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PRISMA systematic review of the risk factors for hepatocellular carcinoma associated with hepatitis C genotype 3 infection

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Abstract

BACKGROUND

Hepatitis C virus (HCV) is a blood-borne virus which globally affects around 79 million people and is associated with high morbidity and mortality. Chronic infection leads to cirrhosis in a large proportion of patients and often causes hepatocellular carcinoma (HCC) in people with cirrhosis. Of the 6 HCV genotypes (G1-G6) genotype-3 accounts for 17.9% of infections. HCV genotype-3 responds least well to directly-acting antivirals and patients with genotype-3 infection are at increased risk of HCC even if they do not have cirrhosis.

AIM

To systematically review and critically appraise all risk factors for HCC secondary to HCV-G3 in all settings. Consequently, we studied possible risk factors for HCC due to HCV-G3 in the literature from 1946 to 2023.

METHODS

This systematic review aimed to synthesise existing and published studies of risk factors for HCC secondary to HCV genotype-3 and evaluate their strengths and limitations. We searched Web of Science, Medline, EMBASE, and CENTRAL for publications reporting risk factors for HCC due to HCV genotype-3 in all settings, 1946-2023.

RESULTS

Four thousand one hundred and forty-four records were identified from the four databases with 260 records removed as duplicates. Three thousand eight hundred and eighty-four records were screened with 3514 excluded. Three hundred and seventy-one full-texts were assessed for eligibility with seven studies included for analysis. Of the seven studies, three studies were retrospective case-control trials, two retrospective cohort studies, one a prospective cohort study and one a cross-sectional study design. All were based in hospital settings with four in Pakistan, two in South Korea and one in the United States. The total number of participants were 9621 of which 167 developed HCC (1.7%). All seven studies found cirrhosis to be a risk factor for HCC secondary to HCV genotype-3 followed by higher age (five-studies), with two studies each showing male sex, high alpha feto-protein, directly-acting antivirals treatment and achievement of sustained virologic response as risk factors for developing HCC.

CONCLUSION

Although, studies have shown that HCV genotype-3 infection is an independent risk factor for end-stage liver disease, HCC, and liver-related death, there is a lack of evidence for specific risk factors for HCC secondary to HCV genotype-3. Only cirrhosis and age have demonstrated an association; however, the number of studies is very small, and more research is required to investigate risk factors for HCC secondary to HCV genotype-3.

Key Words: Hepatocellular carcinoma; Hepatitis C; Genotype 3; Systematic review; Blood-borne viruses; Liver cancer

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Core Tip: Hepatitis C virus (HCV) genotype-3 accounts for 17.9% of HCV infections with an increased risk of hepatocellular carcinoma (HCC) globally. In this systematic review and meta-analysis, we screened 4144 records to find only seven studies which study risk factors for HCC. Conducted primarily in Global South hospital settings, the studies encompassed 9621 participants, revealing cirrhosis and age as consistent risk factors for HCC. While cirrhosis and age emerge as contributors, the scarcity of studies underscores the urgent need for expanded research. Limited evidence exists on other factors, emphasising the need for further research to understand specific risk contributors to HCC secondary to HCV Genotype-3.

INTRODUCTION

Hepatitis C virus (HCV) is a blood-borne virus which globally affects around 79 million people[1] and is associated with high morbidity and mortality. Chronic infection leads to cirrhosis in a large proportion of patients after 30 years of asymptomatic infection and often causes hepatocellular carcinoma (HCC) in people with cirrhosis. HCV has six genotypes (G1-G6) globally with G1 accounting for 49.1% of all HCV infections, followed by G3 (17.9%), G4 (16.8%), G2 (11.0%), G5 (2.0%), and G6 (1.4%)[2].

The highest prevalence of G3 in Western Europe is Norway (50%), England (47%), and Finland (43%) with 10% in North America (22% in Canada) with 26.9% in South America[3-5]. However, the greatest burden of G3 is in South and Central Asia with 71.6% of HCV infections being of this genotype which is very common in Pakistan and India[2,6-8].

G3 infection is not susceptible to the first generation of DAA protease inhibitors and has reduced susceptibility to Sofosbuvir[6,9-13], particularly in patients with cirrhosis. The efficacy of next generation protease inhibitor-based regimens (glecaprevir/pibrentasvir) may also be reduced[14-16]. However even in patients with this genotype viral clearance rates are well over 90% and these effective, affordable oral antiviral treatments are

widely available. However, in patients with HCV induced cirrhosis, viral clearance does not abolish the risk of HCC[17].

HCC is a feared complication of HCV and of all the genotypes, patients with G3 infection have the highest incidence[18,19]. In most patients, cancer is linked to cirrhosis but in subjects infected with G3 even those without cirrhosis are at increased risk[20,21]. The only effective strategy to manage liver cancer is early detection of asymptomatic tumours by screening followed by loco-regional or immunomodulatory/kinase inhibitor combination therapies. Current recommendations are to screen all cirrhotic patients by ultrasound 6-monthly. However, in G3, where cirrhosis is not an adequate risk factor, we need to screen more subjects[22] and require epidemiological risk assessment tools to determine which subjects require surveillance.

There is therefore a need to identify and evaluate risk factors for HCC secondary to HCV-G3 to assist in identification of people at high risk. However, although there are risk factors identified for the most common genotype, G1; this is not the case for G3.

To address this, we aimed to systematically review and critically appraise all risk factors for HCC secondary to HCV-G3 in all settings. Consequently, we studied possible risk factors for HCC due to HCV-G3 in the literature from 1946 to 2023.

