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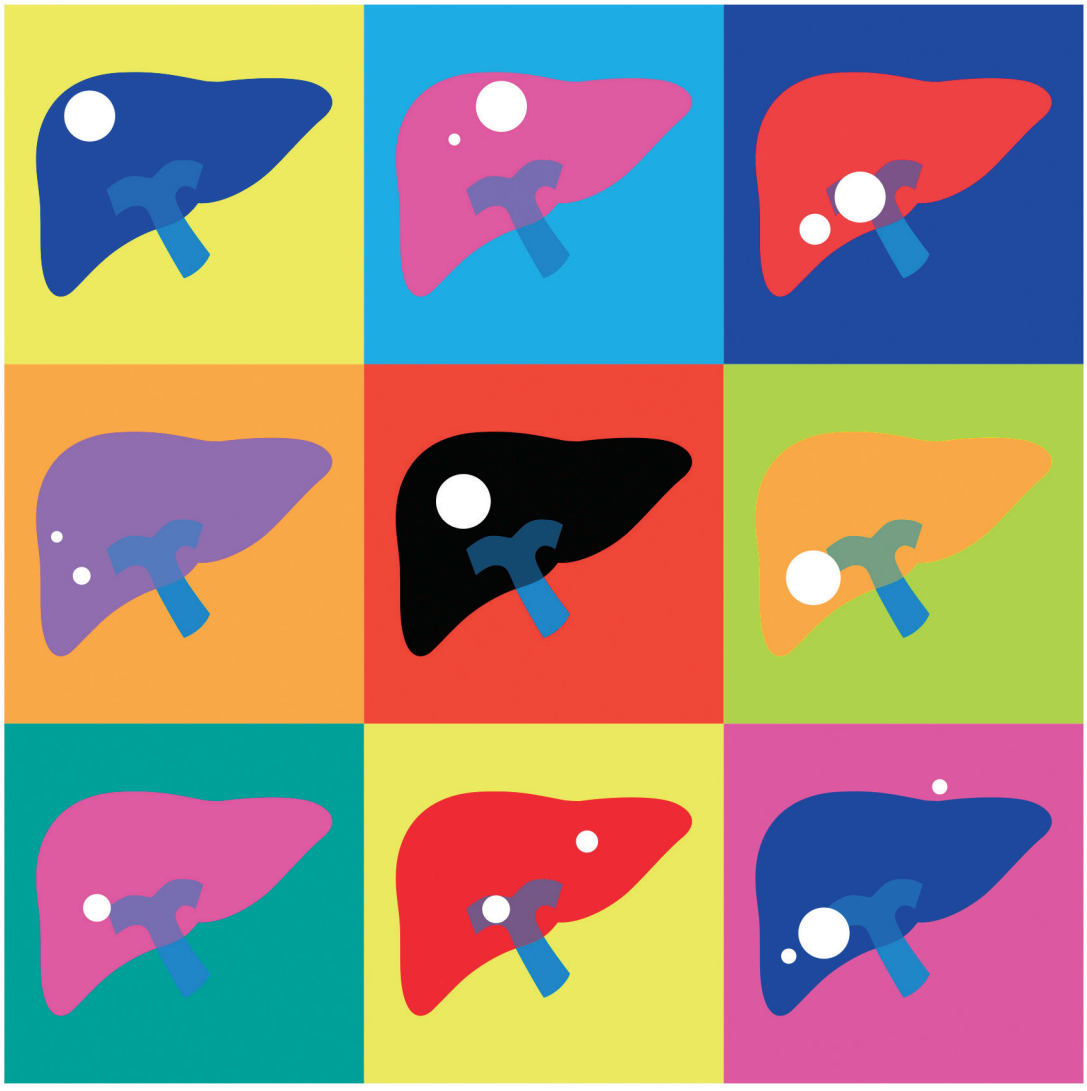

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Review

Impact of diabetes, obesity, and dyslipidemia on the risk of hepatocellular carcinoma in patients with chronic liver diseases

