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META-ANALYSIS

Difference in incidence of developing hepatocellular carcinoma between hepatitis B virus-and hepatitis C virus-infected patients

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Abstract

BACKGROUND

It is generally accepted that the incidence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-associated patients is higher than that in hepatitis B virus (HBV)-associated patients. The reason why this difference in the incidence of HCC occurs in patients with HBV and HCV infections remains unclear. We report the possibility that the contributing power of inflammation, which is the main risk factor for developing HCC, may be different with HBV and HCV infections.

AIM

To investigate this, we surveyed the hazard ratio of inflammation for HCC development which was identified by serum alanine aminotransferase (ALT) levels between patients with HBV and HCV infections.

METHODS
The PubMed database was searched (2001-2021) for studies published in English regarding the incidence of HCC identifying 8924 HBV-and 7376 HCV- infected patients. From these studies, interferon-treated patients with both HBV and HCV infections were excluded. Furthermore, in HBV patients, those administered nucleos(t)ide analogues were excluded, and in HCV patients, those administered direct acting antivirals were also excluded. Studies citing hazard ratios of HCC regarding inflammation (serum elevated alanine aminotransferase levels) were selected. Finally, there were 14 studies of HBV- infected patients and 8 studies of HCV-infected patients. We calculated the hazard ratio in patients in an inflammatory state (serum ALT levels were above the normal range).

RESULTS
In the 14 studies of HBV patients, the average hazard ratio (HR) of elevated ALT for developing HCC was 2.74 [1.98-3.77] and that in the 8 studies of HCV-infected patients was 5.51 [3.08-9.83]. The HR of inflammation for HCC development in HCV-associated liver diseases is about twice that in HBV-associated liver diseases. HR in HCV-infected patients was significantly (P = 0.0391) higher than that in HBV-infected patients. In hepatitis B patients, the abnormal range adopted was 28-45 IU/L, and in hepatitis C patients, it was 20-50 IU/L. It was demonstrated that the abnormal ALT levels adopted in hepatitis B and C patients were very similar in this series.

CONCLUSION
The difference in the incidence of HCC development between HBV and HCV patients may depend on the difference in the hazard risk of ALT between HBV and HCV infections.

Key Words: Hazard ratio of alanine aminotransferase; Hepatitis B virus; Hepatitis C virus; Hepatocellular carcinoma; Elevated alanine aminotransferase

Core Tip: It is generally accepted that the incidence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-associated of patients is higher than that in hepatitis B virus (HBV)-associated patients. We demonstrated that the incidence of HCC in HCV-associated cirrhotic patients was 4.81%/year as compared with 3.23% in HBV-associated patients based on analytic assessment of already published papers. In HBV infection, alanine aminotransferase (ALT) is the second highest risk factor, and in HCV infection, ALT is the highest risk factor, for HCC development. The hazard ratio (HR) for developing HCC in the inflammatory state (serum ALT levels exceeded the normal range) was compared between HBV and HCV patients. In the 14 studies of HBV patients, the average HR was 2.74 as compared with 5.51 in the 8 studies of HCV patients (P = 0.0391). The difference in the incidence of HCC development between HBV and HCV patients may depend on the difference in the hazard risk of ALT for HCC development between HBV and HCV infections.

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INTRODUCTION

It is generally accepted that the incidence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-associated of patients is higher than that in hepatitis B virus (HBV)-associated patients. We demonstrated that the incidence of HCC in HCV-associated cirrhotic patients was 4.81%/year as compared with 3.23% in HBV-associated patients based on analytic assessment of already published papers[1].

However, the reason why this difference in incidence of HCC occurs in patients with HBV and HCV infections remains unclear. We have been considering this for many years, and finally arrived at the possibility that the contributing power of inflammation, which is the main risk factor for developing HCC, may be different with HBV and HCV infections.

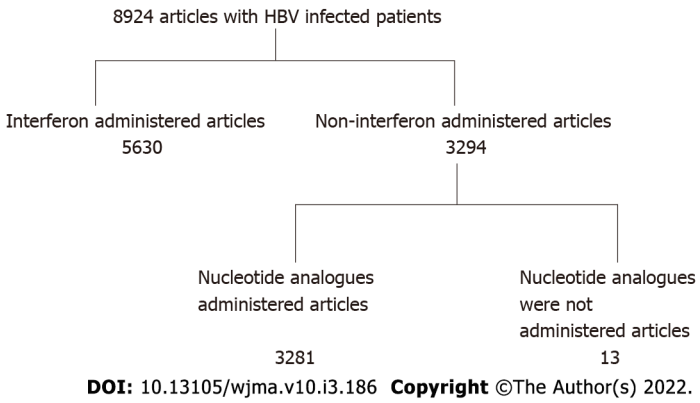

Figure 1 Flow diagram of articles with hepatitis B virus infected patients. HBV: Hepatitis B virus.