MATERIALS AND METHODS

Literature search

We searched the following four databases for articles: Web of Science, Medline, EMBASE and CENTRAL; utilising the search strategy pre-defined by an expert librarian (Supplementary appendix 1) for studies published between 1st January 1946 to 17th December 2022.

The search aimed to include all relevant studies reporting original data for the comparison of HCC risk of patients with HCV G3, from inception up until December 2022. The following keywords: “Hepatocellular carcinoma”, “hepatitis C”, and “genotype 3” were combined with other search terms, using Boolean operators and truncation. Secondly, the reference lists of all included articles were manually reviewed

to identify any unidentified publications and grey literature was searched. No restrictions were set for publication year and status, or geographical area.

Selection criteria

We applied the following inclusion criteria to studies: (1) Participants/population: Patients in primary care, hospital settings and national databases; (2) exposure: Risk factor for HCC secondary to HCV-G3; (3) comparison: Risk factor for HCC secondary to non-HCV-G3 or control; and (4) outcome: Development of HCC.

We included randomized control trials and observational studies (case-control, cohort, and cross-sectional) and excluded any studies which did not fit the above criteria, mathematical modelling studies or were not published in English.

Studies were eligible for the meta-analysis if they fulfilled the following criteria: (1) Study design: Cohort studies, case-control studies or randomized controlled trials based on original data; (2) study population and exposure: For cohort studies, both HCV G3 infected group and a comparison group of HCV non-G3 infected patients in the same study, with at least 10 patients in each group, and for case-control studies at least 10 patients in each group of HCV-G3 HCC cases and non-HCC as controls. In studies where there were all HCV genotypes, we included those which had data (in the main results or supplementary appendices) of individual patients with HCV-G3 who developed HCC; (3) methods: Studies reporting odds ratios (OR), relative risks (RR) or hazard ratios (HR), or sufficient data to calculate the effect size (ES); and (4) outcome: The number of HCC in each patient group is stated.

The manuscript is published as a full paper in a peer-reviewed journal. The following studies were excluded: (1) Animal or *in vitro* studies; (2) studies without clearly reported control or comparison group; (3) studies with unclear HCC outcome; and (4) letters to the editor, review articles, guidelines, and conference abstracts (not peer-reviewed) were excluded.

To ensure the exposure (HCV G3 infection) was present prior to the development of HCC, we excluded all studies where there was combined data in HCV genotypes and

where we could not extract data (in the main results or supplementary appendices) of individual patients with HCV-G3 who developed HCC.

Screening process

We planned for two reviewers (HZF and MJ) to screen all abstracts to ensure a robust screening process with each abstract reviewed by at least two reviewers utilising the Rayyan QCRI programme. Any conflicting decisions were discussed and referred to a third reviewer if required.

Post primary screening, two reviewers (HZF and MJ) screened the full texts to ensure the papers fully fit the criteria with conflicting decisions discussed and referred to a third reviewer if needed.

Data extraction (selection and coding)

Two reviewers (HZF and MJ) independently screened the full text of the included papers and extracted the following data for each included study: (1) Setting of study: Country and whether primary or secondary care; (2) characteristics of study population: Age and sex; (3) study design: Number of study participants in study; (4) type of HCV: Number participants who developed HCC; (5) risk factors identified for HCC; (6) proportion of participants with particular risk factor: Number and percentage; (7) odds ratio of risk factor; (8) hazards ratio of risk factor; and (9) number of participants who cleared HCV or were actively infected.

Study characteristics, context, quality, and findings were captured and summarized with similarities and differences compared across the studies in a tabular form, using appropriate subgroup analysis with comparison of the performance of different risk factors. All data were captured with a spreadsheet (MS Excel) and validated by an independent reviewer (MJ).

Risk of bias (quality) assessment

Two reviewers (HZF and MJ) utilised a standardised data extraction form based on the criteria for assessing the quality of risk factor studies. We utilised the Newcastle-Ottawa Scale (NOS) to assess the quality of the studies, judging studies based on points awarded for selection of study groups, comparability of groups and exposure/outcome ascertainment. Any conflicting decisions were discussed and referred to a third reviewer if required. Studies with scores of < 5, 5-7, and > 7 points were considered to be of low, sufficient, and high quality, respectively. Any conflicting decisions were discussed and referred to a third reviewer (JA) if required.

Statistical analysis

We manually extracted the crude number of patients who developed HCC in patients with HCV-G3 and utilised these data for pooled ES and 95% confidence intervals (CIs) were estimated. As the outcome of HCV G3 HCC is rare with the worldwide HCC incidence of 10.8 cases per 100000 person-years <23>, odds ratios (ORs), relative risk (RR), and hazard ratios (HRs) were deemed to be equivalent. For studies which calculated HRs, we captured these for analysis. Correspondingly, and for those that had no calculated HRs we extracted the crude number of patients who developed HCC and calculated HRs.

Meta-analysis and assessment of heterogeneity

We carried out meta-analysis of hazard ratios in Jamovi version 2.2.5 using the "meta-analysis" package minimally adjusting for age and sex reported in the studies.

We calculated pooled summary effect estimates using the restricted-maximum likelihood model (random effects model) weighting of HRs on the natural logarithmic scale and quantified between-study heterogeneity using the I^2 statistic; significance of heterogeneity was investigated using Cochran's Q test (P threshold = 0.05). Where I^2 was > 0 and heterogeneity were significant, we present random-effects summary estimates. We undertook multiple sensitivity analyses whereby analyses were restricted

to studies adjusting for various additional confounders, and stratified by percentage of G3, to investigate robustness of observed associations.