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Despite the increasing prevalence of metabolic disorders, the potential effects of metabolic factors on hepatocellular carcinoma (HCC) development in individuals with chronic liver diseases (CLDs) are not well understood. For a metabolic factor to be identified as a risk factor for HCC in patients with CLDs, such as hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, there should be a strong synergistic interaction between the carcinogenic mechanisms of the metabolic factor and the CLD itself. This review aims to comprehensively summarize the published data on the relationship between metabolic factors such as diabetes mellitus (DM), obesity, and blood lipids and the risk of HCC in patients with CLDs. DM consistently increases the risk of HCC in patients with CLD. When associated with DM, the risk of HCC seems to be highest in HCV and non-alcoholic fatty liver disease (NAFLD), followed by alcoholic liver disease (ALD) and HBV. Obesity may increase the risk of HCC. Among CLDs, the evidence is relatively consistent and clear for ALD, while clear evidence is limited in other CLDs including HBV, HCV, and NAFLD. Total cholesterol, potentially low-density lipoprotein cholesterol and triglyceride, seems to have strong inverse associations with HCC in individuals with CLDs. Despite evidence from observational studies, statins had no effect in preventing HCC in randomized controlled trials. Whether statins have a preventive effect against HCC is unclear. A better understanding and management of metabolic factors may be beneficial to reduce the risk of HCC in patients with CLDs. **(Clin Mol Hepatol 2022;28:773-789)**

Keywords: Obesity; Dyslipidemias; Diabetes mellitus; Hepatocellular carcinoma

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INTRODUCTION

Liver cancer is the sixth most common cancer worldwide, and hepatocellular carcinoma (HCC) accounts for 75–85% of all primary liver cancers.[1] HCC is the third leading cause of cancer-related death among solid cancers, leading to approximately 1 million deaths yearly.[2] Chronic liver diseases (CLDs), such as hepatitis B virus (HBV) infection and liver cirrhosis (LC), are well known risk factors for the development of HCC.

Recently, increasing evidence has suggested that metabolic factors, including diabetes mellitus (DM), obesity, dyslipidemia, and metabolic syndromes, are risk factors for HCC.[3-6] In populations with a low prevalence of viral hepatitis, the overall impact of metabolic factors on HCC was suggested to be greater than that of viral hepatitis.[7] The effects of metabolic factors on HCC have not been well established in individuals with CLDs. Observational studies have suggested the potential beneficial effects of some pharmaceutical agents for metabolic disorders (e.g., statins) in preventing HCC.

The purpose of this review is to summarize the associations between metabolic factors such as DM, dyslipidemia, and obesity and the risk of HCC in patients with CLDs. In this review, we focused on HBV, hepatitis C virus (HCV) infection, alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), and LC among CLDs. The associations in the general population were briefly summarized for comparison. A clearer understanding of the role of metabolic factors in the development of HCC will help in informed decision-making and patient management aimed at reducing the risk of HCC in patients with CLDs and comorbid metabolic disorders.

ROLE OF METABOLIC FACTORS IN CLDS: A SYNERGISTIC INTERACTION

Patients with CLDs, such as HBV/HCV, have a several dozen-fold higher risk of HCC development compared with individuals without CLDs, while metabolic disorders, such as diabetes and obesity, are associated with a 2–3-fold higher risk of HCC in the general population. If patients with CLD and comorbid metabolic disorders have a higher risk of HCC, then carcinogenic mechanisms by CLDs and metabolic disorders should have a strong synergistic interaction. Let us assume that HBV patients without diabetes have a 50-fold higher risk for HCC development compared to the general population without diabetes and that diabetic patients have a 2-fold higher risk compared with general population without diabetes. If HBV and diabetes are independent risk factors without synergistic interaction, compared to individuals without HBV and diabetes, and HBV patients without diabetes, HBV patients with diabetes will have approximately 51-fold and 1.02-fold higher risk, respectively, for HCC development (likewise, if HBV patients with diabetes have a 2-fold higher risk compared to those without diabetes, then they have a 100-fold higher risk compared with individuals without diabetes and HBV).[8,9] Additionally, the stronger the impact of a certain CLD (such as LC) on HCC development is, the stronger synergistic interaction should exist in individuals with CLD for a metabolic factor to be identified as a risk factor in individuals with CLD. It is common that the associations of a factor are weaker in individuals with diseases than in the general population. Potential mechanisms should be focused on the synergistic interactions of mechanisms by CLDs and metabolic factors (rather than on the general mechanism of a factor *per se*). However, few detailed mechanisms have been proposed, and further research would be needed to explain potential synergic interactions.

