The Association Between Hepatitis C Virus Infection and Renal Cell Cancer, Prostate Cancer, and Bladder Cancer: A Systematic Review and Meta-Analysis

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Abstract

Background: To update the current evidence on whether hepatitis C virus (HCV) infection represents a possible risk factor for renal cell cancer (RCC), prostate cancer (PCa) and bladder cancer (BC).

Methods: We searched literatures on Pubmed, Web of Science and Embases before February 2020. A systematic review and meta-analysis were performed.

Results: Finally, we extracted 12 studies based on the eligible criteria. Across 11 studies for HCV and RCC, the incorporated RR was 1.28 (95% CI 1.05-1.55), which meant that participants with HCV infection were associated with a higher risk of RCC. The pooled RR in hazard ratio (HR) subgroup (HR 1.59, 95% CI 1.22-2.08), cohort studies (CS) subgroup (RR 1.47, 95% CI 1.18-1.82), and North America subgroup (RR 1.71, 95% CI 1.40-2.09) detected a stronger association between HCV and RCC risk. Although an inverse association was seen for PCa (RR 0.75, 95% CI 0.54-1.03) across 7 studies, it was not statistically significant (P = 0.075). There was no significant association between HCV and BC with an incorporated RR of 0.92 (95% CI, 0.82-1.03) across 5 studies.

Conclusions: Our study demonstrated that HCV infection was significantly associated with increased RCC risk. There appeared to be an inverse association for HCV in PCa risk but no statistically significant. No significant association was found between HCV and BC risk. Prospective, large-scale and well-designed cohort studies are required to validate the association between HCV and RCC, and to investigate the role of HCV on PCa.

1. Background

Urologic cancers such as renal cell cancer (RCC), prostate cancer (PCa) and bladder cancer (BC) are the most commonly diagnosed cancers in humans [1]. Both non-modifiable and environmental risk factors are identified as associated with these cancers. However, the role of the hepatitis C virus (HCV) infection on these cancers is still controversial.

HCV infection is a public health problem. It was estimated that approximately 180 million people infected worldwide [2]. HCV infection is involved in both hepatic diseases and a variety of extra-hepatic diseases [3]. Although the mechanism of how HCV could affect theses cancers was not comprehended, the association between HCV and RCC, PCa and BC has been extended researched

A meta-analysis published in 2016 reported an association in terms of HCV infection for RCC risk [4]. However, the state of two studies used in meta-analysis was estimated and crude, which was one of the limitations. Also, more studies were published afterward, and the results were still inconclusive. To conclude a more powerful estimation of their associations, we updated the current evidence on whether

HCV infection represents a possible risk factor for RCC. To our knowledge, there was no meta-analysis focusing on the association between HCV and PCa or BC to our knowledge.

In light of these controversial roles of HCV on RCC, PCa and BC risk, the purpose of the present meta-analysis is to explore whether HCV represents a possible risk factor for RCC, PCa, and BC by taking all available studies meeting our inclusion criteria into consideration,

2. Methods

This systematic review was registered on INPLASY (INPLASY202050086). To perform this study, we followed the guide of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [5].

2.1 Search Strategy

Two independent reviewers searched literatures on Pubmed, Web of Science and Embases before February 2020. Relevant studies restricted to the English language were identified according to the eligibility criteria as follows. The Search terms include Hepatitis C Virus, HCV, Prostatic Neoplasms, Prostate Cancer, Renal Cell Cancer, Renal Cancer, Kidney Neoplasm, Kidney Cancer, Renal Neoplasm, Renal Cell Cancer, Bladder Neoplasm, Bladder Cancer. Negotiated between 2 reviewers or consulted with a third author was used to resolve the disagreements.

2.2 Eligible Criteria

Eligible criteria described as follows. (1) Population: humans with RCC, PCa or BC; (2) Exposure: HCV infection; (3) Comparison: participants control; (4) Outcomes: diagnosis any kind of these three cancers; (5) Study: all study designs. Studies meeting the eligibility criteria listed above and any kind of relative risk (RR) estimates (standardized incidence ratio [SIR], hazard ratio [HR] or odds ratios [OR]) and their 95% confidence interval (CI) could be directly extracted were included in our meta-analysis. Besides, review, meta-analysis, letters, abstracts, case reports, meeting comments, editorials, and congress reports were excluded in our study.