Publication bias

Funnel plots were utilized to assess for publication bias with Egger's regression for small-study effects used to assess the degree of asymmetry, with statistical significance level of $P < 0.05$.

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Funding

The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of this report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit it for publication.

RESULTS

Literature search

Records (4144) were identified from the four databases with 260 records removed as duplicates *via* manual reviewing. Records (3884) were screened with 3514 excluded (Figure 1).

Three hundred and seventy-one full texts were retrieved and assessed for eligibility of which 2 reports could not be retrieved even with contacting the study authors. Of these, 15 studies were initially included with 348 excluded. Post-preliminary analysis, seven studies were included with 363 excluded due to the defined reasons (Figure 1; Supplementary Figure 1).

Study selection

Data were initially extracted from 15 selected studies[18,20,21,22-34] which provided information from a total of 12674 participants (Supplementary Table 3). Preliminary analysis of the studies showed that these studies combined genotype data even with

their primary focus on G3. To ensure robustness of the data with particular reference to G3, the decision was made to exclude those which did not fully categorise G3 (*i.e.*, inability to extract individualised G3 participant data) and thus only seven studies were included in the final data analysis[18,25,27,28,30,32,33] (Table 1).

Of these seven studies, two studies reported on only G3, two studies had participants which were > 90% G3 and two studies had > 5% G3 participants for which de-aggregated individual data could be collected[18,25,27,28,30,32,33] (Table 2).

Study characteristics

Of the seven studies, three studies were retrospective case-control trials, two retrospective cohort studies, one a prospective cohort study and one a cross-sectional study design (Table 2). All were based in hospital settings with four in Pakistan, two in South Korea and one in the United States. All studies required HCV RNA sequencing with genotyping *via* ISO accredited standards to demonstrate HCV infection with diagnosis of HCC based on a combination of serum alpha feto-protein (AFP) and either imaging and/or histological classification. Only one study utilised ICD-coding which was based in the Global North[18].

One study involved a national database cohort (Military Veterans) with the other six studies involving single-centre hospital centres with participants enrolled between October 1999 and December 2016 (Tables 1 and 2).

Study population characteristics

The total number of participants included in the analysis were 113160 with 9541 HCV-G3 of which 162 developed HCC (Table 2). There were 8826 male participants with 796 female participants showing a preponderance of male (91.7%) participants. The demographics of participants are shown in Table 2. The mean duration of follow-up was 19.93 months ranging from six to 59.6 months. Four studies enrolled Pakistani participants (100.0%)[25,28,30,32], with two Korean (100.0%)[27,33] and one study recruiting primarily White and African-American participants (85.8%)[18].

The mean age of participants was 49.77 across the seven studies. The prevalence of cirrhosis was shown in 6 out of the 7 studies with an average of 51% ranging from 12% to 100%. The majority of the studies ensured the removal of the confounding effect of co-infection with HIV and/or hepatitis B virus (HBV) infection due to their exclusion criteria as part of their protocol with only one study (Kanwal *et al*[18]) including 242 out of 8337 HCV-G3 participants (2.9%) and two studies (Cha *et al* and Khan *et al*) including participants with HBV and HCV-G3 [4/98 (4.1%) and 5/147 (3.4%), respectively].

All seven studies demonstrated data of HCV infection status with an average of 83.05% participants having active HCV-G3 infection (ranging from 8.27% to 100.00%) with 37.71% participants clearing HCV-G3 (range 0-92%).

Quality assessment and risk of bias

The majority of the studies were published in Q1 or Q2 quartile journals as per SJR with only one published in a Q3 journal. The quality of the studies was moderate with majority of studies NOS scores ranging from 6 to 8 (out of maximum score of 8) with only one study scoring a very low score of two (Table 3). The study with a low score of two primarily investigated a unique genomic marker for HCC and had a small sample size and thus was included in the analysis. Five of the studies ensured good methodological quality with two of relatively low quality. All but one study had a specified enrolment period with good data on follow-up of participants.

Risk of HCC secondary to HCV-G3

Overall, 162 participants (1.7%) developed HCC during the follow-up period. The risk factors studied by the seven studies can be categorised as either participant background factors, biochemical factors or treatment factors (Supplementary Figure 1). The majority of the studies investigated the potential risk factors of gender at birth (male/female = five studies), cirrhosis (seven), age (five) from a participant background perspective. For treatment factors, the risk factors studied related to achievement of SVR (seven) or use of DAAs (five) with studied biochemical risk factors of high AFP (two), high HCV viral

load (two) with one study each on ALP, low platelets levels, Child-Pugh Score (B or C), and high Model for End-Stage Liver Disease (MELD) score.

From their primary analysis, a total of seven studies assessed demonstrated cirrhosis to be a risk factor for HCC secondary to HCV-G3 followed by higher age (5), with two studies each showing male sex, high AFP, DAA treatment and achievement of SVR as risk factors for developing HCC.

A total of seven studies assessed demonstrated cirrhosis to be a risk factor for HCC secondary to HCV-G3 followed by higher age (5), with two studies each showing male sex, high AFP, DAA treatment and achievement of SVR as risk factors for developing HCC.

