2.27 | 0.022 |
| HCV | 0.0006 | 0.003 | -0.006; 0.008 | 0.18 | 0.85 |
| Hypertension | 0.067 | 0.014 | 0.038; 0.09 | 4.50 | 0.001 |

Tables 3 and 4 report the impact of continuous variables on the aHR (incidence of CKD) and proteinuria frequency among anti-HCV positive patients (meta-regression analysis). As reported in table 3, meta-regression demonstrated a positive impact of ageing ($P < 0.0001$) and duration of follow-up ($P < 0.0001$) on the adjusted HR of incidence of CKD among HCV-positive patients.

## DISCUSSION

There is growing evidence in the medical literature suggesting that HCV infection is not a liver-focused disease but a systemic illness giving several extra-hepatic (including renal) manifestations. This meta-analysis (n = 40 studies; 4,072,867 patients) includes a number of reports almost double compared to the previous one and confirms the higher risk of chronic kidney disease among HCV-infected patients, aHR, 1.43 (95% CI, 1.23; 1.63) ($P = 0.0001$). This result has been observed in longitudinal studies (n = 15) provided with large size and appropriate follow-ups. Also, a higher rate of proteinuria among HCV-infected patients was recorded, adjusted effect estimate of proteinuria with HCV among surveys was 1.633 (95% CI, 1,29; 2.05) ($P < 0.001$) (n = 10 studies; 315,404 unique patients). The findings reported here are in keeping with other pieces of evidence; cohort studies carried out among individuals with biopsy-proven glomerular disease[48] or diabetic nephropathy[49] and patients with HCV-HIV co-infection[50] suggested a consistent link between anti-HCV positive serologic status and incidence or progression of chronic kidney disease. Antiviral therapy towards HCV has been able to slow down the progression of chronic kidney disease in HCV-infected populations. In a retrospective observational cohort of patients with stage 3 CKD, regression models reported that sustained viral response was associated with a 9.3 (95% CI, 0.44 to 18) mL/min per 1.73 $m^2$ increase in eGFR during the 6-month post-treatment follow-up period.[51] IFN-based therapies improved renal survival among diabetics,[52] liver transplant recipients,[53] and HCV-HIV infected patients.[54]

The relationship between anti-HCV positive status and prevalence of chronic kidney disease was not significant in many comparisons. The lack of an appropriate follow-up could explain the discrepancy between longitudinal and cross-sectional studies. According to our meta-regression analysis, the impact of HCV on the incidence of CKD was more prominent in those longitudinal studies provided with longer follow-ups and aged populations. The stratified analysis showed a consistent association between anti-HCV positive serologic status and prevalence of chronic kidney disease in the subset of Asian studies (1.2, 95% CI, 1.01; 1.42) ($P < 0.001$). This conferred robustness to the current meta-analysis even if significant between-study heterogeneity persisted in several comparisons. According to our meta-regression, the impact of HCV on the incidence of CKD was more evident in those longitudinal studies provided with longer follow-ups and aged populations.

The findings from the current meta-analysis present several limitations. First, many reports show retrospective and cohort design- from a theoretical point of view, a randomized controlled trial with placebo gives the best evidence on the efficacy of an intervention. However, a large sample and a long follow-up are needed to perform a RCT in this setting as the frequency of events is low; also, the current availability of safe and effective drugs (DAAs) for the treatment of HCV makes the randomisation to placebo not ethically acceptable. Secondly, multivariate analysis was performed in all the studies retrieved in the current meta-analysis but residual confounding (confounding remaining after adjustment) cannot be excluded as full information was not given on various confounders. As an example, data on life style, illicit drug abuse, and family history were often missed. Thirdly, our stratified analysis and meta-regression was not able to capture the sources of the great heterogeneity we have observed. The high heterogeneity suggests that all the studies included in the analysis are not functionally identical and this precluded the adoption of a fixed-effects model. Fourth, the relationship between HCV infection, as detected by positive HCV RNA in serum, and chronic kidney disease was addressed in a few surveys. Moreover, individual data from each study ('meta-analysis at patient level') were not available; thus, it was impossible to perform our own adjustments even if the studies included in this meta-analysis adjusted for numerous factors ('covariates') that could prove to be potential confounders. Finally, as with all meta-analyses, this study has the potential limitation of publication bias as negative or non-significant studies are less likely to be published ("file-drawer effect").[55] One approach to address this topic is to gather data from as many sources as possible. On the other hand, we have not included trials published as abstracts; information presented in abstract format is often without high quality and can give greater treatment effect.

