BMC Cancer

RESEARCH

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Hepatitis B and C virus infection and risk of multiple myeloma: a systematic review and meta-analysis

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Abstract

Background Multiple myeloma (MM) is a clonal proliferative disorder of plasma cells with limited curative options. Hepatitis B (HBV) and hepatitis C (HCV) viruses have been implicated in the development of various hematological malignancies, but their association with MM remains unclear. This systematic review and meta-analysis aimed to investigate the risk of MM in individuals with HBV and HCV infections.

Methods A comprehensive literature search was conducted across PubMed, Scopus, Web of Science, Embase, and additional sources for cohort and case-control studies published between January 1990 and January 2025. The relative risk (RR) of developing MM in individuals with HBV and HCV infections was pooled using a random-effects model. Subgroup analyses were performed based on age, geographic region, and diagnostic method. The Newcastle-Ottawa Scale (NOS) was used to assess study quality. Statistical heterogeneity was evaluated using the I^2 statistic, and publication bias was assessed using Egger's test.

Results Seventeen studies, comprising 1 cohort and 16 case-control studies, were included. Nine studies examined the association between HBV and MM, yielding a pooled RR of 1.25 (95% CI: 0.99–1.58) with moderate heterogeneity ($I^2 = 56.52\%$). Fifteen studies evaluated the association between HCV and MM, with a pooled RR of 1.84 (95% CI: 1.27–2.67), indicating a higher risk in HCV-infected individuals. Subgroup analysis revealed a stronger association in European populations for both HBV (RR: 1.67, 95% CI: 1.05–2.66) and HCV (RR: 2.27, 95% CI: 1.21–4.25). No significant publication bias was detected for either HBV or HCV analyses.

Conclusion HBV and HCV infections are associated with an increased risk of developing multiple myeloma, with HCV demonstrating a stronger association. These findings highlight the importance of screening and monitoring patients with chronic hepatitis for potential hematological malignancies, especially in high-risk regions.

Keywords Multiple myeloma, Hepatitis B virus, Hepatitis C virus, Evidence synthesis

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Introduction

Multiple myeloma (MM) is a clonal proliferative disorder of plasma B cells in the bone marrow, which is mostly incurable [1, 2]. Clinically, it often presents with hypercalcemia, renal dysfunction, anemia, and skeletal disability [1, 3]. Genetic factors in first-degree relatives and non-genetic factors such as racial disparities have been identified as contributing to the increased risk of developing MM [4–6].

Over time, there has been a significant increase in treatment options for managing multiple myeloma. Since the introduction of combination chemotherapy regimens involving steroids, these treatments have become the backbone of multiple myeloma therapy. Cytotoxic agents and immunosuppressive treatments, such as the use of steroids, may lead to uncontrolled proliferation of hepatitis viruses and subsequent exaggerated immune responses to the infected liver cells, which can result in the reactivation or acute exacerbation of chronic hepatitis virus infection [7, 8].

Recent studies have shown that a history of chronic infection increases the risk of non-Hodgkin's lymphoma, which includes a heterogeneous group of malignancies such as Hodgkin's lymphoma, multiple myeloma, acute lymphoblastic leukemia, and chronic lymphocytic leukemia [9, 10]. Data from studies have demonstrated the potential for an increased risk of chronic hepatitis B (HBV) infection to raise the risk of Non-Hodgkin Lymphoma (NHL) [11, 12]. Additionally, an association between hepatitis C virus (HCV) infection and multiple myeloma has been reported [13, 14]. A cohort study in the United States compared 3,888 patients with chronic hepatitis B to non-HBV controls. After adjusting for confounding factors, the rate of NHL was approximately three times higher in patients with chronic hepatitis B [15].

Studies worldwide have investigated the association between hepatitis B/C virus infection and multiple myeloma risk, yet reported findings remain inconsistent [16–18]. To address this knowledge gap, we conducted a systematic review and meta-analysis to: (1) quantitatively estimate the relative risk of MM in HBV and HCV infected populations separately, (2) compare these associations across demographic subgroups, and (3) identify potential effect modifiers. Our findings provide crucial insights into the etiological role of viral hepatitis in MM pathogenesis and may inform evidence-based screening strategies for high-risk populations.

Table 1 PECOT structure

Element	Description
Population	Individuals with hepatitis B (HBV) or hepatitis C (HCV) infection.
Exposure	Documented history of HBV or HCV infection, confirmed through serological or molecular diagnostic tests.
Comparison	Individuals without HBV or HCV infections, representing either the general population or negative test results.
Outcome	Diagnosis of multiple myeloma (MM) based on clinical, laboratory, and imaging criteria.
Time	January 1990 to March 2024.
Databases	PubMed, Scopus, Web of Science, and Embase.
Keywords	"Multiple myeloma", "Hepatitis B", "Hepatitis C",

Materials and methods

This meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-2020) guidelines [19].

Eligibility criteria

Studies included in this meta-analysis met the following criteria: cohort or case-control design, with participants diagnosed with HBV or HCV infection. The primary outcome reported was the development of MM. Excluded were clinical trials, letters to the editor, case reports or case series, and review articles. Only studies published in English were eligible for inclusion (Table 1).