Utilising the individual participant data and pooling the data from the seven studies, we only found a strong association between age > 50 (HR: 1.86, 95%CI: 1.05-2.55). We also found a relatively moderate association with cirrhosis (HR: 1.44, 95%CI: 0.78-2.10), high AFP (HR: 0.97, 95%CI: 0.57-1.37), male gender (HR: 0.93, 95%CI: 0.45-1.41) and weight gain (HR: 0.84, 95%CI: 0.37-1.31), high HCV VL (HR: 0.43, 95%CI: 0.03-0.83), ALP > 68 (HR: 0.43, 95%CI: 0.03-0.83), and alcohol intake > 40 g/dL (HR: 0.24 (0.17-0.34) (Figure 2).

Some studies also showed an association between DAA use, MELD Score >9.5, Female, Diabetes, NRAS Oncogene (Figure 2). However, high statistical heterogeneity (I^2 = 79.84%, with P < 0.001) was observed. As the heterogeneity was high, the factors were not fully combined for a pooled HR: to demonstrate an appropriate view of the data. The funnel plot did demonstrate asymmetry (Egger's test = 4.936, P < 0.001) did not indicate for small-study effects (Figure 3).

Sub-group analysis

We performed a sub-analysis of risk factors where there were more than three studies studying the uniform risk factor. We pooled the HRs of to show an overall effect size, utilising the random effects model (Figure 4).

When exclusively pooling the studies, the combined HR: for cirrhosis is 0.49 (95%CI: 0.02-0.96, I^2 = 98.96%, $P \leq 0.001$, n = 3), for age 1.43 (95%CI: 0.73-2.13, I^2 = 96.44%, n = 4) and for male gender 0.41 (95%CI:-0.11 to 0.94, I^2 = 99.45%, $P \leq 0.001$, n = 3).

DISCUSSION

HCV infection represents a significant global health burden, with millions of individuals affected worldwide. Considered a "viral time bomb"[35], the World Health Organization's (WHO) ambitious target of eliminating HCV as a public health threat by 2030 has spurred unprecedented efforts to increase screening, diagnosis, and treatment access. While advances in DAA therapy have led to remarkable rates of viral clearance, the emergence of HCC in post-treatment patients has raised concerns and new challenges.

Among the various HCV genotypes, G3 has attracted particular attention due to its distinctive association with HCC development. Notably, patients infected with G3 have a higher predisposition to developing HCC, even in the absence of cirrhosis. This unique genotype's enhanced hepatocarcinogenic potential warrants further exploration and the need to investigate risk factors associated with the development to HCC.

This systematic review of seven HCV-G3 studies with 9541 HCV-G3 participants shows that cirrhosis and age greater than 40 are principal risk factors for developing HCC in people with HCV-G3. It is the largest study focussing on HCC secondary to HCV-G3 of which 162 developed HCC.

This study shows that there are few published studies on HCV-G3 and HCC and the majority of the studies are observational studies of retrospective design which do not have the ability to fully investigate confounding factors. It also demonstrates that the data is very heterogenous in HCV-G3 studies with a lack of high-quality studies and randomised control trials with a focus on HCV-G3. Of note, there is a lack of data and association with diabetes, HBV co-infection and/or high BMI especially with the increasing prevalence of metabolic dysfunction-associated steatotic liver disease.

This may be due to the lack of G3 patients and participants in the countries where the majority of HCV and HCC clinical trials occur. The highest global prevalence is of G3 in South and Central Asia (71.6% of HCV infection), contrasting to 24.8% in Western Europe and 10%-12% in the United States[5], where the highest number of HCV and HCC clinical trials occur. Without adequate G3 participants in the Global North, it is difficult to power studies to demonstrate appropriate risk factors for HCC in HCV-G3.

Correspondingly, in this study we have noted that there is only a moderate association of HCV-G3 with cirrhosis leading to HCC. This contrasts to G1 where there has been established a high association of cirrhosis with HCC[36-38] with some studies demonstrating a significant HR of 6.686 (4.319-10.350)[39]. Similar significant associations with cirrhosis and HCC were noted in G4[40] and G6[41], with a lack of data for G5 due to its low global prevalence. Majority of HCC predictive scores aim to quantify HCC risk in the presence of cirrhosis due to the high association with HCC[42-45]. However, these scores have been developed and validated on a predominance of G1 and G2 participants with a low percentage of G3 participants, warranting further studies for HCC in G3-predominant populations.

Efforts to eliminate HCV, especially in regions with high endemicity of G3, such as in India and Pakistan, face substantial challenges. The efficacy of treatment strategies in curbing HCV transmission must be supported by surveillance for potential risk of subsequent HCC development in patients with G3 mono-infection and those with co-infection with HBV and/or HIV. The evolving epidemiological landscape demands careful surveillance and long-term follow-up of patients treated for HCV, particularly those belonging to high-risk populations.

To supplement the WHO's ambitious HCV elimination goals and reduce the burden of associated disease, it is imperative to implement proactive measures for identifying and managing HCC risk in patients post viral clearance. Strategies may include intensified surveillance, targeted risk stratification, and tailored treatment approaches based on HCV genotype and individual patient characteristics.

There is currently a lack of data in the literature regarding the risk factors for HCC secondary to hepatitis HCV-G3. Yet, no confirmed risk factors have been identified. To better understand the risk factors for HCC secondary to HCV-G3, a case-control trial is needed. Such a trial would allow for a more in-depth investigation of the risk factors associated with this condition.

CONCLUSION

The global initiative to eliminate HCV by 2030 represents a remarkable public health undertaking. However, the emergence of HCC as a significant concern in patients post viral clearance, particularly in HCV-G3 infections, demands careful consideration. Collaborative efforts between healthcare providers, researchers, and policymakers are essential to develop effective risk mitigation strategies while ensuring the successful elimination of HCV on a global scale. Continued research into the mechanistic basis of HCC development in HCV-G3 infections will be crucial in shaping preventive and therapeutic interventions to safeguard the progress made towards an HCV-free future.