We need more studies based on nucleic acid tests (instead of serological assays) to evaluate the link between HCV infection and occurrence of CKD. CKD appears more frequently in viraemic patients than HCV negative individuals. As reported above, this information was not available in most studies; however, the absence of statistical heterogeneity confers reliability to our results.

The results of the current meta-analyses support the notion that the kidneys appear an important target of the extra-hepatic activity of HCV, and various mechanisms of

renal disease among patients with chronic HCV have been described. In the context of membrano-proliferative glomerular disease, HCV gives glomerular damage through activation and deposition of cryoglobulins. Also, HCV may cause tubulo-interstitial damage via a direct cytopathic effect or antibody immune complex. Additionally, non-immunological pathways (i.e., oxidative stress, pro-inflammatory cytokines, and others) help the development of renal disease by vascular injury.[56] Some investigators addressed the influence of HCV eradication on extra-hepatic outcomes. In a prospective French study, 668 cirrhotic patients (50.5%) underwent antiviral treatment for HCV and achieved SVR; they had a lower risk of cardiovascular events (HR, 0.42; 95% CI, 0.25-0.69; P = 0.001) and bacterial infections (HR, 0.44; 95% CI, 0.29-0.68; P < 0.001).[57]

This meta-analysis of observational studies shows a link between anti-HCV positive serologic status and greater frequency of low eGFR and/or abnormal proteinuria in the adult general population. We need more studies in order to identify the pathophysiological mechanisms underlying such association and to deepen the sources of the heterogeneity identified. In the meantime, early initiation of antiviral therapy for HCV is encouraged to improve kidney survival regardless staging of liver disease.

## ABBREVIATIONS

- **ACEi:** angiotensin-converting enzyme inhibitor.
- **AH:** arterial hypertension.
- **aHR:** adjusted hazard ratio.
- **ALT:** alanine aminotransferase.
- **aOR:** adjusted odds ratio.
- **ARB:** angiotensin II receptor blocker.
- **aRR:** adjusted relative risk.
- **AST:** aspartate aminotransferase.
- **CI:** confidence intervals.
- **CKD:** chronic kidney disease.
- **CNI:** calcineurin inhibitors.
- **CRF:** chronic renal failure.
- **CV:** cardiovascular.
- **DAAs:** direct-acting antiviral agents.
- **DM:** diabetes mellitus.
- **eGFR:** estimated glomerular filtration rate.
- **EOT:** end of treatment.
- **ESRD:** end-stage renal disease.
- **GN:** glomerulonephritis.
- **HCV:** hepatitis C virus.
- **HD:** haemodialysis.
- **HIV:** human immunodeficiency virus.
- **ICD-9-CM:** International Classification of Diseases: Ninth Revision: Clinical Modification.
- **IFN:** interferon.
- **ITT:** intention-to-treat analysis.
- **MC:** mixed cryoglobulinemia.
- **MDRD:** modification of diet in renal disease.
- **NA:** not available.
- **NOS:** Newcastle/Ottawa Scale.
- **NSAID:** non-steroidal anti-inflammatory drug.
- **PRISMA:** Preferred Reporting Items for Systemic Reviews and Meta-Analyses statement.
- **RBV:** ribavirin.
- **SVR:** sustained virological response.

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## CONFLICT OF INTEREST STATEMENT

Fabrizio Fabrizi: consultant or advisor to AbbVie, Merck & Co; Maria Francesca Donato: speaker bureau Abbvie, Gilead, MSD.