Search strategy and screening

A comprehensive search strategy was developed to identify relevant case-control and cohort studies from major international databases including PubMed, Scopus, Web of Science, and Embase. The search focused on studies examining the relationship between MM and infections with HBV and HCV. Key search terms included "multiple myeloma", "hepatitis B", "hepatitis C", and their synonyms from the MeSH database to ensure inclusion of all relevant studies. Retrieved articles were managed and organized using Endnote version 20 software. The screening process began with the removal of duplicate records, followed by screening based on titles and abstracts. Articles that passed this stage underwent full-text review. The search covered publications from January 1990 to January 2025. Two authors independently conducted the screening to ensure accuracy and consistency, and any disagreements were resolved through consultation with a third reviewer.

In addition to database searches, a comprehensive grey literature search was performed. This involved reviewing the first 10 pages of Google Scholar search results and conducting a manual search to identify relevant studies that may not have been captured through the initial search strategy. This thorough approach minimized bias and ensured that all relevant studies were considered.

Data extraction process

For data extraction from the selected articles, a checklist developed with the input of subject matter experts was used. The checklist included information such as author names, study type, year of publication, total sample size, country of study, method of hepatitis B diagnosis, and the number of individuals with hepatitis B and C reported in the studies (Table 2).

Risk of bias assessment

The Newcastle-Ottawa Quality Assessment Scale (NOS) checklist was used to assess the quality of the cross-sectional studies. Each item on the checklist was scored 1 if the criteria were met, with a maximum score of 9 for each study. This assessment was independently performed by two authors, and any disagreements were resolved by a third reviewer.

Statistical analysis

The effect size of interest in this meta-analysis was the relative risk (RR). RR and its corresponding 95% confidence interval (CI) were extracted from the included studies. The natural logarithm of RR and its standard error were calculated and used in the meta-analysis.

Cochran's Q test and the I^2 statistic were used to assess heterogeneity and between-study variance. Due to the presence of both clinical and statistical heterogeneity, a random-effects model (DerSimonian and Laird method) was applied for the overall pooled estimates to account for variability across studies. In subgroup analyses, a fixed-effect model was initially used when heterogeneity was minimal and study characteristics were comparable. Based on reviewer feedback and in accordance with Cochrane and PRISMA guidelines, the statistical approach was revised and a random-effects model was applied in subgroups with I^2 values exceeding 50%. Subgroup analyses were conducted based on participants' age, continent of study, and method of hepatitis B diagnosis to explore potential sources of heterogeneity. All statistical analyses were performed using STATA version 18 (StataCorp, College Station, TX, USA), and a two-tailed *p*-value of <0.05 was considered statistically significant.

Results

In this meta-analysis, after conducting the search strategy and retrieving all the articles, 421 articles were retrieved from the PubMed database, 543 articles from the Scopus database, and 413 articles from other databases, including the Cumulated Index to Nursing and Allied Health Literature (CINAHL), SPORT Discuss via the EBSCO interface, Web of Science, and Embase. After removing 64 duplicate articles, 1,313 articles were screened based on the title. At this stage, 855 articles were excluded based on the title, and 458 articles were screened based on the abstract and then the full-text. Ultimately, a total of 441 articles were excluded during these stages. For the meta-analysis and the present study, 1 cohort study and 16 case-control studies were selected (Table 2) (Fig. 1). Finally, 9 studies reported on HBV, and 15 studies reported on HCV (Fig. 1).

Relationship between hepatitis B and MM

The risk of developing MM in individuals with HBsAg positivity was examined in 9 studies. The results of these studies, after pooling, showed that the lowest RR was 0.61 (95% CI: 0.15–2.39) from the study by Vahap Okan, and the highest RR was 2.64 (95% CI: 1.32–5.28) from the study by Silvia Franceschi. The pooled RR after combining these studies was 1.25 (95% CI: 0.99–1.58) with a heterogeneity of 56.52% (I^2). The publication bias assessment in this meta-analysis was performed using Egger's test, and the results are reported in Table 2. According to the Egger's test, there was no evidence of publication bias in the analysis and pooling of studies examining the association between hepatitis B infection and the occurrence of MM (B: -0.20; SE: 0.84; *P*-value: 0.81). To examine the relationship between age and the year of publication of the studies, a meta-regression analysis was conducted. The results showed that the year of publication (coefficient = -0.180, SE = 0.083, $P = 0.05$) and age (coefficient = -0.012, SE = 0.17, $P = 0.77$) were not significantly associated with MM (Fig. 2) (Table 3).

In the subgroup analysis, the risk of developing MM in individuals with hepatitis living in Europe (RR: 1.67; 95% CI: 1.05–2.66; I^2: 27.49%) was examined in 3 studies, which was higher than the risk in individuals living in Asia (RR: 1.16; 95% CI: 0.84–1.61; I^2: 68.16%) and America (RR: 1.01; 95% CI: 0.66–1.54). The pooled RR for *chronic HBV infection* was 1.29 (95% CI: 0.84–1.98), while studies that categorized infection as *chronic/active* showed a similar pooled RR of 1.29 (95% CI: 1.10–1.52) (Table 3).