ARTICLE HIGHLIGHTS

Research background

Neglected hepatitis C genotype 3 (HCV-G3) is a global health concern as it is more oncogenic than other genotypes.

Research motivation

It leads to hepatocellular carcinoma (HCC) in people without cirrhosis and HCV-G3 HCC risk factors are currently unknown with no validated risk assessment tools.

Research objectives

To systematically review and critically appraise all risk factors for HCC secondary to HCV-G3 in all settings. Consequently, we studied possible risk factors for HCC due to HCV-G3 in the literature from 1946 to 2023.

Research methods

We searched the following four databases for articles: Web of Science, Medline, EMBASE, and CENTRAL; for studies published between 1st January 1946 to 17th December 2022.

Research results

Cirrhosis, higher age, and male gender were found to be strongly associated with HCC due to HCV-G3.

Research conclusions

There is currently a lack of data in the literature regarding the risk factors for HCC secondary to HCV-G3. As of yet, no confirmed risk factors have been identified.

Research perspectives

With limited studies on HCV-G3 and HCC, further research is needed to provide a risk assessment tool for HCC secondary to HCV-G3.

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Figure Legends

Figure 1 Study selection process for studies from 1st January 1946 to 17th December 2022. HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus; OR: Odd ratio.

Figure 2 Meta-analysis with hazard ratios of all included studies on risk factors for Hepatocellular carcinoma associated with Hepatitis C Genotype 3. SOF: DAC: RBV: AFP: ALP: HCV: Hepatitis C virus.

Figure 3 Funnel plot of all included studies

Figure 4 Forest plot. A: Forest plot of studies studying age as a risk factor for hepatocellular carcinoma associated with hepatitis C genotype 3 (HCV-G3); B: Forest

plot of studies studying male sex as a risk factor for hepatocellular carcinoma associated with HCV-G3; C: Forest plot of studies studying cirrhosis as a risk factor for hepatocellular carcinoma associated with HCV-G3.

Table 1 Study level characteristics, risk estimates of hepatocellular carcinoma and adjusted covariates of included studies

Ref.	Study No.	Country	Journal	SJR ranking quartile	Study design	Enrolment period	Study setting	Average follow-up (months)	HCV diagnosis	HCC diagnosis	Risk estimate of HCC	Covariates adjusted for
Aziz et al (2019)	HCCHCV003	Pakistan	*Pak J Med Sc*	Q3	Cross-sectional	June 2016 to January 2018	Hospital	6.0	HCV Ab, HCV RNA and genotyping	USS abdomen, serum AFP, CT abdomen	Crude numbers	Exclusions: HBV, HIV, Age < 18 yr or > 70 yr, pregnancy, previous liver lesion, "extremely fragile", low bodyweight (not defined), known mental health issues, patients who were taking phenytoin, rifampicin, carbamazepine, patients with pancytopenia
Cha et al (2016)	HCCHCV005	Korea	*Medicine*	Q3	Retrospective case-control	January 2005 to December 2014	Hospital	59.6	HCV Ab, HCV RNA and genotyping	USS abdomen, serum AFP, CT abdomen, histological examination	HR with 95% confidence interval	Patients with < 6 months of follow-up or patients with HCC diagnosed within 6 months of enrolment in the study
Khan et al (2009)	HCCHCV006	Pakistan	*Journal of Medical Virology*	Q1	Retrospective case-control	January 2006 to September 2007	Hospital	6.0	HCV Ab, HCV RNA and genotyping	2 of 3 criteria: Serum AFP > 400 IU/mL, CT/MRI or liver biopsy	Crude numbers	Co-infection with HBV or HDV
Kanwal et al (2014)	HCCHCV008	United States	*Journal of Hepatology*	Q1	Retrospective cohort study	October 1999 to September 2009	Hospital	12.0	HCV Ab, HCV RNA and genotyping	HCC (ICD-9 code 155.1)	HR with 95% confidence interval	< 1 yr of follow-up
Maryam et al	HCCHCV010	Pakistan	*Journal of Medical*	Q1	Retrospective case-control	ND	Hospital	ND	HCV RNA and	Liver biopsy	Crude numbers	Nil

(2018)			*Virology*						genotyping			
Park et al (2019)	HCCHCV013	Korea	*BMC Cancer*	Q1-Q2	Retrospective cohort study	January 2005 to December 2016	Hospital	24.0	HCV Ab, HCV RNA and genotyping	USS abdomen, serum AFP, CT Abdomen, histological examination	Crude numbers	People with HIV and/or HBV, < 6 months of follow-up
Tayyab et al (2020)	HCCHCV015	Pakistan	*BMC Gastroenterology*	Q2	Prospective cohort	October 2014 to March 2017	Hospital	12.0	HCV Ab, HCV RNA and genotyping	USS abdomen, serum AFP, CT abdomen	HR with 95% confidence interval	HBV co-infection

HCV: Hepatitis C virus; Ab: Antibody; USS: Ultrasound sonography; AFP: alpha fetoprotein; HBV: Hepatitis B virus; HIV: Human immunodeficiency virus; SJR: Scimago Journal & Country Rank; Q: Quartile; HR: Hazard ratio.