2.3 Data Extraction and Quality Assessment

Two reviewers independently assessed study quality followed by extracting data from the individual study. Discussion and reevaluation of the methodology would be adopted to resolve the disagreements. Information including the name of the first author, study location, study period, study design, publication year, sample size, measurement of cancers (RCC, PCa, and BC), and the RR (95% CIs) for each category of cancers. The checklist was used to evaluate the quality used was the Newcastle-Ottawa Scale [6] (NOS) tool. The total score of each study was 9 and a score of more than 6 were classified into the high quality group.

2.4 Statistical Analyses

Effect measures (SIR, OR, and HR) with 95% CI were extracted from the eligible study, and a final combined RR and its 95% CI were obtained by the inverse-variances method. The I^2 statistics with the Q test was used to assess heterogeneity among included studies [7]. For pooled RR, the level of statistical heterogeneity was used to choose the primary statistical model. When heterogeneity was significant (I^2 > 50% or P < 0.1), the random effect model would be used. Otherwise, the fixed-effect model was applied when substantial heterogeneity was not observed. Next, subgroup analyses were performed to identify which clinical factor might contribute to the potential source of heterogeneity. Then, we performed a sensitivity analysis by omitting individual studies one by one. Finally, both the Begg and Egger test was performed to detect publication bias. A two-sided P < 0.05 in our study indicated a significant statistical difference. Statistical analyses were performed with Stata version 14 software (Stata Corporation, College Station, TX, USA).

3. Results

A total of 644 studies using the search criteria were identified. Finally, we extracted 12 studies [8-19] based on the eligible criteria (Supplementary Fig. S1). The characteristics were demonstrated in Table 1. Among these 12 studies, no prospective trial was identified. We found 7 cohort studies (CS) and 5 case-control studies (CCS) that investigated the role of HCV for RCC. 7 studies were reporting the association between HCV and PCa, in which 5 were CS. For studies that explore the role of HCV on BC, 3 were CS and 2 were CCS. The detailed NOS score of each study belong to CS and CCS design was shown in Supplementary Tables S1 and S2, respectively.

3.1 HCV and RCC

For HCV and RCC, 11 studies[8-13,15-19] had sufficient data for meta-analysis. As shown in Fig. 1, the summary of RR obtained by the random-effects model (I^2 = 70.1%; P < 0.001) was 1.28 (95% CI 1.05-1.55), which meant participants with HCV infection had a significantly higher risk of RCC.

We further assessed the clinical factors that might potential contribute to the heterogeneity (Table 2). The pooled RR in HR subgroup (HR 1.59, 95% CI 1.22-2.08; I^2 = 13.5%, P =0.315), CS subgroup (RR 1.47, 95% CI 1.18-1.82; I^2 = 45.6%, P = 0.088), and USA subgroup (RR 1.71, 95% CI 1.40-2.09; I^2 = 0, P = 0.991) detected a stronger association between HCV and RCC risk.

Sensitivity analyses were shown in Fig. 2. By omitting individual study yielded nonsignificant RR change ranging from 1.22 (95% CI 1.01-1.49) to 1.36 (95% CI 1.15-1.61). Both Begg rank correlation test (P > |z| = 0.938) (Supplementary Fig. S2) and Egger linear regression (P > |t| = 0.172) demonstrated that there was no significant publication bias among these studies

3.2 HCV and PCa

Across a total of 7 studies[8,10,12-15,17,19] which examined the role of HCV for PCa, there was no significant association between HCV and PCa was found, with a pooled RR of 0.75 (95% CI 0.54-1.03). Between-study heterogeneity was significantly based on the I^2 = 93% and Q statistic (P < 0.001) and, so a random-effects model was applied (Supplementary Fig. S3).

Analyses in CCS subgroup (RR 1.71, 95% CI 1.40-2.09; I^2 = 0, P = 0.991), Europe subgroup (RR 1.71, 95% CI 1.40-2.09; I^2 = 0, P = 0.991), studies published before 2012 subgroup (RR 1.71, 95% CI 1.40-2.09; I^2 = 0, P = 0.991), and subgroup with lower NOS score (RR 1.71, 95% CI 1.40-2.09; I^2 = 0, P = 0.991) found a significant inverse association with very low heterogeneity. However, we must treat it with caution because of the limited number and relatively low methodological quality studies included in these subgroups. Similarly, a significant inverse association observed in SIR subgroup (RR 0.58, 95% CI 0.45-0.76) should be interpreted carefully because of the substantial heterogeneity (I^2 = 66.1, P = 0.031) (Table 2).