DM

General population

In general population studies, DM has been associated with an increased risk of HCC. A Korean study using the National Health Insurance Service-Health Screening Cohort (NHIS-HEALS) reported that DM was associated with a higher risk of HCC (hazard ratio [HR], 1.82).[10] Two meta-analyses showed that DM was associated with a risk ratio (RR) of 2.01

Abbreviations:

ALD, alcoholic liver disease; BMI, body mass index; CI, confidence interval; CLD, chronic liver disease; DM, diabetes mellitus; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDL, high-density lipoprotein; HR, hazard ratio; LC, liver cirrhosis; LDL, low-density lipoprotein; NAFLD, non-alcoholic fatty liver disease; NHIS-HEALS, National Health Insurance Service-Health Screening Cohort; RR, risk ratio; TC, total cholesterol; TG, triglyceride; WC, waist circumference

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and 2.31 for HCC development.[11,12] However, liver diseases themselves increase the risk of DM development.[13-15] Thus, at least some part of the association between DM and HCC in the general population may be due to reverse causation.

Patients with viral hepatitis

DM has been associated with an increased risk of HCC in patients with CLD. The magnitude of association between DM and HCC somewhat differed for each liver disease (Table 1).[16-30] A recent Korean study on 214,167 male patients with HBV reported that the presence of DM was significantly associated with a higher risk of HCC (HR, 1.23).[16] In a recent systematic review and meta-analysis of 36 studies, DM was associated with an HR of 1.36 for HCC development in patients with HBV.[17] A systematic review of seven studies in 10,700 patients with HCV reported that DM increased the risk of HCC by approximately 2-fold.[19] The HCC risk associated with DM appears to be stronger in HCV than in HBV.[19,29] However, in a US study in 52,671 HCV-LC patients (7,605 HCC cases), DM was not associated with the risk of HCC.[20]

Patients with LC

In ALD-LC patients, DM was associated with approximately 1.5-fold increased risk of HCC.[20,23] A recent systematic review reported that DM increases 2.65-fold the risk of HCC incidence in NAFLD patients.[30] In NAFLD patients with/without LC, HRs associated with DM for HCC were 1.24 (407 HCC cases), 1.93 (608 HCC cases), 1.30 (291 HCC cases), and 2.77 (253 HCC cases) in studies with >200 HCC cases, while the corresponding HRs were 4.18 (30 HCC cases), 2.90 (28 HCC cases), 4.72 (41 HCC cases), and 3.21(16 HCC cases) in studies with <50 HCC cases.[20,23-28] The magnitude of association between DM and the risk of HCC in NAFLD patients may be comparable to that in HCV patients or in general populations.

Patients with ALD and NAFLD

The HCC risk associated with DM seemed to be highest in NAFLD, followed by ALD and HBV. However, HCV and NAFLD are well known to increase the DM incidence by approximately 2-fold.[14,15] Comorbid DM is considered a marker of severity in NAFLD.[31,32] Therefore, the strongest associations do not necessarily mean strongest causal effect of DM on HCC development in NAFLD. Overall, diabetes may have causal effects on HCC in patients with CLDs. However, part of the effects of DM may reflect the underlying severity of the liver disease.

Anti-diabetic drugs in CLDs

Only a few studies on the effects of anti-diabetic drugs on the HCC risk in patients with CLDs have been conducted, and the results have been inconsistent (Table 2). In HBV patient, some recent cohort studies reported that metformin increased the HCC risk.[33,34] Whereas, another cohort study reported that metformin was not associated with HCC.[35] While in studies on patients with NAFLD, metformin did not have a significant association with HCC risk.[24,36] In contrast, thiazolidinediones reduced the risk of HCC in patients with HBV (HR, 0.46).[35] Kramer et al.[37] reported that insulin and sulfonylureas alone had no effect on HCC risk, but insulin in combination with oral medication (metformin, sulfonylurea) had a higher risk of HCC with NAFLD. Overall, there is a lack of evidence, and it is unclear whether the use of anti-diabetic medication itself affects HCC development or whether different types of diabetic medications differently affect the development of HCC in patients with CLD.