Table 2-Patients level characteristics for studies included in the meta-analysis

Ref.	Study No.	Total number of participants	Percentage genotype 3, *n* (%)	Number of HCV GT3 participants	Age, yr, median or mean	Sex (M/F)	Number of HCC, *n* (%)	Patients without HCC, *n* (%)	Risk factor	Number with risk factor who developed HCC, *n* (%)	Cirrhosis	Active HCV	Cleared HCV	HIV, *n* (%)	HBV, *n* (%)	Hazards ratio of risk factor	OR/HR/RR calculation (in study or calculated independently)
Aziz et al (2019)	HCCHCV003	300	300 (100.00)	300	55.08 +/-5.62	179/121	10 (3.33)	290 (96.67)	DAA treatment (SOF + DAC +/- RBV)	10 (3.33)	1.0000	1.000	276 (92.00)	0 (0)	0 (0)		Independent calculation
		300	300 (100.00)	300	55.08 +/-5.62	179/121	10 (3.33)	290 (96.67)	Child Pugh A (compensated cirrhosis) and SVR not achieved	2 (0.67)	1.0000	1.000	276 (92.00)	0 (0)	0 (0)		Independent calculation
		300	300 (100.00)	300	55.08 +/-5.62	179/121	10 (3.33)	290 (96.67)	Child Pugh B (compensated cirrhosis) and SVR achieved	5 (1.67)	1.0000	1.000	276 (92.00)	0 (0)	0 (0)		Independent calculation

	300	300 (100.00)	300	55.08 +/-5.62	179/121	10 (3.33)	290 (96.67)	Child Pugh B (Decompensated cirrhosis) and SVR not achieved	3 (1.00)	1.0000	1.000	276 (92.00)	0 (0)	0 (0)		Independent calculation
	300	300 (100.00)	300	55.08 +/-5.62	179/121	10 (3.33)	290 (96.67)	Male	7 (2.33)	1.0000	1.000	276 (92.00)	0 (0)	0 (0)		Independent calculation
	300	300 (100.00)	300	55.08 +/-5.62	179/121	10 (3.33)	290 (96.67)	Female	3 (1.00)	1.0000	1.000	276 (92.00)	0 (0)	0 (0)		Independent calculation
Cha et al (2016) HCCHCV005	1335	98 (7.30)	98	41.8 +/-10.5	79/19	4 (4.10)	94 (95.92)	Age > 40 yr	ND	0.2550	1.000	34 (34.70)	0 (0)	4 (4.1)	2.697 (0.436-16.683), P = 0.286	Calculated in study
	1335	98 (7.30)	98	41.8 +/-10.5	79/19	4 (4.10)	94 (95.92)	Cirrhosis at enrolment	25 (25.50)	0.2550	1.000	34 (34.70)	0 (0)	4 (4.1)	33.834 (2.088-548.269), P = 0.013	Calculated in study
	1335	98 (7.30)	98	41.8 +/-10.5	79/19	4 (4.10)	94 (95.92)	Alcohol intake > 40 g/d	53 (54.60)	0.2550	1.000	34 (34.70)	0 (0)	4 (4.1)	8.556 (0.693-105.623), P = 0.094	Calculated in study

	1335	98 (7.30)	98	41.8 +/- 10.5	79/19	4 (4.10)	94 (95.92)	SVR	34 (34.70)	0.2550	1.000	34 (34.70)	0 (0)	4 (4.1)	0.848 (0.063-11.445), *P* = 0.901	Calculated in study
	1335	98 (7.30)	98	41.8 +/- 10.5	79/19	4 (4.10)	94 (95.92)	Decompensated cirrhosis and achieved SVR	1	0.2550	1.000	34 (34.70)	0 (0)	4 (4.1)		Independent calculation
	1335	98 (7.30)	98	41.8 +/- 10.5	79/19	4 (4.10)	94 (95.92)	Did not achieve SVR	1	0.2550	1.000	34 (34.70)	0 (0)	4 (4.1)		Independent calculation
	1335	98 (7.30)	98	41.8 +/- 10.5	79/19	4 (4.10)	94 (95.92)	Low platelet count	ND	0.2550	1.000	34 (34.70)	0 (0)	4 (4.1)	1.00 (1.00-1.00), *P* = 0.872	Calculated in study
Khan et al HCCHCV006 (2009)	158	147 (93.00)	147	47.3 +/- 12.5	102/56	65 (44.20)	82 (55.78)	Male	51	0.1769	0.871	30 (18.99)	0 (0)	5		Independent calculation
	158	147 (93.00)	147	47.3 +/- 12.5	102/56	65 (44.20)	82 (55.78)	Female	14	0.1769	0.871	30 (18.99)	0 (0)	5		Independent calculation
	158	147 (93.00)	147	47.3 +/- 12.5	102/56	65 (44.20)	82 (55.78)	Age > 46.9 yr	65	0.1769	0.871	30 (18.99)	0 (0)	5		Independent calculation
	158	147 (93.00)	147	47.3 +/- 12.5	102/56	65 (44.20)	82 (55.78)	High AFP	65	0.1769	0.871	30 (18.99)	0 (0)	5		Independent calculation