Relationship between hepatitis C and MM

The second association examined in this meta-analysis was the estimation of the risk of developing MM in individuals with HCV infection. The total sample size was 3,268 HCV-infected patients, of whom 115 had MM, across 15 included studies. These 15 studies aimed to determine the risk of developing MM in individuals with HCV infection. The lowest and highest effect sizes reported in these studies were from the study by Silvia Franceschi et al. (RR: 0.50; 95% CI: 0.07–3.37) and the study by M. Montella et al. (RR: 3.67; 95% CI: 2.14–6.28), respectively. After pooling the studies, the overall risk ratio for HCV was 1.84, indicating that the risk of developing MM in individuals with HCV infection was 1.84

Table 2 The charactreistics of included studies

	Authors (Years) (*R*) Country	Type of Study (ToS)	Study Population	Sample Size	multiple myeloma	AGE	Data sources	HbsAG detection
(1)	L. A. Anderson (2008) USA	Nested case-Control	CASE = hematopoietic malignancy	CASE = 61,464 Control = 122,531 CASE + HBV = 111 Control + HBV = 242 CASE + HCV = 195 Control + HCV = 264	MM = 9995 MM + HBV = 20 MM + HCV = 31		SEER-Medicare	ICD-9
(2)	Vahap Okan (2008) Turkey	Case–Control study	CASE = lymphoproliferative disorder	ALLCASE = 334 CASE + HBV = 21 CASE + HCV = 9 Control = 802 Control + HBV = 40 Control + HCV = 9	MM = 67 HBV + MM = 2 HCV + MM = 1	50.3 ± 4.9		ELISA and PCR
(3)	Silvia Franceschi (2011) Europe	Nested case–Control study		Control = 2028 Control + HBV = 0.8% Control + HCV = 0.9% MM = 238 MM + HBV = 6 MM + HCV = 1	MM = 238 MM + HBV = 6 MM + HCV = 1	57.9 ± 7.9		ELISA
(4)	Jun Kang (2011) South Korea	Case–Control study	CASE = hematopoietic malignancy	CASE = 3932 CASE + HBV = 408 CASE + HCV = 94 CONTROL = 15,562 Control + HBV = 636 Control + HCV = 173	MM = 593 MM + HBV = 40 MM + HCV = 15	52.78 ± 15.8		ELISA
(5)	E. K. Lindqvist (2011) Sweden	Case–Control study	CASE = multiple myeloma (MM) and monoclonal gammopathy of undetermined significance (MGUS)	MM = 19,112 MM + HBV = 1 MM + HCV = 5 MM Control = 75,408 MM Control L + HBV = 4 MM Control + HCV = 10 MGUS = 5403 MGUS + HBV = 0 MGUS + HCV = 2 MGUS Control = 21,209 MGUS Control + HBV = 2 MGUS Control + HCV = 5	MM = 19,112 MM + HBV = 1 MM + HCV = 5	MED 71 (24–101)		NA
(6)	Nikolaus Becker (2012) European	Case–Control		Control = 1496 CASE = 1518 Control + HBV = 170	MM-HBV = 144 MM + HBV = 27			ELISA

Table 2 (continued)

	Authors (Years) (*R*) Country	Type of Study (ToS)	Study Population	Sample Size	multiple myeloma	AGE	Data sources	HbsAG detection
(7)	B. Huang(2012)	Case–Control	MM = 299 acute leukemia (AL) = 299	MM = 299 MM + HBV = 58 MM + HCV = 6 AL = 299 AL + HBV = 36 AL + HCV = 2	299	58(24–91)		ELISA
(8)	T. H. Su(2019)	Cohort study	patients diagnosed with chronic hepatitis B	HBV = 203,031 NONHBV = 203,031	MM = 105 MM + HBV = 56	43.2 ± 13.5		ICD-9
(9)	F. Silvestri(1996) Italy	Case–Control study		Case:78 Case + HCV = 3 Control:6917 Control + HCV = 199	MM = 78 MM + HCV = 9			EIA II
(10)	E. Bianco(2004) Italy	Case–Control study		Case:107 Case + HCV = 5 Control:396 Control + HCV = 22	MM = 107 MM + HCV = 5			
(11)	P. Hausfater(2001) France	Case–Control study		Case:54 Case + HCV = 1 Control:694 Control + HCV = 3	MM = 54 MM + HCV = 1	53 (12–93)		
(12)	G. De Rosa(1997) Italy	Case–Control study		Case = 56 Case + HCV = 9 Control = 1661 Control + HCV = 35	MM = 56 MM + HCV = 9	62 (15–88)		
(13)	S. de Sanjose(2004) Spain	Case–Control study		Case = 74 Case + HCV = 2 Control = 599 Control + HCV = 22	MM = 74 MM + HCV = 2			
(14)	S. Gharagozloo(2001) Iran	Case–Control study		Case = 45 Case + HCV = 8 Case + HBV = 7 Control = 95 Control + HCV = 32 Control + HBV = 4	MM = 45 MM + HCV = 8 MM + HBV = 3			ELISA
(15)	M. Montella(2001) Italy	Case–Control study		Case = 41 Case + HCV = 13 Control = 226 Control + HCV = 17	MM = 41 MM + HCV = 13	65 (43–82)		

Table 2 (continued)

	Authors (Years) (*R*) Country	Type of Study (ToS)	Study Population	Sample Size	multiple myeloma	AGE	Data sources	HbsAG detection
(16)	Paydas(1999) Turkey	Case–Control study		Case = 47 Case + HCV = 5 Control = 36,226 Control + HCV = 192	MM = 47 MM + HCV = 5	51 ± 16		
(17)	M. Takeshita(2006) Japan	Case–Control study	cases of malignant lymphoma	Case = 81 Case + HCV = 4 Control = 15,567 Control + HCV = 396	MM = 81 MM + HCV = 4	68.7 ± 12.3		

NHL: Non-Hodgkin Lymphoma, HBV: Hepatitis B Virus, HCV: Hepatitis C Virus, MM: Multiple Myeloma