OBESITY

In this review, the international standard of body mass index (BMI) classification, namely underweight (BMI <18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obesity (≥30 kg/m^2), was used, instead of the classification by the Korean Society for the Study of Obesity that defines obesity as BMI ≥25 kg/m^2.

General population

Obesity is considered a risk factor for HCC, especially in populations of European origin.[38,39] Meta-analyses in the general, mostly Western, populations showed that obesity increased the risk of HCC (or primary liver cancer) by approximately two times.[40,41] In Asian populations, despite their slim body shape, obesity-related HCC risks were substantially lower than Western populations and the summed relative risk was approximately 1.5 in a meta-analysis.[10,40-44]

Table 1. Association between diabetes mellitus and hepatocellular carcinoma

Study	Region	Etiology	Study design	Patients/HCC cases	Result (95% CI)	*P*-value
Kim et al.[16] (2018)	Korea	HBV	Population-based cohort study	214,167/11,241	HR, 1.23 (1.15–1.34)	<0.01
Campbell et al.[17] (2021)		HBV	Meta-analysis	40 studies (536,456)	HR, 1.36 (1.20–1.32)	<0.01
Hsu et al.[18] (2018)	Taiwan	HBV	Population-based cohort study	23,851/596	HR, 1.3 (1.1–1.6)	
Dyal et al.[19] (2016)		HCV	Meta-analysis	9 studies	HR, 1.73 (1.30–2.30); RR, 3.52 (1.29–9.24)	
Yang et al.[29] (2022)		HBV	Meta-analysis	11 studies	RR, 1.37 (1.24–1.51); OR, 1.99 (0.73–5.48)	
		HCV		15 studies	RR, 1.76 (1.42–2.17); OR, 1.77 (1.18–2.64)	
Chen et al.[30] (2022)		NAFLD-LC	Meta-analysis	8 studies	HR, 4.55 (2.34–8.87)	
		NAFLD			HR, 2.65 (2.02–3.49)	
Ioannou et al.[20] (2018)	USA	HCV-LC	Retrospective cohort study	44,007/7,605	HR, 1.02	0.6
		ALD-LC		29,326/1,388	HR, 1.54	<0.01
		NAFLD-LC		13,456/608	HR, 1.93	<0.01
Huang et al.[21] (2015)	Taiwan	HCV	Population-based cohort study	2,187/82	HR, 1.91 (1.10–3.30)	0.02
Arase et al.[22] (2013)	Japan	HCV	Retrospective cohort study	4,302/393	HR, 1.73 (1.30–2.30)	<0.01
Ioannou et al.[23] (2019)	USA	ALD-LC	Retrospective cohort study	16,175/871	HR, 1.46	<0.01
		NAFLD-LC		7,068/407	HR, 1.24	0.10
Yang et al.[24] (2020)	USA	NAFLD-LC	Hospital-based cohort study	354/30	HR, 4.18 (1.23–14.2)	0.02
			Retrospective cohort study	6,630/291	HR, 1.30 (1.02–1.66)	0.03
Kanwal et al.[25] (2020)	USA	NAFLD	Retrospective cohort study	271,906/253	HR, 2.77 (2.03–3.77)	
Bertot et al.[26] (2018)	Australia	NAFLD	Hospital-based cohort study	284/28	HR, 2.9 (1.2–7.3)	0.02
Vilar-Gomez et al.[27] (2018)	Spain, Australia, Hong Kong, and Cuba	NAFLD	Cohort study	456/41	HR, 4.72 (2.13–10.45)	<0.01
Kawamura et al.[28] (2012)	Japan	NAFLD	Retrospective cohort study	6,508/16	HR, 3.21 (1.09–9.50)	0.04

HCC, hepatocellular carcinoma; CI, confidence interval; HBV, hepatitis B virus; HR, hazard ratio; HCV, hepatitis C virus; RR, risk ratio; OR, odds ratio; NAFLD, non-alcoholic fatty liver disease; LC, liver cirrhosis; ALD, alcoholic liver disease.