	158	147 (93.00)	147	47.3 +/- 12.5	102/56	65 (44.20)	82 (55.78)	High HCV VL	65	0.1769	0.871	30 (18.99)	0 (0)	5	Independent calculation
	158	147 (93.00)	147	47.3 +/- 12.5	102/56	65 (44.20)	82 (55.78)	ALP > 68	65	0.1769	0.871	30 (18.99)	0 (0)	5	Independent calculation
	158	147 (93.00)	147	47.3 +/- 12.5	102/56	65 (44.20)	82 (55.78)	Anti-HBc	46	0.1769	0.871	30 (18.99)	0 (0)	5	Independent calculation
	158	147 (93.00)	147	47.3 +/- 12.5	102/56	65 (44.20)	82 (55.78)	HCV viraemia	58	0.1769	0.871	30 (18.99)	0 (0)	5	Independent calculation
Kanwal et al (2014) HCCHCV008	110484	8337 (7.54)	8337	50.2 +/- 6.4	8095/242	ND	ND	Cirrhosis	ND	0.1200	0.860	1167 (14.00)	242 (2.9)	0 (0)	1.44 (1.23-1.68) Calculated in study
	110484	8337 (7.54)	8337	50.2 +/- 6.4	8095/242	ND	ND	Diabetes	ND	0.1200	0.860	1167 (14.00)	242 (2.9)	0 (0)	1.30 (1.88-1.90) Calculated in study
	110484	8337 (7.54)	8337	50.2 +/- 6.4	8095/242	ND	ND	Age > 50 yr	ND	0.1200	0.860	1167 (14.00)	242 (2.9)	0 (0)	1.79 (1.53-2.11) Calculated in study
	110484	8337 (7.54)	8337	50.2 +/- 6.4	8095/242	ND	ND	Age < 50 yr	ND	0.1200	0.860	1167 (14.00)	242 (2.9)	0 (0)	1.86 (1.56-2.22) Calculated in study
Maryam et al (2018) HCCHCV010	50	50 (100.00)	50	58 (47-73)	37/23	27 (54.00)	23 (46.00)	NRAS oncogene	27 (54.00)	ND	1.000	0	ND	ND	Independent calculation
	50	50 (100.00)	50	58 (47-73)	37/23	27 (54.00)	23 (46.00)	Male	22	ND	1.000	0	ND	ND	Independent calculation
	50	50 (100.00)	50	58 (47-73)	37/23	27 (54.00)	23 (46.00)	Female	5	ND	1.000	0	ND	ND	Independent calculation

Park et al (2019)	HCCHCV013	180	16 (8.88)	16	46 (40-53)	45306	16 (100.00)	0 (0)	Male	15 (93.80)	1.0000	1.000	2 (12.50)	0 (0)	0 (0)		Independent calculation
		180	16 (8.88)	16	46 (40-53)	45306	16 (100.00)	0 (0)	Diabetes	6 (40.00)	1.0000	1.000	2 (12.50)	0 (0)	0 (0)		Independent calculation
		180	16 (8.88)	16	46 (40-53)	45306	16 (100.00)	0 (0)	Cirrhosis	16 (100.00)	1.0000	1.000	2 (12.50)	0 (0)	0 (0)		Independent calculation
		180	16 (8.88)	16	46 (40-53)	45306	16 (100.00)	0 (0)	Alcohol intake > 60 g/d	3 (18.80)	1.0000	1.000	2 (12.50)	0 (0)	0 (0)		Independent calculation
		180	16 (8.88)	16	46 (40-53)	45306	16 (100.00)	0 (0)	High HCV VL	6 (37.70)	1.0000	1.000	2 (12.50)	0 (0)	0 (0)		Independent calculation
		180	16 (8.88)	16	46 (40-53)	45306	16 (100.00)	0 (0)	MELD-score > 9.5	16 (100.00)	1.0000	1.000	2 (12.50)	0 (0)	0 (0)		Independent calculation
		180	16 (8.88)	16	46 (40-53)	45306	16 (100.00)	0 (0)	Female	1 (6.25)	1.0000	1.000	2 (12.50)	0 (0)	0 (0)		Independent calculation
		180	16 (8.88)	16	46 (40-53)	45306	16 (100.00)	0 (0)	High AFP	16 (100.00)	1.0000	1.000	2 (12.50)	0 (0)	0 (0)		Independent calculation
		180	16 (8.88)	16	46 (40-53)	45306	16 (100.00)	0 (0)	Not achieved SVR	2	1.0000	1.000	2 (12.50)	0 (0)	0 (0)		Independent calculation
Tayyab et al (2020)	HCCHCV015	653	593 (90.81)	593	50 (41-56)	319/334	40 (6.13)	613 (93.87)	Age, per 10-yr increase	ND	0.4931	54 (8.27)	599 (91.78)	ND	0 (0)	1.71 (1.25-2.33), *P* = 0.001	Calculated in study

653	593 (90.81)	593	50 (41-56)	319/334	40 (6.13)	613 (93.87)	Use of SOF/DCV/RBV	9 (22.50)	0.4931	54 (8.27)	599 (91.78)	ND	0 (0)	17.05 (2.09-139.47), *P* = 0.01	Calculated in study
653	593 (90.81)	593	50 (41-56)	319/334	40 (6.13)	613 (93.87)	Cirrhosis	40 (6.13)	0.4931	54 (8.27)	599 (91.78)	ND	0 (0)	ND	Independent calculation
653	593 (90.81)	593	50 (41-56)	319/334	40 (6.13)	613 (93.87)	Male	18	0.4931	54 (8.27)	599 (91.78)	ND	0 (0)	ND	Independent calculation
653	593 (90.81)	593	50 (41-56)	319/334	40 (6.13)	613 (93.87)	Female	22	0.4931	54 (8.27)	599 (91.78)	ND	0 (0)	ND	Independent calculation
653	593 (90.81)	593	50 (41-56)	319/334	40 (6.13)	613 (93.87)	High BMI	5	0.4931	54 (8.27)	599 (91.78)	ND	0 (0)	ND	Independent calculation
653	593 (90.81)	593	50 (41-56)	319/334	40 (6.13)	613 (93.87)	Hypertension	3	0.4931	54 (8.27)	599 (91.78)	ND	0 (0)	ND	Independent calculation
653	593 (90.81)	593	50 (41-56)	319/334	40 (6.13)	613 (93.87)	Diabetes	19	0.4931	54 (8.27)	599 (91.78)	ND	0 (0)	ND	Independent calculation
653	593 (90.81)	593	50 (41-56)	319/334	40 (6.13)	613 (93.87)	HBV Co-infection	12	0.4931	54 (8.27)	599 (91.78)	ND	0 (0)	ND	Independent calculation
653	593 (90.81)	593	50 (41-56)	319/334	40 (6.13)	613 (93.87)	Achieved SVR	35	0.4931	54 (8.27)	599 (91.78)	ND	0 (0)	ND	Independent calculation
653	593 (90.81)	593	50 (41-56)	319/334	40 (6.13)	613 (93.87)	Not achieved SVR	5	0.4931	54 (8.27)	599 (91.78)	ND	0 (0)	ND	Independent calculation