One individual study affected the overall results, a significant inverse association was found between HCV and PCa (RR 0.65, 95% CI 0.54-0.77) (Supplementary Fig. S4). However, substantial heterogeneity was still high (I^2 = 64.2, P = 0.016). Publication bias was not significant based on Begg (P > |z| = 0.293) (Supplementary Fig. S5). and Egger (P > |t| = 0.882) tests.

3.3 HCV and BC

The pooled RR enrolling 5 studies [10,12,13,17,19] was 0.92 (95% CI, 0.82-1.03), representing no significant association between HCV infection and BC risk. Heterogeneity was not significant based on the I^2 = 19.2% and Q statistic (P = 0.293), so a fixed-effects model was used (Supplementary Fig. S6).

Subgroup analyses revealed that the pooled RR in higher NOS score subgroup was statistic significant (RR 0.87, 95% CI 0.77-0.99; I^2 = 0, P = 0.728) (Table 2). Influence analysis revealed that no study had a greater impact on the pooled RR (Supplementary Fig. S7). No significant publication bias was found according to the Begg (P > |z| = 1.000) (Supplementary Fig. S8). and Egger (P > |t| = 0.536) tests.

4. Discussion

This meta-analysis had several important findings concerning the role of HCV infection on RCC, PCa, and BC. First, we found a significantly increased risk of association between HCV and RCC (Fig. 1). This association was detected stronger in the HR subgroup, CS subgroup, and North America subgroup accompany with the decreased heterogeneity (Table 2). As we omitted each study in sensitivity analyses (Fig. 2) but a nonsignificant trend appeared. Second, although an inverse association was seen for PCa

(RR 0.75) in meta-analysis enrolling 7 studies, it was not statistically significant (P = 0.075). In subsequent subgroup analyses,

HCV infection was associated with a significantly decreased risk of PCa in CCS subgroup, Europe subgroup, studies published before 2012 subgroup, and lower NOS score subgroup (Table 2). However, we must interpret it carefully because of the limited number and relatively low methodological quality studies included in these subgroups. Third, regardless of sensitivity analyses, pooled RR remained nonsignificant between HCV infection and BC risk.

RCC incidence has increased over the past two decades, the role of HCV infection on RCC was still inconclusive. A recent meta-analysis [4] found that HCV infection had an increased risk of RCC, but the state of two studies used in meta-analysis was estimated and crude. Therefore, our study provided a more precise estimation of the role of HCV for RCC. The association was most strong (RR = 1.71) in USA subgroup analyses seemed to be intriguing. As we know, an estimated 4.1 million individuals in the USA have been exposed to HCV [20]. Besides, RCC incidence has increased particularly among African Americans [21]. Therefore, it seems to be reasonable to consider screening newly diagnosed RCC for HCV infection in the USA.

Although the mechanism by which HCV increased the risk of RCC is not completely understood, the most important explanation is that HCV-associated chronic kidney disease (CKD) might play an important role. HCV infection was found to be associated with developing CKD and end-stage renal disease [22]. Besides, several other hypotheses have been proposed. First, the HCV virus core protein and the NY-REN-54 protein contribute to the influence of HCV on RCC [23]. Second, serine protease inhibitor Kazal (SPIK) protein can inhibit serine protease-related apoptosis and HCV was found that it could increase the expression of SPIK [24]. Third, cytotoxic T-cell dependent apoptosis plays a pilot role in host immunity and normal tissue. HCV can disturb this process and lead to renal oncogenesis [25]. In conclusion, our evidence supported the promoting role of HCV on RCC and the mechanism needs to be elucidated in future studies.

For HCV and PCa, there was no significant association according to our overall meta-analysis (Table 2). Up to now, few explanations about this issue were reported. Amin et al [19] and Lee et al [26] were first to report an association between HCV and PCa incidence, HCV and PCa mortality, respectively. However, both did not discuss potential reasons. Krystyna et al[27] reported that HCV infection increased the risk of PCa because they believed more serologic testing would be down if their physician suspected cancer. On the contrary, Mahale et al [12] reported an inverse association between HCV and PCa. They concluded that those HCV-infected individuals often come from lower socioeconomic status groups, so the rate of prostate cancer screening is relatively low. As we know, controlling confounding factors well was methodologically challenged in studies which tried to conclude the modifiable risk factors for cancers because the carcinogenesis of cancers was multifactorial. In fact, there will be more meaningful to explore the HCV based on PCa grade or stage, because many of PCa were not clinically relevant. In summary, we did not find that HCV was associated with PCa. Although some subgroup analyses showed

an inverse association, further prospective, large-scale, long follow-up, and well-controlled confounders cohort studies are needed to investigate this association.