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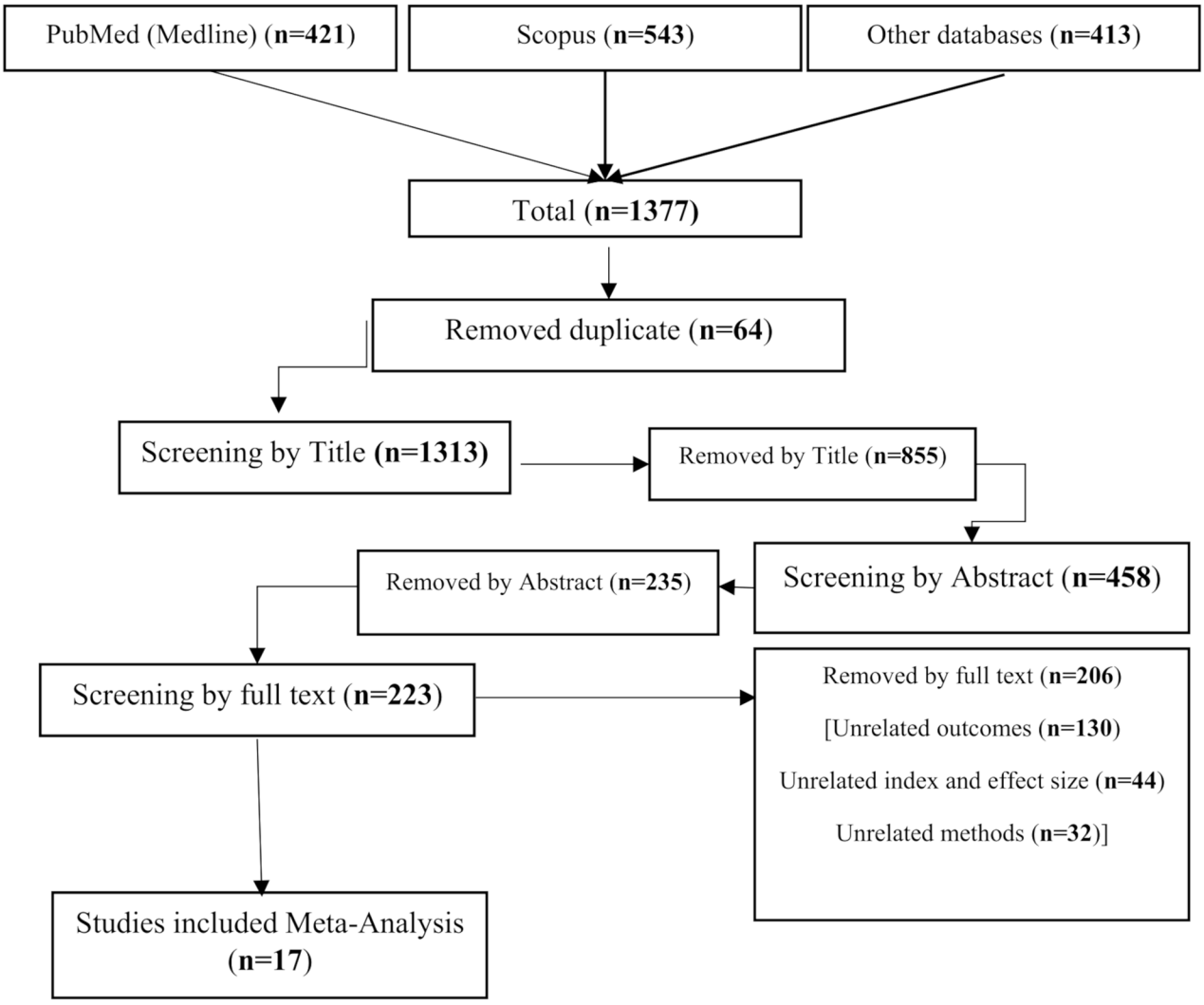

Fig. 1 A flow diagram demonstrating the study selection process

times higher than in healthy individuals (RR: 1.84; 95% CI: 1.27–2.67; I^2: 75.15%; $P < 0.001$) (Fig. 2). Studies that specifically reported chronic HCV infection showed a significantly elevated risk of multiple myeloma (RR: 2.22; 95% CI: 1.37–3.58). In contrast, studies reporting chronic/active infection, where the inclusion of resolved cases could not be ruled out, reported a lower and non-significant pooled RR of 1.25 (95% CI: 0.77–2.04) (Table 3).

The publication bias assessment in this meta-analysis was performed using Egger's test, and the results are reported in Table 2. According to the Egger's test, there was no evidence of publication bias in the analysis and pooling of studies examining the association between hepatitis C infection and the occurrence of MM (B: -0.80; SE: 0.96; *P*-value: 0.40). The funnel plot was also used to visualize the publication bias (Fig. 3). The meta-regression analysis showed that the year of publication (coefficient = 0.01, SE = 0.06, $P = 0.81$) and age (coefficient = 0.11, SE = 0.02, $P = 0.05$) were not significantly associated with MM (Table 3) (Fig. 4).

In the subgroup analysis, the risk of developing MM in individuals with HCV living in Europe (RR: 2.27; 95% CI: 1.21–4.25; I^2: 76.11%) was examined in 8 studies, which was higher than the risk in individuals living in Asia (RR: 1.46; 95% CI: 1.92–2.31; I^2: 58.52%) and America (RR: 1.39; 95% CI: 1.00–1.95) (Table 3).