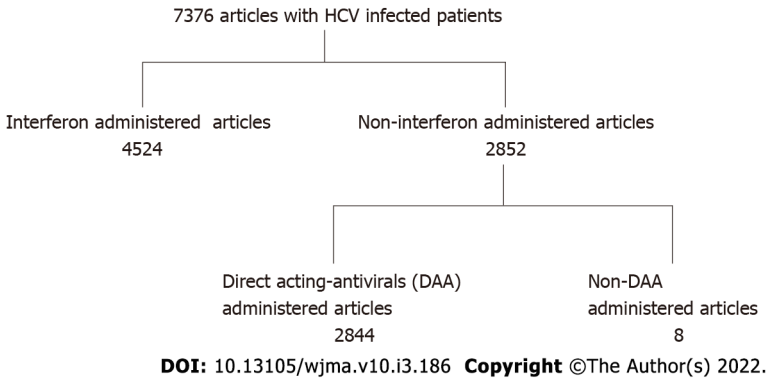

Figure 2 Flow diagram of articles with hepatitis C virus infected patients. HCV: Hepatitis C virus; DAA: Direct acting antivirals.

To investigate this, we surveyed the hazard ratio (HR) of inflammation which was identified by serum alanine aminotransferase (ALT) levels between patients with HBV and HCV infections.

Why ALT, not AST was adopted in this study was as follows: We previously demonstrated[2] the strong association between sustained high serum ALT levels (≥ 80 international units (INU) annual average) and the development of HCC in patients with HCV-LC (Child Stage A) by long-term observation lasting about 7 years, (Cancer 1999; 86: 589-595). In this series of the study, we also investigated the association between sustained high serum AST levels (≥ 80 INU) and development, but the association was not so strong as ALT. Moreover, many studies have demonstrated a close association between severe inflammation as estimated by higher serum ALT level and initiation of HCC development (Veldt *et al*[3]; Miyakawa *et al*[4]).

MATERIALS AND METHODS

Search strategy

The PubMed database was searched (2001-2021) for studies published in English regarding the incidence of HCC in HBV or HCV infected patients. There were 8924 studies involving HBV patients, and 7376 studies of HCV patients. From these studies, interferon-treated patients with both HBV and HCV infections were excluded. Furthermore, in HBV patients, those who were administered nucleos(t)ide analogues were excluded, and HCV patients administered direct acting antivirals were also excluded. We also excluded articles which include co-existing liver disease such as alcoholic liver diseases and/or fatty liver diseases. Then, studies which dealt with the HR of HCC regarding inflammation (serum elevated ALT levels) were selected. Finally, there were 13 studies of HBV-infected patients[5-17], and 8 studies of HCV-infected patients[13,18-24] (Figures 1 and 2). In these selected papers, the HR of patients in a non-inflammatory state (serum ALT levels within normal range) was set as 1. We then calculated the HR in patients in an inflammatory state (serum ALT levels were above normal range).

Furthermore, for the purpose of comparing elevated ALT levels between hepatitis B and C patients, we examined the actual ALT levels cited in patients with chronic hepatitis B and hepatitis C included in this series (Tables 1 and 2) .

Table 1 Actual elevated alanine aminotransferase levels cited in patients with chronic hepatitis B

Ref.	Actual elevated ALT levels
Kim *et al*[5]	Above normal levels
Du *et al*[6]	Above normal levels
Choi *et al*[7]	Above normal levels
Wen *et al*[8]	≥ 25 IU/L
Hann *et al*[11]	Elevated
Chen *et al*[12]	≥ 45 IU/L
Kumada *et al*[13]	Absence of persistently normal ALT levels
Chen *et al*[14]	Above normal levels
Ishiguro *et al*[15]	≥ 30 IU/L
Ando *et al*[16]	≥ 23 IU/L
Yamada *et al*[17]	≥ 40 IU/L

ALT: Alanine aminotransferase.