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Table 2. Association between anti-diabetic drugs and hepatocellular carcinoma

Study	Region	Drug	Etiology	Study design	Patients/HCC cases	Result (95% CI)	*P*-value
Chen et al.[33] (2015)	Taiwan	Metformin	HBV	Population-based cohort study	71,824/1,753	HR, 1.25 (1.06–1.47)	<0.01
Hsu et al.[34] (2018)	Taiwan	Metformin	HBV	Population-based cohort study	27,820/802	HR, 2.20 (1.86–2.60)	<0.01
Yip et al.[35] (2020)	Hongkong	Thiazolidinediones	HBV	Retrospective cohort study	28,999/2,307	HR, 0.46 (0.24–0.88)	0.19
Yang et al.[24] (2020)	USA	Metformin	NAFLD	Retrospective cohort study	354/30	HR, 1.93 (0.84–4.41)	0.12
Lee et al.[36] (2017)	Taiwan	Metformin	NAFLD	Population-based cohort study	18,080	HR, 1.29 (0.47–3.54)	0.62
Kramer et al.[37] (2022)	USA	Insulin	NAFLD	Retrospective cohort study	85,963/524	HR, 1.05 (0.88–1.27)	0.57
		Sulfonylureas				HR, 0.98 (0.84-.1.16)	0.84
		Insulin-metformin				HR, 1.53 (1.25-1.86)	<0.01
		Insulin-metformin-sulfonylureas				HR, 1.71 (1.41-2.08)	<0.01

HCC, hepatocellular carcinoma; CI, confidence interval; HBV, hepatitis B virus; HR, hazard ratio; NAFLD, non-alcoholic fatty liver disease.

Patients with viral hepatitis

Most studies on patients with HBV have been conducted in Asia, especially Taiwan (Table 3).[45-49] The Taiwanese studies did not show consistent association between obesity and HCC risk.[45-48] A recent study on Korean adults with chronic HBV showed that obesity, compared to a BMI of 18.5–22.9, was associated with 22% (men: HR, 1.22; 95% confidence interval [CI], 1.09–1.36]) and 46% (women: HR, 1.46; 95% CI, 1.24–1.71) higher risk of HCC.[49] This large-scale study using five categories of BMI identified relatively weak associations between obesity and HCC. Previous studies may not have found these subtle results consistently, probably due to the small number of participants, the crude categories of obesity generally used (such as obesity vs. non-obesity), and the inclusion of only men in some cases.[45-48] Obesity may be a risk factor for HCC in patients with HBV; however, the effect size seemed to be weaker than that in the general population.

Most studies reported that BMI or obesity were not associated with HCC in patients with HCV infections.[21,22,50-54] Two studies, one Japanese and one Taiwanese, which are commonly cited concerning the higher HCC risk associated with obesity, have a major limitation.[55,56] In the Japanese study, relative risks associated with obesity were calculated by comparing with underweight, not with normal weight.[55] In the Taiwanese study, the higher HCC risk associated with obesity was based on a very small number of HCC cases (five cases of obesity).[56] Overall, the association between obesity and HCC has been inconsistent in patients with HCV. Considering the similarity of the impact of HBV and HCV on HCC, obesity might impact HCC in individuals with HCV infections similarly to that in individuals with HBV infection; that is, obesity may modestly increase HCC development in individuals with HCV.

Patients with LC

In individuals with LC, the associations have been complex and inconsistent and have shown the potential to differ according to LC etiology, which includes ALD, NAFLD, HBV, and HCV.[20,23,24,57-63] In two studies on NAFLD-LC patients who received care in the US Veterans Affairs healthcare system from the same authors, one showed a potentially higher HCC risk associated with high BMI, whereas the other did not.[20,23] The associations appeared to be clearer and stronger in alcoholic LC than in viral LC.[20,57] These results suggest a strong syner-