Several potential limitations should not be ignored. First, the heterogeneity in the meta-analysis for RCC and PCa was high. On the one hand, random-effects models were applied for making results to be conservative. On the other hand, we explored the potential clinical factors which might contribute heterogeneity by subgroup analysis methods. Nevertheless, the residual heterogeneity could not be interpreted sufficiently. Second, a small number of studies included in the meta-analysis for BC was a limitation. Third, this study was limited by pooling a few low NOS score (< 7) studies. Lastly, the absence of stratification on grade or stage in these cancers (RCC, PCa, and BC) was a limitation that prevented us from better investigating the clinical significance of HCV on these cancers.

5. Conclusion

With or without sensitivity analyses, the summary estimates from our meta-analysis demonstrated that HCV infection was significantly associated with increased RCC risk, especially enrolling studies in USA location. Although an inverse association was seen for HCV and PCa risk, it was not statistically significant. There was no significant association between HCV infection and BC risk. Prospective, large-scale, and well-designed cohort studies are needed to validate the association between HCV and RCC and to investigate the role of HCV on PCa.

Abbreviations

HCV: Hepatitis C virus.

RCC: Renal cell Cancer.

PCa; Prostate Cancer.

BC: Bladder Cancer.

CI: Confidence Interval.

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

INPLASY: International Platform of Registered Systematic Review and Meta-analysis Protocols.

SIR: Standardized Incidence Ratio.

HR: Hazard Ratio.

RR: Relative Risk.

OR: Odds Ratio.

NOS: Newcastle-Ottawa Scale.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request

Competing Interest

The authors declare that they have no conflict of interest.

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Author’s contribution

JZ: project development, data collection, and management, manuscript writing and revising; MY: data collection, data analysis; LH: manuscript editing and revising; WK: project design and development, data interpretation, manuscript editing and revising. All authors read and approved the final manuscript.

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Tables

Table 1 Characteristics of studies included in the systematic review and meta-analysis

Study	Publication year	Study design	Study location	Study period	Total numbers	Outcomes RR;95%CI	NOS score
Nyberg AH [8]	2019	CS	California, USA	2008-2012	24484 in HCV	[A] HR 1.71; 1.29, 2.25 [B] HR 1.45; 1.24, 1.69	7
Liu B [9]	2019	CCS	China	2008-2016	1287 in RCC	[A] OR 0.71; 0.23, 2.25	5
Liu X [10]	2017	CS	Sweden	1990-2010	29271 in HCV	[A] SIR 1.42; 0.91, 2.12 [B] SIR 0.73; 0.59, 0.90 [C] SIR 1.20; 0.84, 1.67	6
Lin YS [11]	2017	CCS	Taiwan	2000-2011	17747 in RCC	[A] OR 1.24; 1.07, 1.44	7
Mahale P [12]	2017	CCS	United Kingdom	1993-2011	35960 in RCC; 90360 in BC; 283367 in PCa	[A] OR 0.89; 0.76, 1.04 [B] OR 0.84; 0.48, 1.46 [C] OR 0.88; 0.77, 1.00	8
Kamiza AB [13]	2016	CCS	Taiwan	1995-2014	35320 in HCV	[A] HR 0.98; 0.49, 1.93 [B] HR 1.55; 1.04, 2.32 [C] HR 1.20; 0.75, 1.90	6
Gonzalez HC [14]	2015	CCS	Michigan, USA	2011-2013	140 in RCC	[A] OR 24.20; 2.4, N/A	N/A
Allison RD [15]	2015	CS	USA	2006-2010	12126 in HCV	[A] SIR 1.7; 1.1, 2.2 [B] SIR 0.6; 0.5, 0.7	8
Hofmann JN [16]	2011	CS	Sweden	1990-2006	43000 in HCV	[A] SIR 1.2; 0.8, 1.7	6
Omland LH [17]	2010	CS	Denmark	1994-2003	4349 in HCV	[A] SIR 3.6; 0.98, 9.22 [B] SIR 1.02; 0.12, 3.7 [C] SIR 0.92; 0.11, 3.31	7
Gordon SC [18]	2010	CS	USA	1997-2006	3057 in HCV	[A] HR 1.77; 1.05, 2.98	8
Amin J [19]	2006	CS	Sydney	1990-2002	75834 in HCV	[A] SIR 0.9; 0.6, 0.4 [B] SIR 0.4; 0.3, 0.6 [C] SIR 0.7; 0.4, 1.2	8