Table 2 Actual elevated alanine aminotransferase levels cited in patients with chronic hepatitis C

Ref.	Actual elevated ALT levels
Ishiguro *et al*[15]	≥ 30 IU/L
Chen *et al*[18]	≥ 45 IU/L
Sun *et al*[19]	Elevated
Tanaka *et al*[20]	Elevated
Kumada *et al*[21]	> 20 IU/L
Ito *et al*[22]	> 35 IU/L
Suruki *et al*[23]	> 35 IU/L
Lee *et al*[24]	Always ≥ 45 IU/L

ALT: Alanine aminotransferase.

Statistical analysis

To compare HR of ALT for HCC between HBV and HCV patients, we calculated the weighted mean of HR for each type using the random effect model (Ref.: Dersimonian R, Laird N. Meta-analysis in Clinical trials. Controlled Clinic Trials 1986; 7: 177-188). To assess whether the mean HR among HBV patients was lower than that among HCV patients, we calculated the *P* value using a *Z* test. All reported p- values correspond to two-sided tests, and those $P < 0.05$ were considered significant. All analyses were performed using R (version 4.1.2) and R Studio (version 1.4) software.

RESULTS

In the 14 studies of HBV patients[5-17], the average HR of elevated ALT for developing HCC was 2.74 [1.98-3.77] (Figure 3), and that in 8 studies of HCV-infected patients[12,15-21] was 5.51 [3.08-9.83] (Figure 4). It was demonstrated that the HR of inflammation for HCC development in HCV-associated liver diseases is about twice that in HBV-associated liver diseases. The HR in HCV-infected patients was significantly ($P = 0.0391$) higher than that in HBV-infected patients.

In hepatitis B patients, the abnormal range adopted was 28-45 IU/L (Table 1), and in hepatitis C patients, it was 20-50 IU/L (Table 2). It was demonstrated that the abnormal ALT levels adopted in hepatitis B and C patients were very similar in this series.

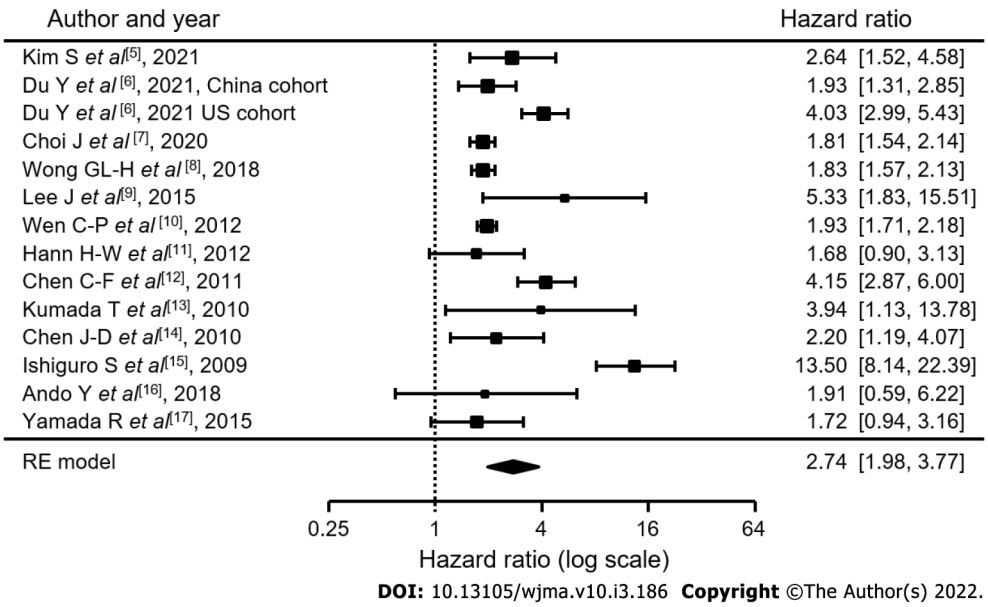

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Figure 3 In hepatitis B virus patients, a non-inflammatory state (serum alanine aminotransferase levels were within normal range) were set as 1. Hazard ratios of patients in an inflammatory state (serum alanine aminotransferase levels above normal range) were calculated.