Discussion

This meta-analysis found that both HBV and HCV infections increase the risk of multiple myeloma, with HCV showing a stronger link. These findings inform MM etiology and may guide improved risk assessment and prevention. The pooled RR for HBV infection and MM indicated a modest but significant increase in MM risk among HBV-infected individuals. This finding aligns

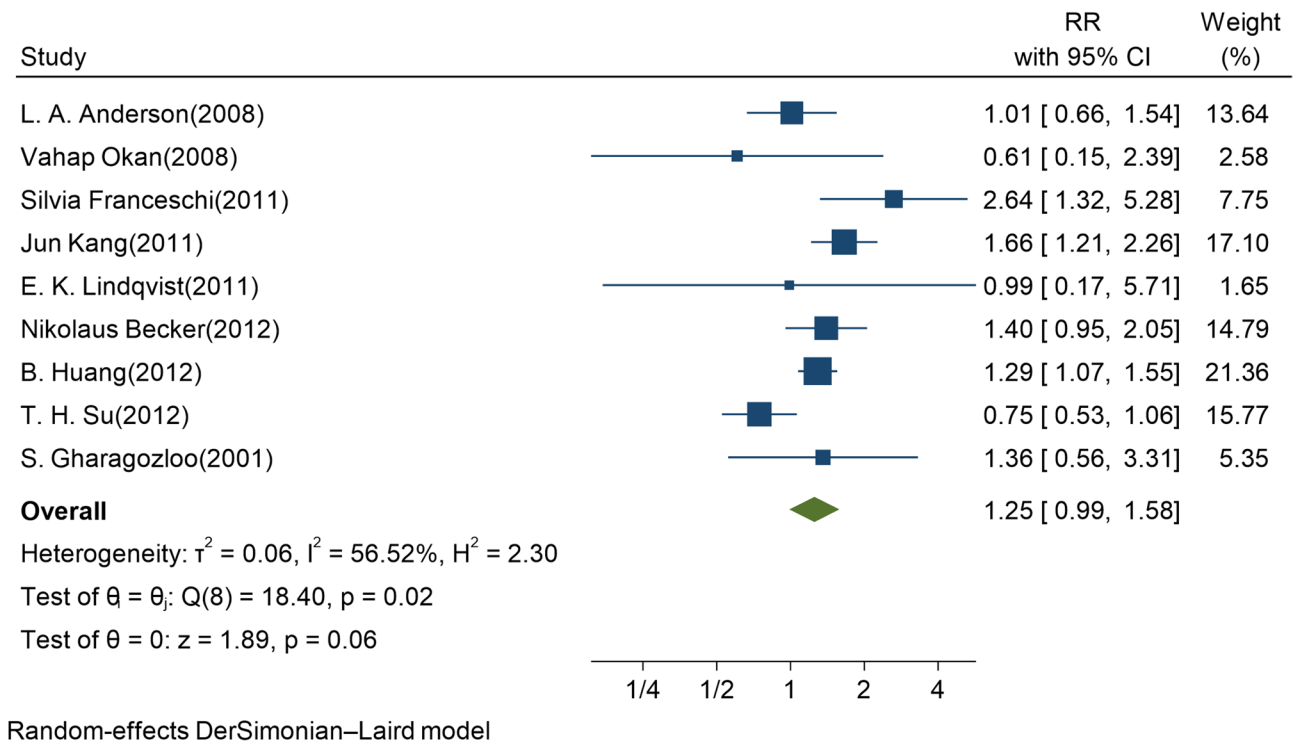

Fig. 2 The pooled RR of MM occurrence in people living with HBV

Table 3 Pooled estimate of the risk of MM in people with HBV OR HCV based on reported important variables in primary studies

	Variables	Category	No. study	Pooled RR (% 95 CI)	Heterogeneity Assessment between studies		Heterogeneity Assessment between subgroup	Publication bias assessments		
					I^2	*P*-value	*P*-value	B	SE	*P* value
HBV	Over all		9	1.25 (0.99–1.58)	56.52%	0.06	-	-0.20	0.84	0.81
	Continent	America	1	1.01 (0.66–1.54)	-	-	0.27			
		Asia	5	1.16 (0.84–1.61)	68.16%	0.01				
		Europe	3	1.67 (1.05–2.66)	27.49%	0.25				
	Age	< 60	4	1.27 (0.68–2.36)	82.25%	> 0.001	0.94			
		> 60	3	1.24 (1.05–1.46)	0.00%	0.57				
	Type	chronic	5	1.29 (0.84–1.98)	76.11%	> 0.001	0.99			
		active/chronic	4	1.29 (1.10–1.52)	0.00%	0.70				
	HbsAG detection	ICD-9	2	0.85 (0.63–1.14)	15.27%	0.28	> 0.001			
		ELISA	6	1.45 (1.19–1.75)	23.31%	0.26				
HCV	Over all		15	1.84 (1.27–2.67)	75.15%	> 0.001	-	-0.80	0.96	0.40
	Continent	America	1	1.39 (1.00–1.95)	-	-	0.39			
		Asia	6	1.46 (0.92–2.31)	58.52%	0.03				
		Europe	8	2.27 (1.21–4.25)	76.11%	> 0.001				
	DAAs	< 2011	10	1.88 (1.08–3.26	82.81%	0.00	0.79			
		> 2011	5	1.73 (1.31–2.29)	0.00%	0.46				
	Type	chronic	10	2.22 (1.37–3.58)	77.21%	> 0.001	0.10			
		active/chronic	5	1.25 (0.77–2.04)	51.17%	0.08				
	Age	< 60	4	2.04 (1.30–3.18)	0.00%	0.43	0.87			
		> 60	6	2.15 (1.28–3.03)	78.57%	> 0.001				