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**Annex 1.** PRISMA 2009 checklist. PRISMA's items and their application within the paper.

| Section/topic | N | Checklist item<br>on page n | Reported |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 4 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 5 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 7 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 6-7 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 6-7 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 6-7 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 7 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 8-9 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 8-9 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 9-10 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 9-10 |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 9-10 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 9-10 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 11 |

| | | | |
|---|---|---|---|
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | Tables 1-8 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | Tables 1-8 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Tables 1-8 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 12-13 Tables 9-10 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 12-13 Tables 9-10 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 13-14 Tables 11-12 |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 15 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 16 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 17 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 18 |

*From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097. For more information, visit: www.prisma-statement.org.*

**Annex 2A.** Quality study. Details on the quality study process (longitudinal studies).

**A. NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE (cohort studies)**

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability (maximum 8 items, 9 stars).

**Selection** (Maximum 4 stars)

1) Representativeness of the exposed cohort.
   a) Truly representative of the average _____ (describe) in the community.
   b) Somewhat representative of the average _____ in the community.
   c) Selected group of users e.g. nurses, volunteers.
   d) No description of the derivation of the cohort.

2) Selection of the non exposed cohort.
   a) Drawn from the same community as the exposed cohort.
   b) Drawn from a different source.
   c) No description of the derivation of the non exposed cohort.

3) Ascertainment of exposure.
   a) Secure record (e.g. surgical records).
   b) Structured interview.
   c) Written self report.
   d) No description.

4) Demonstration that outcome of interest was not present at start of study.
   a) Yes.
   b) No.

**Comparability** (Maximum 2 stars)

1) Comparability of cohorts on the basis of the design or analysis.
   a) Study controls for _____ (select the most important factor).
   b) Study controls for any additional factor (This criteria could be modified to indicate specific control for a second important factor).

**Outcome** (Maximum 3 stars)

1) Assessment of outcome.
   a) Independent blind assessment.
   b) Record linkage.
   c) Self report.
   d) No description.

2) Was follow-up long enough for outcomes to occur.
   a) Yes (select an adequate follow up period for outcome of interest).
   b) No.

3) Adequacy of follow up of cohorts.
   a) Complete follow up - all subjects accounted for.
   b) Subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost).
   c) Follow up rate < ____% (select an adequate %) and no description of those lost.
   d) No statement.

**Annex 2B.** Quality study. Details on the quality study process (longitudinal studies).

**NEWCASTLE-OTTAWA QUALITY ASSESSMENT SCALE (cohort studies)**

Crook E, *et al. (Diabetes Care,* 2005)
- SELECTION
  - 1c
  - 2a one star
  - 3a one star
  - 4b
- COMPARABILITY
  - 1a one star
- OUTCOME
  - 1b one star
  - 2b
  - 3a one star
  - *N* = 5 stars

Tsui J, *et al. (Arch Intern Med*, 2007)
- SELECTION
  - 1c
  - 2a one star
  - 3a one star
  - 4b
- COMPARABILITY
  - 1a one star
- OUTCOME
  - 1b one star
  - 2a one star
  - 3a one star
  - *N* = 6 stars

Moe S, *et al. (Am J Kidney Dis*, 2016)
- SELECTION
  - 1a one star
  - 2a one star
  - 3a one star
  - 4b
- COMPARABILITY
  - 1a one star
- OUTCOME
  - 1b one star
  - 2a one star
  - 3a no star
  - *N* = 7 stars

Asrani S, *et al. (Clin Gastroenterol Hepatol*, 2010)
- SELECTION
  - 1a one star
  - 2a one star
  - 3a one star
  - 4b
- COMPARABILITY
  - 1a one star
- OUTCOME
  - 1b one star
  - 2a one star
  - 3a no star
  - *N* = 7 stars

Butt A, *et al. (Am J Kidney Dis*, 2011)
- SELECTION
  - 1c
  - 2a one star
  - 3a one star
  - 4b
- COMPARABILITY
  - 1a one star
- OUTCOME
  - 1b one star
  - 2a one star
  - 3a one star
  - *N* = 6 stars

Hofmann J, *et al. (Eur J Cancer Prev*, 2011)
- SELECTION
  - 1a one star
  - 2a one star
  - 3a one star
  - 4b
- COMPARABILITY
  - 1a one star
- OUTCOME
  - 1b
  - 2a one star
  - 3a one star
  - *N* = 6 stars