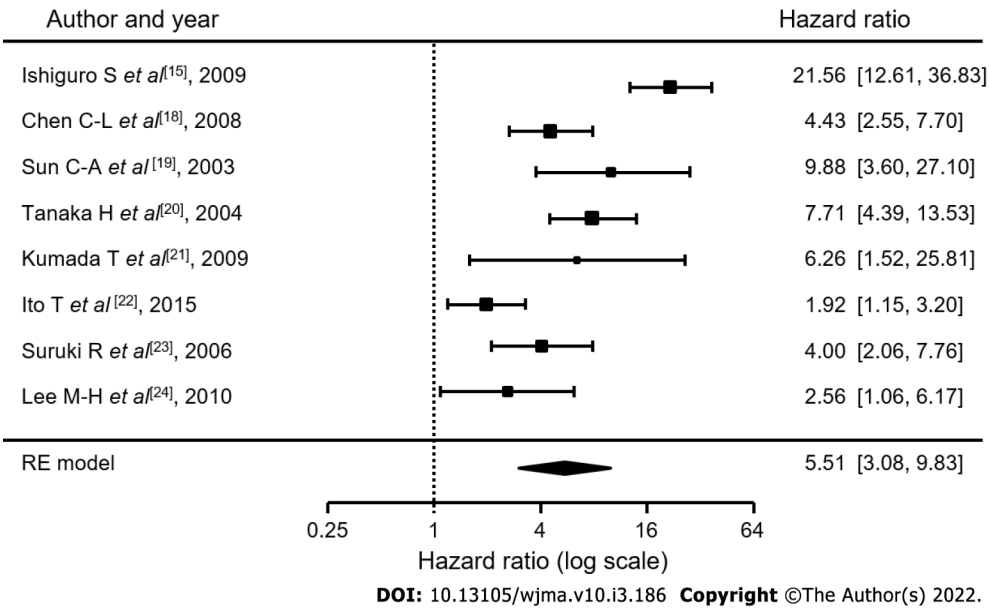

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Figure 4 In hepatitis C virus patients, Hazard ratios of patients in a non-inflammatory state (serum alanine aminotransferase levels were within normal range) were set as 1. Hazard ratios of patients in an inflammatory state (serum alanine aminotransferase levels above normal range) were calculated.

DISCUSSION

There are many risk factors for developing HCC: Sex, age, ALT, α-fetoprotein, presence of cirrhosis, habitual alcohol consumption, tabaco, and diabetes mellitus are typically cited, and HBV-DNA[1,3,6-8, 10] and the HBV genotype[9] are added for chronic HBV infection. The HCV genotype is also cited for HCV infection[21]. To study the impact of ALT on HCC development in chronic hepatitis B and chronic hepatitis C virus infections, we initially surveyed risk factors for HCC that are strongly associated with its development.

As shown in Table 3, the HR for developing HCC for each item in patients with chronic hepatitis B virus infection was 2.52 for sex, 3.15 for age, 2.212 for HBV-DNA, 3.37 for ALT, and 6.42 for presence of cirrhosis. Except for the presence of cirrhosis, ALT shows the highest risk ratio for HCC development.

As shown in Table 4, in patients with chronic hepatitis C virus infection, it was 5.486 for age and 5.877 for ALT. The value for ALT was higher than that for age. In HBV infection, ALT is the second-highest

Table 3 Hazard ratio for developing hepatocellular carcinoma for each item in various reports of patients with chronic hepatitis B virus infection

Ref.	Sex	Age	HBV-DNA	ALT	AFP	Presence of cirrhosis	HBV genotype	Alcohol use	Tabaco	DM
Kim *et al*[5]	2.782	1.080	0.986	2.641		2.955		2.105		2.00
Du *et al*[6]	2.94	3.30		2.55		2.45				
Choi *et al*[7]	1.67	1.05	1.02	1.54	1.21	1.54				
Wen *et al*[10]	1.93	5.34		1.93						
Hann *et al*[11]				1.21						2.60
Chen *et al*[12]			3.12	5.75		7.961	2.05 (Type C)			
Kumada *et al*[13]	6.011		5.125	3.939	6.779	18.033				
Chen *et al*[14]	1.2	2.0	1.6	1.7				2.3	1.9	
Ishiguro *et al*[15]				10.5	2.183					
Ando *et al*[16]	2.200	3.395	1.442	1.914	1.967					
Yamada *et al*[17]	1.44	5.867				5.59				
Average	2.52	3.15	2.212	3.37		6.42				

ALT: Alanine aminotransferase; AFP: α-fetoprotein; DM: Diabetes mellitus; HBV: Hepatitis B virus.