NHL: Non-Hodgkin Lymphoma, HBV: Hepatitis B Virus, HCV: Hepatitis C Virus, MM: Multiple Myeloma, RR: Relative Risk, CI: Confidence Interval, DAA: Direct-Acting Antiviral

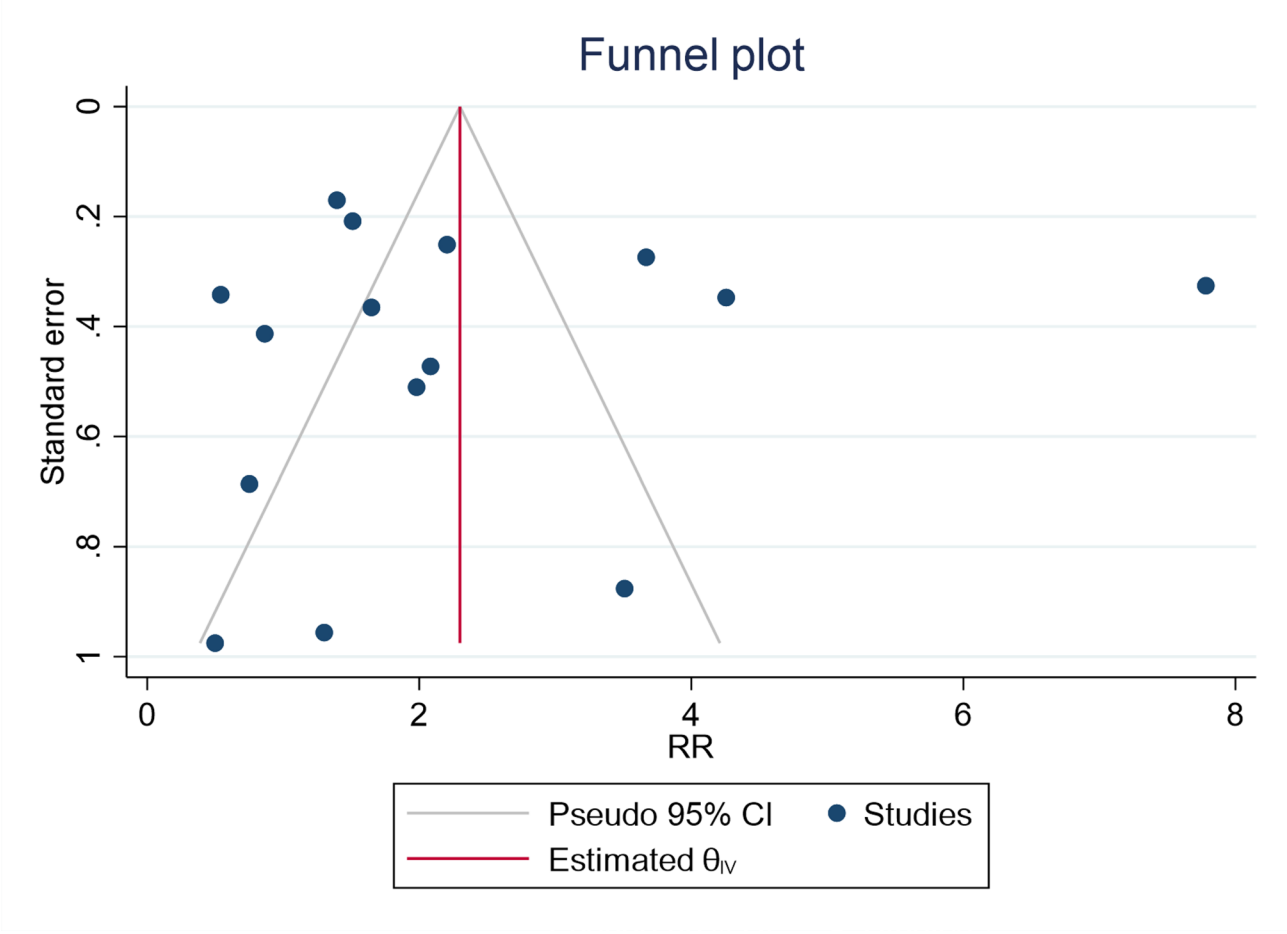

Fig. 3 The results of publication bias based on funnel plot about effect of MM occourance in people living with HCV

with previous studies that have reported an association between HBV and hematological malignancies [20, 21]. Recent research has further supported this association, with a large-scale study by Su et al. demonstrating an increased risk of B-cell non-Hodgkin lymphoma and MM in patients with chronic HBV infection [22].

B-cell non-Hodgkin lymphoma and MM have been reported in patients with chronic HBV infection [22]. The mechanisms linking HBV infection to MM are not yet fully understood, but several hypotheses have been suggested. First, chronic inflammation from persistent HBV infection may create a pro-tumorigenic environment that extends beyond the liver, contributing to the development of various cancers [23]. Second, the immune dysregulation associated with HBV infection may disrupt the balance of T-cell subsets and impair the functionality of natural killer cells, potentially weakening the immune system's ability to detect and eliminate cancerous cells [24]. Third, while the integration of HBV DNA into host genomes is primarily linked to hepatocellular carcinoma, this integration could also occur in B cells, leading to genomic instability [25]. Finally, chronic HBV infection may induce changes in the bone marrow microenvironment, which could promote the survival and proliferation of malignant plasma cells [26].