653	593 (90.81)	593	50 (41-56)	319/334	40 (6.13)	613 (93.87)	SOF/RBV use	29	0.4931	54 (8.27)	599 (91.78)	ND	0 (0)	ND	Independent calculation
653	593 (90.81)	593	50 (41-56)	319/334	40 (6.13)	613 (93.87)	SOF/RBV /PEG-IFN use	1	0.4931	54 (8.27)	599 (91.78)	ND	0 (0)	ND	Independent calculation
653	593 (90.81)	593	50 (41-56)	319/334	40 (6.13)	613 (93.87)	SOF/DCV use	1	0.4931	54 (8.27)	599 (91.78)	ND	0 (0)	ND	Independent calculation

NB: Risk factor highlighted in red was not deemed statistically significant in the study's own analysis. Crude numbers were extracted to pool and calculate hazard ratios. HR: Hazard ratio; OR: Odds ratio; RR: Relative risks; ND: Not determined; SOF: Sofosbuvir; RBV: Ribavirin; PEG-IFN: Pegylated interferon; DCV: Daclatasvir; SVR: Sustained virologic response; HBV: Hepatitis B virus; HCV: Hepatitis C virus; AFP: Alpha feto protein; MELD: Model for end-stage liver disease; VL: Viral load.

Table 3 The Newcastle-Ottawa Scale assessment for included studies

Ref.	Year	Type of Study	Selection								Comparability	Exposure						Total score
			Adequate case definition	Representativeness of cases	Selection of controls	Definition of controls	Representative of exposed cohort[1]	Selection of non-exposed cohort[1]	Ascertainment of exposure[1]	Demonstration that outcome of interest was not present at start of study[1]	Comparability based on the design or analysis	Ascertainment of exposure	Same method of ascertainment for participants	Nonresponse rate	Assessment of outcome[1]	Was follow-up long enough for outcomes to occur[1]	Adequacy of follow up of cohorts[1]	
Aziz et al (2019)	2019	Cross-Sectional	NA	NA	NA	NA	⋆	⋆	⋆	⋆	⋆	NA	NA	NA	⋆		⋆	7
Cha et al (2016)	2016	Cohort	NA	NA	NA	NA	⋆	⋆	⋆	⋆	⋆	NA	NA	NA	⋆	⋆	⋆	8
Khan et al (2009)	2009	Case-control	⋆			⋆	NA	NA	NA	NA	⋆	⋆	⋆	⋆	NA	NA	NA	6
Kanwal et al (2014)	2014	Cohort	NA	NA	NA	NA	⋆	⋆	⋆	⋆	⋆	NA	NA	NA	⋆	⋆	⋆	8
Maryam et al (2018)	2018	Case-control				⋆	NA	NA	NA	NA			⋆	⋆	NA	NA	NA	3
Park et al (2019)	2019	Cohort	NA	NA	NA	NA	⋆	⋆	⋆	⋆	⋆	NA	NA	NA	⋆	⋆	⋆	8
Tayyab et al (2020)	2020	Cohort	NA	NA	NA	NA	⋆	⋆	⋆	⋆	⋆	NA	NA	NA	⋆	⋆	⋆	8

[1]Highlighted green: For cohort or cross-sectional studies, highlighted yellow: for case-control studies. NA: Not applicable.

Table 4 Pooled individual participant data for all participants with hepatitis C genotype 3 who developed hepatocellular carcinoma

Risk factor	Number of participants
Patient-dependent factors	
Cirrhosis	66
Male	118
Female	62
Age > 40 yr	65
Alcohol intake > 40 g/d	56
Anti-HBc	46
Diabetes	25
Age < 50	0
NRAS oncogene	27
Age, per 10-yr increase	0
High BMI	5
Hypertension	3
HBV co-infection	12
Treatment dependent factors	
DAA treatment	66
SVR achieved	74
SVR not achieved	13
Decompensated cirrhosis and achieved SVR	1
Use of SOF/DCV/RBV	9
Biochemical factors	
Low platelet count	16
High AFP	65
High HCV VL	71
ALP > 68	65
HCV viraemia	58
MELD-score > 9.5	16

HBc: Hepatitis B virus core protein; BMI: Body mass index; DAA: SVR: Sustained virologic response; SOF: Sofosbuvir; DCV: Daclatasvir; RBV: Ribavirin; HBV: Hepatitis B virus; HCV: Hepatitis C virus; AFP: Alpha feto protein; MELD: Model for end-stage liver disease; VL: Viral load.

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