[A] = kidney cancer; [B] = bladder cancer; [C] = prostate cancer; N/A = not available; HCV = hepatitis C; RCC = renal cell cancer; BC = bladder cancer; PCa = prostate cancer; RR = relative risk; HR = hazard ratio; OR = odds ratio; SIR = standardized incidence ratio; NOS = Newcastle-Ottawa Scale; CS = cohort study; CCS = case-control study; N/A = not available; not evaluated

Table 2 Subgroup analysis of association between HCV and RCC, BC, PCa risk

Category of variables	Studies, n	Heterogeneity		RR (95%CI)	P value for difference
		I^2, %	P value		
RCC	***11***	***70.1***	***<0.001***	***1.28(1.05-1.55)***	***0.013***
Type of RR					
HR	3	13.5	0.315	1.59(1.22-2.08)	***0.001***
OR	3	79.0	0.009	1.03(0.76-1.39)	0.866
SIR	5	53.4	0.072	1.37(1.01-1.84)	***0.040***
Study design					
Cohort study	7	45.6	0.088	1.47(1.18-1.82)	<0.001
Case-control study	4	68.7	0.023	1.02(0.79-1.33)	0.857
Geographic area					
North America	3	0	0.991	1.71(1.40-2.09)	***<0.001***
Asia	3	0	0.521	1.22(1.05-1.40)	***0.008***
Europe	3	71.9	0.014	1.23(0.85-1.79)	0.267
Australia	1	-	-	0.90(0.59-1.37)	0.626
Publication year					
After 2012	7	76.6	<0.001	1.26(0.99-1.59)	0.057
Before 2012	4	59.9	0.058	1.37(0.90-2.07)	0.142
NOS score					
≥7	7	81.0	<0.001	1.34(1.04-1.73)	***0.024***
≤6	4	0	0.625	1.21(0.94-1.56)	0.144
PCa	***7***	***93.0***	***<0.001***	***0.75(0.54-1.03)***	***0.075***
Type of RR					
HR	2	70.6	0.065	1.18(0.71-1.98)	0.529
OR	1	-	-	0.73(0.66-0.81)	<0.001
SIR	4	66.1	0.031	0.58(0.45-0.76)	***<0.001***
Study design					
Cohort study	5	95.1	<0.001	0.74(0.44-1.22)	0.231
Case-control study	2	0	0.627	0.73(0.66-0.82)	***<0.001***
Geographic area					
North America	2	98.2	<0.001	0.93(0.39-2.21)	0.873
Asia	1	-	-	0.84(0.48-1.47)	0.539

Europe	3	0	0.930	0.73(0.66-0.81)	*<0.001*
Australia	1	-	-	0.40(0.28-0.57)	<0.001
Publication year					
After 2012	5	94.3	<0.001	0.83(0.59-1.16)	0.274
Before 2012	2	9.1	0.294	0.43(0.26-0.71)	*0.001*
NOS score					
≥7	5	95.3	<0.001	0.73(0.48-1.13)	0.160
≤6	2	0	0.644	0.74(0.61-0.91)	*0.003*
BC	*5*	*19.2*	*0.293*	*0.92(0.82-1.03)*	*0.154*
Type of RR					
HR	1	-	-	1.03(0.77-1.37)	0.851
OR	1	-	-	0.88(0.77-1.37)	0.055
SIR	3	25.2	0.262	1.37(1.01-1.84)	0.442
Study design					
Cohort study	3	25.2	0.262	1.37(1.01-1.84)	0.442
Case-control study	2	36.9	0.208	0.90(0.79-1.02)	0.102
Geographic area					
North America	0	-	-	-	-
Asia	1	-	-	1.20(0.75-1.91)	0.442
Europe	3	26.9	0.255	0.92(0.81-1.03)	0.154
Australia	1	-	-	0.70(0.40-1.21)	0.203
Publication year					
After 2012	3	49.4	0.138	0.93(0.83-1.05)	0.238
Before 2012	2	0	0.765	0.72(0.43-1.21)	0.215
NOS score					
≥7	3	0	0.728	0.87(0.77-0.99)	*0.031*
≤6	2	0	1.000	1.20(0.91-1.58)	0.196