The subgroup analysis revealed geographic variations in the HBV-MM association, with the strongest association observed in European studies. This variation could be due to differences in HBV genotypes, host genetic factors, or environmental cofactors across regions [27]. Recent research has highlighted the role of HBV genotypes in disease progression and treatment response, suggesting that genotype-specific effects on MM risk warrant further investigation [28]. The association between HCV infection and MM is notably more pronounced compared to HBV. This observation aligns with previous studies and meta-analyses that have indicated an increased risk of lymphoproliferative disorders, including MM, in individuals infected with HCV [12, 29]. Several factors may explain the stronger association between HCV and MM. First, HCV has a direct lymphotropic nature, allowing it to infect and replicate in B cells, which can lead to chronic antigenic stimulation and an increased risk of B-cell malignancies. Second,

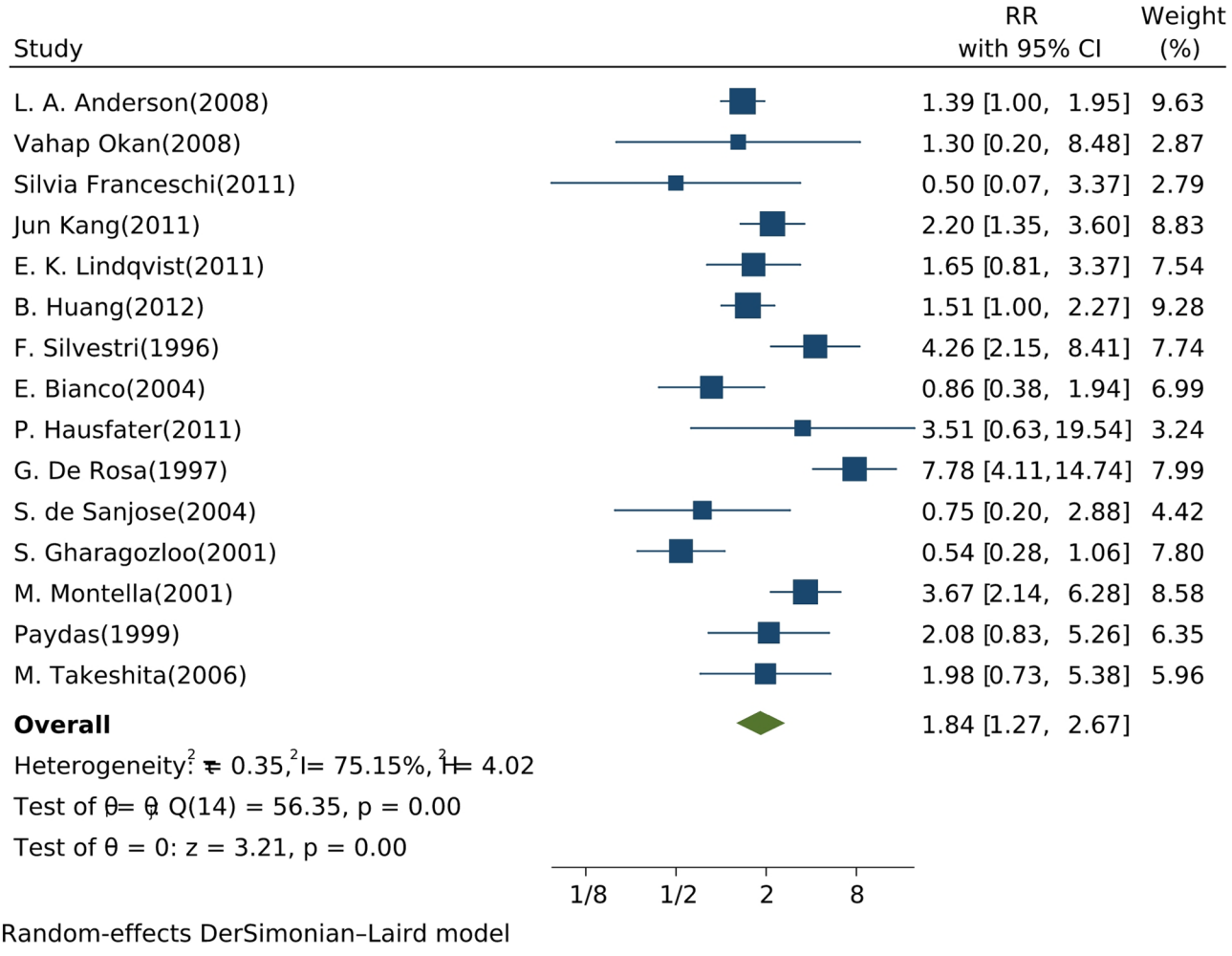

Fig. 4 The pooled RR of MM occurrence in people living with HCV

the formation of immune complexes during HCV infection can produce mixed cryoglobulins, potentially promoting B-cell proliferation and facilitating malignant transformation. Third, HCV is known to induce genetic alterations in infected cells, including the activation of oncogenes and the inactivation of tumor suppressor genes, contributing to oncogenesis. Lastly, HCV infection is associated with metabolic dysregulation, such as insulin resistance and altered lipid metabolism, which may further increase the risk of developing MM [30–32]. Recent studies have provided additional insights into the HCV-MM association. A large population-based study by Mahale et al. found that HCV infection was associated with an increased risk of MM, particularly in the first year after HCV diagnosis, suggesting a potential role for HCV in accelerating MM progression [33].