Table 3. Association between obesity and hepatocellular carcinoma

Study	Region	Etiology	Study design	Patients/ HCC cases	Result (95% CI)	*P*-value
Yu et al.[45] (2008)	Taiwan	HBV	Cohort study	2,903/134	HR, 1.48 (1.04–2.12); BMI 25–30[†]	
					HR, 1.96 (0.72–5.38); BMI >30[†]	
Fu et al.[46] (2015)	Taiwan	HBV	Cohort study	4,179/111	HR, 0.31 (0.04–2.24); obesity*	0.25
Loomba et al.[47] (2010)	Taiwan	HBV	Cohort study	2,260/135	HR, 1.00 (0.93–1.06)[‖]	0.54
Chao et al.[48] (2011)	Taiwan	HBV	Cohort study	1,142/124	HR, 1.58 (1.16–2.17); BMI ≥25*	<0.01
Kim et al.[49] (2018)	Korea	HBV	Population-based cohort study	370,322/14,609	HR, 1.04 (0.99–1.09); men; BMI 25.0–29.9[‡]	
					HR, 1.22 (1.09–1.36); men; BMI ≥30[‡]	<0.01
					HR, 1.25 (1.15–1.36); women; BMI 25.0–29.9[‡]	<0.01
					HR, 1.46 (1.24–1.71); women; BMI ≥30[‡]	<0.01
Huang et al.[21] (2015)	Taiwan	HCV	Population-based cohort study	2,187/82	HR, 1.79 (0.43–7.44); obesity*	0.42
Arase et al.[22] (2013)	Japan	HCV	Retrospective cohort study	4,302/393	uHR, 1.37 (1.12–1.66); BMI ≥22*	<0.01
Veldt et al.[50] (2008)	Europe, Canada	HCV	Prospective	541	HR, 0.94 (0.84–1.05); BMI[‖]	0.29
Arano et al.[51] (2011)	Japan	HCV	Retrospective cohort study	325/122	HR, 1.01 (0.93–1.09); men[‖]	0.76
					HR, 1.09 (0.99–1.19); women[‖]	0.06
Yang et al.[52] (2016)	USA	HCV	Hospital-based cohort study	739/69	uHR, 1.0 (1.0–1.0); BMI[‖]	0.74
Lok et al.[53] (2009)	USA	HCV	Cohort study	1,005/48	Lower BMI was associated with HCC (unadjusted)	0.04
McMahon et al.[54] (2017)	USA	HCV	Population-based cohort study	1,080/40	uHR, 1.06 (0.5–2.1); BMI ≥30*	0.87
Ohki et al.[55] (2008)	Japan	HCV	Retrospective cohort study	1,431/122	HR, 1.86 (1.09–3.16); BMI 25–30[§]	0.02
					HR, 3.10 (1.41–6.81); BMI >30[§]	0.01
Hung et al.[56] (2011)	Taiwan	HCV	Cohort study	1,470/87	HR, 1.31 (0.83–2.05); BMI ≥25*	0.24
Ioannou et al.[20] (2018)	USA	LC	Retrospective study	116,404/10,042	HR, 1.0; BMI 24.5–28; HCV–LC[††]	0.96
					HR, 0.93; BMI 28–32; HCV–LC[††]	0.04
					HR, 0.84; BMI >32; HCV–LC	<0.01
					HR, 1.2; BMI 24.5–28; NAFLD–LC	0.48
					HR, 1.52; BMI 28–32; NAFLD–LC	0.09
					HR, 1.45; BMI >32; NAFLD–LC	0.10
					HR, 1.59; BMI 24.5–28; ALD–LC[††]	<0.01
					HR, 1.74; BMI 28–32; ALD–LC[††]	<0.01
					HR, 1.88; BMI >32; ALD–LC[††]	<0.01