Table 4 Hazard ratio for developing hepatocellular carcinoma in each item in various reports of patients with chronic hepatitis C virus infection

Ref.	Sex	Age	ALT	AFP	Presence of cirrhosis	DM	HCV-genotype
Ishiguro *et al*[15]		11.4	10.5				
Chen *et al*[18]	1.65	5.83	4.43			3.46	
Sun *et al*[19]		6.5	7.7				
Tanaka *et al*[20]	2.63	4.47	6.23				
Kumada *et al*[21]		2.42	6.263		10.003		
Ito *et al*[22]	1.448	2.187	1.916	6.5			
Suruki *et al*[23]							
Lee *et al*[24]							2.8 (HCV-1)
Average		5.486	5.877				

ALT: Alanine aminotransferase; AFP: α-fetoprotein; DM: Diabetes mellitus; HCV: Hepatitis C virus.

risk factor, and in HCV infection, ALT is the higher risk factor.

In support of our findings, Benvegnù *et al*[25] demonstrated that patients with HCV infection with persistently elevated or fluctuating ALT levels during the observation period demonstrated a significantly higher rate of HCC development compared with patients in whom ALT remained or became normal during follow-up. This observation confirms that the activity of liver disease, which is characterized by inflammation, necrosis, and regeneration, plays an important role in promoting HCC development and suggests that medical interventions that limit disease activity may prevent or delay neoplastic transformation and tumor growth.

Furthermore, we demonstrated that the average HR of ALT for HCC development in HCV patients is about twice that in HBV patients ($P < 0.05$).

CONCLUSION

In conclusion, the difference in the incidence of HCC development between HBV and HCV patients may depend on the difference in the HR of ALT between HBV and HCV infections.

ARTICLE HIGHLIGHTS

Research background

It is generally accepted that the incidence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-associated patients is higher than that in hepatitis B virus (HBV)-associated patients. We demonstrated that the incidence of HCC in HCV-associated cirrhotic patients was 4.81%/year compared with 3.23% in HBV-associated patients based on analytic assessment of already published papers.

Research motivation

The reason why this difference in incidence of HCC occurs in patients with HBV and HCV infections remains unknown. We considered the possibility that the contributing power of inflammation, which is the main risk factor for developing HCC, may be different with HBV and HCV infections.

Research objectives

To investigate this, we surveyed the hazard ratio of inflammation for HCC development, which was identified by serum alanine aminotransferase levels between patients with HBV and HCV infections.

Research methods

The PubMed database was searched (2001-2021) for studies published in English regarding the incidence of HCC, identifying 8924 HBV-and7376 HCV-infected patients. From these studies, interferon-treated patients with both HBV and HCV infections were excluded. Furthermore, in HBV patients, those administered nucleos(t)ide analogues were excluded, and in HCV patients, those administered direct acting antivirals were also excluded. Studies citing hazard ratios of HCC regarding inflammation (serum elevated alanine aminotransferase levels) were selected. Finally, there were 14 studies of HBV-infected patients and 8 studies of HCV-infected patients. We calculated the hazard ratio in patients in an inflammatory state (serum ALT levels were above the normal range).

Research results

In the 14 studies of HBV patients, the average hazard ratio (HR) of elevated ALT for developing HCC was 2.74 [1.98-3.77], and that in the 8 studies on HCV-infected patients was 5.51 [3.08-9.83]. HR in HCV-infected patients was about twice that in HBV-infected patient, and was significantly (P = 0.0391) higher than that in HBV-infected patients. In hepatitis B patients, the abnormal range adopted was 28-45 IU/L, and in hepatitis C patients, it was 20-50 IU/L. It was demonstrated that the abnormal ALT levels adopted in hepatitis B and C patients were very similar in this series.

Research conclusions

The difference in the incidence of HCC development between HBV and HCV patients may depend on the difference in the HR of ALT between HBV and HCV infections.

Research perspectives

In this study, it was demonstrated that the HR of inflammation for HCC development in HCV-associated liver diseases is about twice that in HBV-associated liver diseases. So, we must optimally suppress inflammation in patients with HCV-associated liver diseases to prevent HCC development.

FOOTNOTES

Author contributions: Tarao K summarized the data and wrote the paper; Nozaki A, Komatsu H, Ideno N, Komatsu T, Ikeda T, Maeda S were involved in the interpretation of data, and the development and critical revision of the manuscript for important intellectual content; Taguri M conducted statistical analysis.

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