Su F, *et al. (Am J Kidney Dis*, 2012)
- SELECTION
  - 1a one star
  - 2a one star
  - 3a one star
  - 4b
- COMPARABILITY
  - 1a one star
- OUTCOME
  - 1b one star
  - 2a one star
  - 3a one star
  - *N* = 7 stars

Chen Y, *et al. (BMC Nephrol*, 2013)
- SELECTION
  - 1a one star
  - 2a one star
  - 3a one star
  - 4b
- COMPARABILITY
  - 1a one star
- OUTCOME
  - 1b one star
  - 2a one star
  - 3a one star
  - *N* = 7 stars

Chen Y, *et al. (Kidney Int*, 2014)
- SELECTION
  - 1a one star
  - 2a one star
  - 3a one star
  - 4
- COMPARABILITY
  - 1a one star
- OUTCOME
  - 1b one star
  - 2a one star
  - 3a one star
  - *N* = 7 stars

Lee J, *et al. (PLos One*, 2014)
- SELECTION
  - 1a one star
  - 2a one star
  - 3a one star
  - 4b
- COMPARABILITY
  - 1a one star
- OUTCOME
  - 1b one star
  - 2a one star
  - 3a one star
  - *N* = 7 stars

Molnar M, *et al. (Hepatology* 2015)
- SELECTION
  - 1c
  - 2a one star
  - 3a one star
  - 4b
- COMPARABILITY
  - 1a one star
- OUTCOME
  - 1b one star
  - 2a one star
  - 3a one star
  - *N*=6 stars

Hwang J, *et al. (Medicine* 2016)
- SELECTION
  - 1c
  - 2a one star
  - 3a one star
  - 4b
- COMPARABILITY
  - 1a
- OUTCOME
  - 1b
  - 2a one star
  - 3a one star
  - *N* = 4 stars

| Rogal S, *et al.* (*Dig Dis Sci* 2016) | Lai T, *et al. (Hepatology* 2017) | Park E, *et al. (Hepatology* 2017) |
|---|---|---|
| SELECTION | SELECTION | SELECTION |
| 1c | 1a one star | 1a one star |
| 2a one star | 2a one star | 2a one star |
| 3a one star | 3a one star | 3a one star |
| 4b | 4b | 4b |
| COMPARABILITY | COMPARABILITY | COMPARABILITY |
| 1a one star | 1a one star | 1a one star |
| OUTCOME | OUTCOME | OUTCOME |
| 1b one star | 1b one star | 1b one star |
| 2a one star | 2a one star | 2b |
| 3a one star | 3a one star | 3a one star |
| *N* = 6 stars | *N* = 7 stars | *N*= 6 stars |