HCV = hepatitis C; RCC = renal cell carcinoma; BC = bladder cancer; PCa = prostate cancer; RR = relative risk; HR = hazard ratio; OR = odds ratio; SIR = standardized incidence ratio; NOS = Newcastle-Ottawa Scale;

Figures

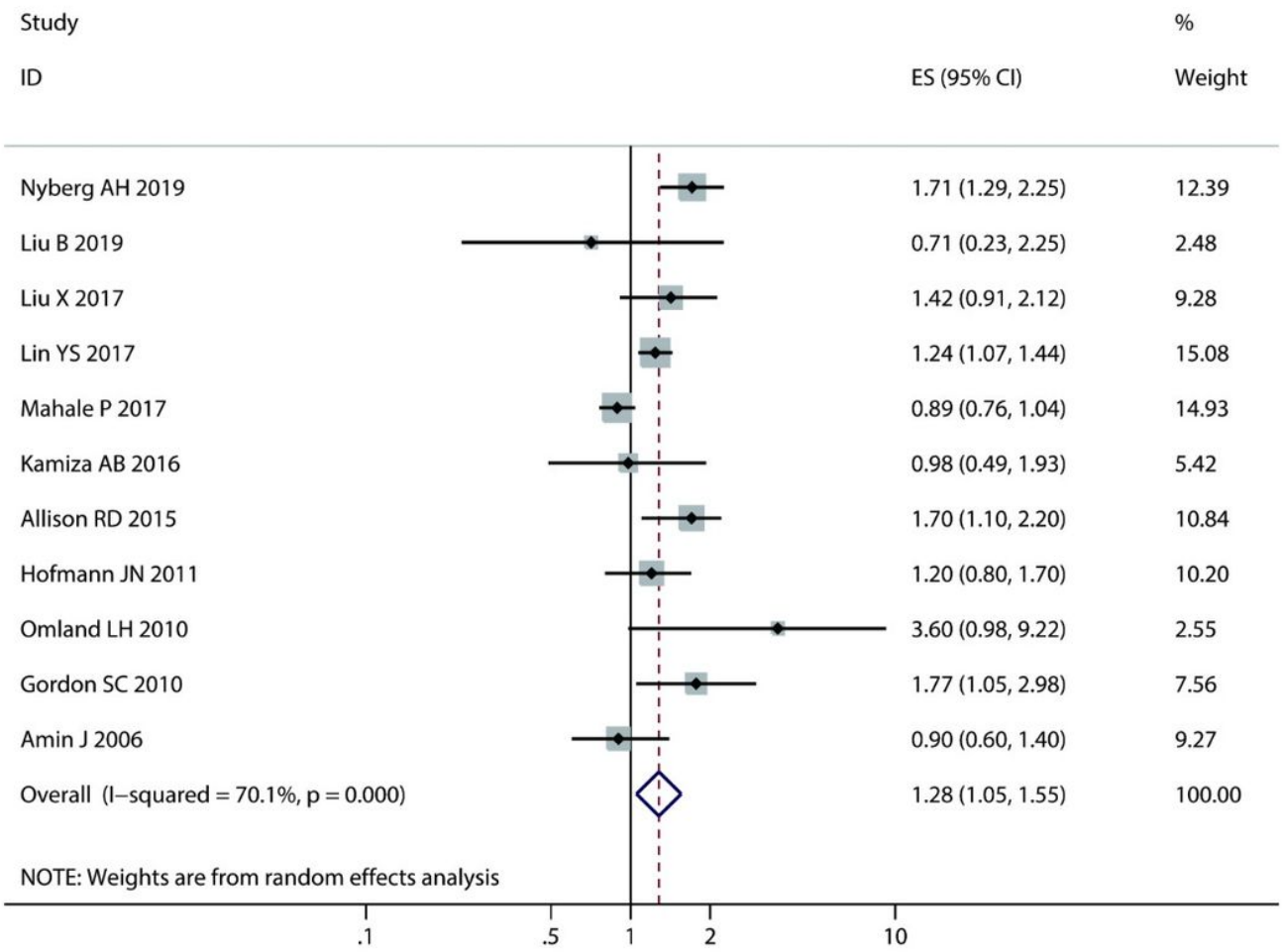

Figure 1

Forest plots of the relative risk of studies investigating the association between hepatitis C virus infection and renal cell cancer. Random effects models were used for the primary meta-analysis.