Similar to HBV, we observed geographic variations in the HCV-MM association, with the strongest association in European studies. This variation could be attributed to differences in HCV genotypes, host genetic factors, or regional environmental exposures [34]. The strongest association observed in European populations may be partially influenced by regional differences in HBV and HCV genotypes, which are known to vary in virulence, immune response, and oncogenic potential; however, due to limited genotype-specific data in the included studies, this hypothesis could not be thoroughly explored and warrants further investigation [35]. The weaker association observed in Asian studies might be due to the higher prevalence of HCV in some Asian countries, potentially leading to an underestimation of the true effect size due to a higher background risk in the general population [36]. Recent genomic studies have identified host genetic factors influencing HCV clearance and disease progression [37–39]. These genetic variations may also play a role in modulating the risk of HCV-associated MM, offering a potential explanation for the observed geographic differences and suggesting avenues for personalized risk assessment. The biological link between viral hepatitis and MM involves complex interactions between the virus, the immune system, and cellular processes. Chronic viral antigen stimulation leads to continuous

B-cell activation, increasing the risk of genetic mutations and malignancy, while cytokine imbalances especially involving IL-6 and BAFF, may promote the survival and growth of malignant plasma cells [35, 40–46].

Epigenetic changes, including DNA methylation and histone modifications induced by HBV and HCV infections, contribute to MM development. Viral hepatitis also disrupts microRNA regulation, increases oxidative stress causing DNA damage, and impairs immune surveillance by promoting T-cell exhaustion and checkpoint inhibitor alterations. These complex mechanisms collectively enhance the risk of multiple myeloma in infected individuals [47–50].

The link between viral hepatitis and MM has important clinical implications. First, enhanced MM screening using biomarkers like serum free light chain assays is needed for individuals with chronic HBV or HCV. Second, effective antiviral treatments may reduce MM risk, though data specifically on MM remain limited. Third, MM treatments can cause viral reactivation, highlighting the need for viral screening and prevention in these patients. Finally, robust HBV vaccination and efforts toward an HCV vaccine are crucial for lowering MM incidence related to viral hepatitis [51–56].

A key finding of this meta-analysis is that infection classification significantly affects the observed association between viral hepatitis and multiple myeloma risk. Studies clearly defining chronic HCV infection reported a higher risk than those including resolved cases, suggesting that mixing resolved and chronic infections may underestimate the true risk due to differing biological effects like persistent inflammation and viral replication. In studies assessing HBV, the distinction between chronic and active infections was often not clearly defined, suggesting that persistent hepatic inflammation may contribute to MM risk regardless of replication status. However, the lack of precise differentiation between resolved and active infections in some studies introduces the possibility of misclassification bias. Accurate virological classification is essential in observational research to ensure more reliable risk estimates. Both HBV and HCV may influence MM development through common pathways, particularly chronic immune activation. Persistent infection drives sustained inflammation, oxidative stress, and continuous B-cell stimulation, fostering a microenvironment that promotes malignant plasma cell proliferation. This immune dysregulation may enhance genomic instability and facilitate tumorigenesis. Despite these shared mechanisms, virus-specific differences likely influence the strength of association with MM. HCV's lymphotropism and its impact on immune signaling pathways (e.g., NF-κB, STAT3) provide a plausible direct link to lymphoproliferative disorders. Conversely, HBV primarily affects hepatocytes, and its role in MM may involve indirect effects, including immune modulation or DNA integration into host B cells. These differences suggest that HCV may exert a more direct oncogenic influence on lymphoid tissues compared to HBV.

Strengths and limitations

This meta-analysis has several strengths, including a comprehensive search strategy and the inclusion of both cohort and case-control studies from diverse geographic regions, which strengthen the assessment of viral hepatitis and multiple myeloma risk. However, limitations include the observational nature of the studies, which limits causal inference, and inconsistent reporting of important confounders such as alcohol use and smoking. Key factors like viral genotype, antiviral treatment status, and HBV/HCV coinfection were rarely reported, restricting detailed subgroup analyses. The heterogeneity among studies and potential residual confounding also affect the reliability of pooled results. Additionally, limited data prevented the use of Trial Sequential Analysis to confirm findings. These limitations highlight the need for more detailed and well-designed future studies.

Future research directions

Future research should focus on prospective studies clarifying the link between viral hepatitis and multiple myeloma, including the roles of viral genotypes, antiviral treatments, and host factors. Expanding geographic diversity and exploring novel biomarkers and mechanisms will improve risk assessment and early detection.

Conclusion

This meta-analysis presents compelling evidence establishing a correlation between HBV and HCV infections and an elevated risk of MM, with a particularly strong association identified for HCV. These findings possess important implications for public health and clinical practice, underscoring the necessity for enhanced surveillance and potential preventive strategies for individuals afflicted with chronic viral hepatitis. The complex interplay between viral infections, host factors, and the pathogenesis of MM highlights the significance of interdisciplinary research aimed at elucidating these relationships and developing targeted interventions to mitigate the risk of MM within this population.

Abbreviations

CI	Confidence Interval
CI	Confidence Interval
DAA	Direct-Acting Antiviral
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
MM	Multiple Myeloma
NHL	Non-Hodgkin Lymphoma
NOS	The Newcastle-Ottawa Quality Assessment Scale
PRISMA-2020	The Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RR Relative Risk
RR Relative Risk

Acknowledgements
None.

Author contributions
YM formulated the concept for this review, developed the study question and objectives, helped create the final methods, participated in the data analysis/interpretation, and authored the manuscript. KZ, MA, PR, RRD and YM all contributed to writing the manuscript.

Funding
None.

Data availability
Data and materials are available within the complementary materials, and further information can be available by request to the corresponding author (Dr. Yousef Moradi).

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 23 March 2025 / Accepted: 30 May 2025
Published online: 04 June 2025

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