**Annex 3**. List of full-text papers assessed for eligibility (sorted by publication year).

| Full text articles assessed for eligibility (n = 230). |
|---|


1. Bonomo L, Casato M, Afeltra A, Caccavo D. Treatment of idiopathic mixed cryoglobulinemia with alpha interferon. *Am J Med* 1987; 83: 726-30.
2. Casato M, Lagana B, Antonelli G, Dianzani F, Bonomo L. Long-term results of therapy with interferon-alpha for type II essential mixed cryoglobulinemia. *Blood* 1991; 78: 3142-7.
3. Johnson R, Gretch D, Yamabe H, Hart J, Bacchi C, Hartwell P, Couser W, et al. Membranoproliferative glomerulonephritis associated with hepatitis C virus infection. *N Engl J Med* 1993; 328: 465-70.
4. Johnson R, Gretch D, Couser WG, Alpers C, Wilson J, Chung M, Hart J, et al. Hepatitis C virus-associated glomerulonephritis. Effect of alpha-interferon therapy. *Kidney Int* 1994; 46: 1700-04.
5. Dammacco F, Sansonno D, Han J, Shymala V, Cornacchiulo V, Iacobelli A, Lauletta G, et al. Natural interferon alpha versus its combination with 6-methylprednisolone in the therapy of type II mixed cryoglobulinemia: a long-term randomized cross-over controlled trial. *Blood* 1994; 84: 3336-43.
6. Pucillo LP, Agnello V. Membranoproliferative glomerulonephritis associated with hepatitis B and C viral infections: from virus like particles in the cryoprecipitate to viral localization in paramesangial deposits, problematic investigations prone to artifacts. *Curr Opin Nephrol Hypertens* 1994; 3: 465-70.
7. Misiani R, Bellavita P, Fenili D, Vicari O, Marchesi D, Sironi P, Zilio P, et al. Interferon alfa-2a therapy in cryoglobulinemia associated with hepatitis C virus. *N Engl J Med* 1994; 330: 751-6.
8. Davis C, Gretch D, Perkins J, Harris A, Wener M, Alpers C, Lesniewski R, et al. Hepatitis C-associated glomerular disease in liver transplant recipients. *Liver Transplant Surg* 1995; 1: 166-75.
9. Migliaresi S, Tirri G. Interferon in the treatment of mixed cryoglobulinemia. *Clin Exp Rheumathol* 1995; 13 (Suppl. 13): S175-S180.
10. Altraif I, Abdulla A, Al Sebayel M, Said R, Al Suhaibani M, Jones A. Hepatitis C associated glomerulonephritis. *Am J Nephrol* 1995; 15: 407-10.
11. Yamabe H, Johnson R, Gretch D, Osawa H, Inuma H, Sasaki T, Kaizuka M, et al. Membranoproliferative glomerulonephritis associated with hepatitis C virus responsive to interferon-alpha. *Am J Kidney Dis* 1995; 25: 67-9.
12. Stehman-Breen C, Willson R, Alpers C, Gretch D, Johnson R. Hepatitis C virus associated glomerulonephritis. *Curr Opin Nephrol Hypertens* 1995; 4: 287-94.
13. Roth D. Hepatitis C virus: the nephrologist's view. *Am J Kidney Dis* 1995; 25: 3-16.
14. Komatsuda A, Imai H, Wakui H, Hamai K, Ohtani H, Kodama T, Oyama Y, et al. Clinicopathological analysis and therapy in hepatitis C virus-associated nephropathy. *Intern Med* 1996; 35: 529-33.
15. Gilli P, Stabellini N, Storari A, Gualandi G, Guerra G, Ghinelli F. Effect of human leukocyte alpha interferon on cryoglobulinemic membranoproliferative glomerulonephritis associated with hepatitis C virus infection. *Nephrol Dial Transplant* 1996; 11: 526-8.
16. Morosetti M, Sciarra G, Meloni C, Palmieri G, Palombo G, Taccone-Gallucci M, Casciani C. Membranoproliferative glomerulonephritis and hepatitis C: effects of interferon-alpha therapy on clinical out come and histological pattern. *Nephrol Dial Transplant* 1996; 11: 532-4.
17. Matyus J, Kovacs J, Ujhelyi L, Karpati I, Dalmi L, Kakuk G. Interferon therapy in cryoglobulinemic membranoproliferative glomerulonephritis associated with hepatitis C virus infection. *Orv Hetil* 1996; 137: 2527-30.
18. Kendrick E, McVicar J, Kowdley K, Bronner M, Emond M, Alpers C, Gretch D, et al. Renal disease in hepatitis C-positive liver transplant recipients. *Transplantation* 1997; 63: 1287-93.
19. Moses P, Krawitz E, Aziz W, Corwin H. Renal failure associated with hepatitis C virus infection. Improvement in renal function after treatment with interferon-alpha. *Dig Dis Sci* 1997; 42: 443-6.
20. Sarac E, Bastacky S, Johnson J. Response to high-dose interferon-alpha after failure of standard therapy in MPGN associated with hepatitis C virus infection. *Am J Kidney Dis* 1997; 30: 113-5.
21. Casato M, Agnello V, Pucillo L, Knight G, Leoni M, Del Vecchio S, Mazzilli C, et al. Predictors of long-term response to high-dose interferon therapy in type II cryoglobulinemia associated with hepatitis C virus infection. *Blood* 1997; 90: 3865-73.
22. Adinolfi L, Utili R, Zampino R, Ragone E, Mormone G, Ruggiero G. Effects of long-term course of alpha-interferon in patients with chronic hepatitis C associated to mixed cryoglobulinemia. *Eur J Gastroenterol Hepatol* 1997; 29: 343-50.
23. Mazzaro C, Carniello G, Colle R, Doretto P, Mazzi G, Crovatto M, Santini G, et al. Interferon therapy in HCV-positive mixed cryoglobulinemia: viral and host factors contributing to efficacy of the therapy. *Ital J Gastroenterol Hepatol* 1997; 29: 343-50.
24. Pham H, Feray C, Samuel D, Gigou M, Azoulay D, Paradis V, Ducret F, et al. Effects of ribavirin on hepatitis C-associated nephrotic syndrome in four liver transplant recipients. *Kidney Int* 1998; 54: 1311-9.
25. Fabrizi F, Pozzi C, Farina M, Dattolo P, Lunghi G, Badalamenti S, Pagano A, et al. Hepatitis C virus infection and acute or chronic glomerulonephritis: an epidemiological and clinical appraisal. *Nephrol Dial Transplant* 1998; 13: 1991-7.
26. D'Amico G. Renal involvement in hepatitis C infection: cryoglobulinemic glomerulonephritis. *Kidney Int* 1998; 54: 650-71.
27. Stehman-Breen C, Johnson R. Hepatitis C virus-associated glomerulonephritis. *Adv Intern Med* 1998; 43: 79-97.
28. Cresta P, Musset L, Cacoub P, Frangeoul L, Vitour D, Poynard T, Opolon P, et al. Response to interferon-alpha treatment and disappearance of cryoglobulinemia in patients infected by hepatitis C virus. *Gut* 1999; 45: 122-8.