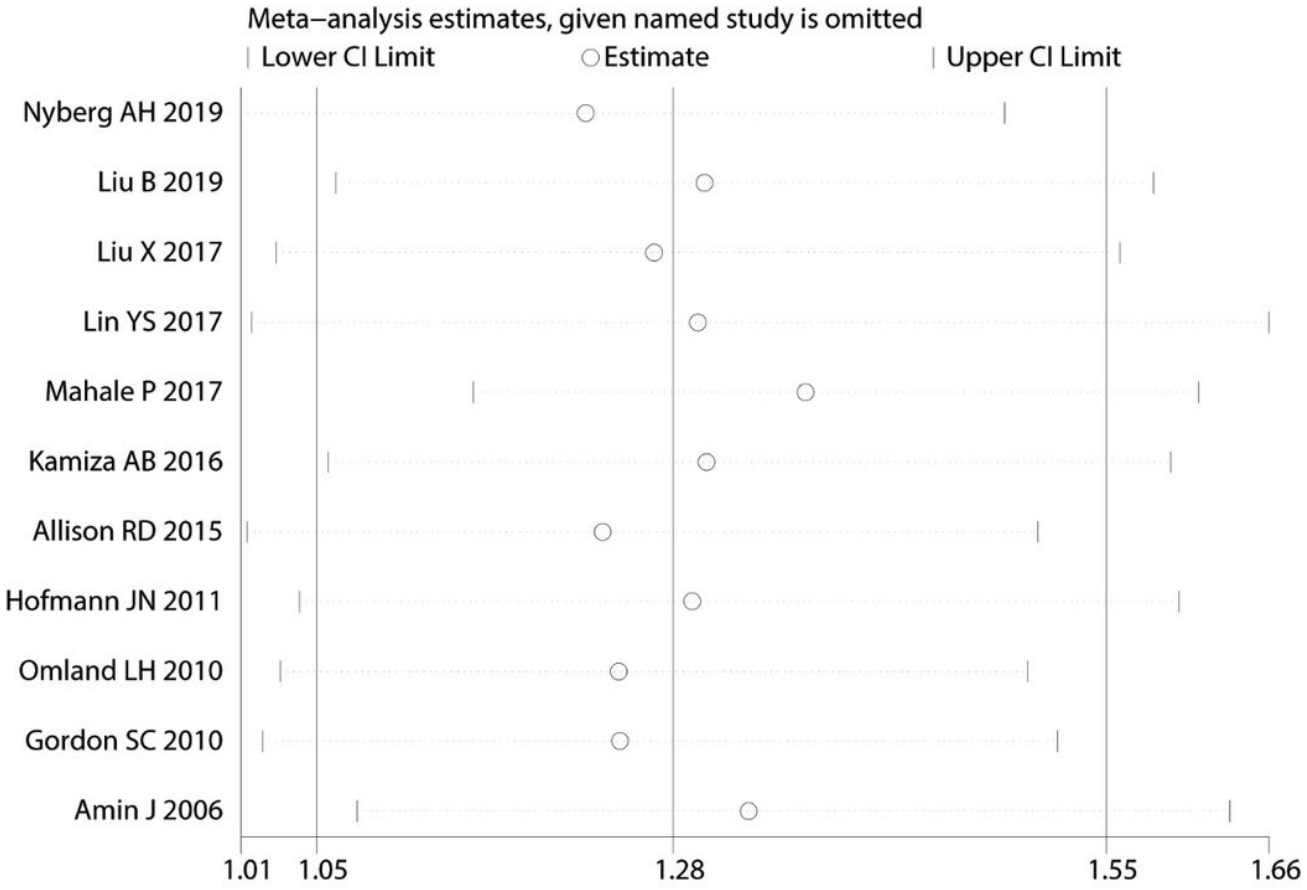

Figure 2

Sensitivity analyses by omitting individual study yielded nonsignificant RR change.

Supplementary Files

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- FigureS1.tif
- FigureS2.tif
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- FigureS8.tif
- PRISMA2009checklist.doc