29. Kiyomoto H, Hitomi H, Hosotani Y, Hashimoto M, Uchida K, Kurokoucji K, Nagai M, et al. The effect of combination therapy with interferon and cryofiltration on mesangial proliferative glomerulonephritis originating from mixed cryoglobulinemia in chronic hepatitis C virus infection. *Ther Apher* 1999; 3: 329-33.
30. Misiani R, Bellavita P, Baio P, Caldara R, Ferruzzi S, Rossi S, Tengattini F. Successful treatment of HCV-associated cryoglobulinemic glomerulonephritis with a combination of interferon-alpha and ribavirin. *Nephrol Dial Transplant* 1999; 14: 1558-60.
31. Stehman-Breen C, Alpers C, Fleet W, Johnson R. Focal segmental sclerosis among patients infected with HCV. *Nephron* 1999; 81: 37-40.
32. Ezaki Y, Tanaka U, Minoshima S, Endou M, Kuwaki K, Arimura Y, Nakabayashi K, et al. Focal segmental glomerulosclerosis associated with type C virus hepatitis and decrement of proteinuria by interferon-alpha therapy. *Nippon Jinzo Gakkai Shi* 1999; 41: 83-8.
33. Daghestani L, Pomeroy C. Renal manifestations of hepatitis C infection. *Am J Med* 1999; 106: 347-54.
34. Stehman-Breen C, Alpers C, Fleet W, Johnson R. Focal segmental sclerosis among patients infected with HCV. *Nephron* 1999; 81: 37-40.
35. Al-Wakeel J, Mitwalli A, Tarif N, Al-Mohaya S, Malik G, Khalil M. Role of interferon-alpha in the treatment of primary glomerulonephritis. *Am J Kidney Dis* 1999; 33: 1142-6.
36. Kiyomoto H, Hitomi H, Hosotani Y, Hashimoto M, Uchida K, Kurokouchi K, Nagai M, et al. The effect of combination therapy with interferon and cryofiltration on mesangial proliferative glomerulonephritis originating from mixed cryoglobulinemia in chronic hepatitis C virus infection. *Ther Apher* 1999; 3: 329-33.
37. Calleja J, Albillos A, Moreno-Otero R, Rossi I, Cacho G, Domper F, Yebra M, et al. Sustained response to interferon-alpha or to interferon-alpha plus ribavirin in hepatitis C virus associated symptomatic mixed cryoglobulinemia. *Aliment Pharmacol Ther* 1999; 13: 1179-86.
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*The papers that appear in bold are those that were included in the meta-analysis.*