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Table 3. Continued

Study	Region	Etiology	Study design	Patients/ HCC cases	Result (95% CI)	*P*-value
Ioannou et al.[23] (2019)	USA	LC	Retrospective cohort study	23,243/1,278	HR, 1.32; BMI 25.2–29.3; ALD-LC‡‡	<0.01
					HR, 1.39; BMI 29.3–33.8; ALD-LC ‡‡	<0.01
					HR, 1.49; BMI 33.8–38.5; ALD-LC‡‡	<0.01
					HR, 1.31; BMI >38.5; ALD-LC ‡‡	0.06
					HR, 0.91; BMI 25.2–29.3; NAFLD-LC ‡‡	0.64
					HR, 0.9; BMI 29.3–33.8; NAFLD-LC ‡‡	0.60
					HR, 0.8; BMI 33.8–38.5; NAFLD-LC‡‡	0.28
					HR, 0.77; BMI >38.5; NAFLD-LC ‡‡	0.22
Yang et al.[24] (2020)	USA	LC	Hospital-based cohort study	354/30	uHR, 0.99 (0.95–1.03); Mayo cohort; BMI‖	0.59
			Cohort study	6,630/291	uHR, 1.00 (0.98–1.02); UNOS cohort; BMI‖	0.83
Nair et al.[57] (2002)	USA	LC	Large-population database study	19,271/659	HR, 1.65 (1.22–2.22); BMI ≥30*	<0.01
Pais et al.[58] (2015)	France	LC	Retrospective study	110/29	OR, 8.24 (2.04–33.32); BMI >25*	<0.01
Grimaudo et al.[59] (2020)	Italy	LC	Prospective study	162/13	HR, 0.86 (0.21–3.51); BMI ≥30*	0.83
N'Kontchou et al.[60] (2006)	France	LC	Retrospective cohort study	771/220	HR, 2.0 (1.4–2.7); BMI 25.0–29.9**	<0.01
					HR, 2.8 (2.0–4.0); BMI ≥30**	<0.01
Archambeaud et al.[61] (2015)	France	LC	Case-control study	905/282	OR, 1.56 (1.02–2.37); past obesity*	0.03
					uOR, 1.04 (0.72–1.48); current obesity*	0.84
Brichler et al.[62] (2019)	France	LC	Prospective cohort study	317/27	HR, 2.67 (1.04–6.84); BMI ≥30*	0.04
Ioannou et al.[63] (2007)	USA	LC	Cohort study	2,126/173	HR, 2.8 (1.4–5.4); BMI 25.0–29.9**	
					HR, 2.5 (1.3–4.9); BMI ≥30	
Kanwal et al.[25] (2020)	USA	NAFLD	Retrospective cohort study	271,906/253	HR, 1.31 (0.98–1.74); BMI >30*	
Ito et al.[64] (2020)	Japan	NAFLD	Retrospective study	179/7	uHR, 1.07 (0.21–5.51); BMI ≥25*	0.94
Fan et al.[66] (2021)	China	HBV	Cohort study	5,754/142	HR, 1.63 (1.11–2.38); waist-to-height ratio >0.50*	0.01
Lee et al.[67] (2016)	Korea	HBV	Cohort study	102/7	uHR, 0.88 (0.17–4.53); WC ≥90 (men) or ≥80 (women)*	0.88
					uHR, 1.94 (0.23–15.87); waist-to-hip ratio ≥0.9*	0.39
					uHR, 1.69 (0.43–8.71), visceral fat area ≥100 cm^2 *	0.50

HCC, hepatocellular carcinoma; CI, confidence interval; HBV, hepatitis B virus; HR, hazard ratio; BMI, body mass index (kg/m^2); HCV, hepatitis C virus; uHR, unadjusted HR; LC, liver cirrhosis; HCV, hepatitis C virus; NAFLD, non-alcoholic fatty liver disease; ALD, alcoholic liver disease; UNOS, United Network for Organ Sharing; OR, odds ratio; uOR, unadjusted OR; WC, waist circumference (cm).

*Two group analysis, for example obesity vs. no obesity, BMI ≥25 vs. BMI <25 kg/m^2.

†Reference: BMI 18.5–24.9 kg/m^2.

‡Reference: BMI 18.5–22.9 kg/m^2.

§Reference: BMI ≤18.5 kg/m^2.

‖HR per 1 unit increase in BMI.

**Reference: BMI <25 kg/m^2.

††Reference: BMI 18.0–24.5 kg/m^2.

‡‡Reference: BMI ≤25.2 kg/m^2.

gistic interaction between ALD (or alcohol consumption) and obesity, which was also observed in general populations.[47]

Patients with NAFLD

The studies conducted among NAFLD patients of Western populations, including those without cirrhosis/fibrosis, found that BMI or obesity was not statistically significantly associated with HCC.[25,59,64] It is surprising that the impact of obesity on HCC development has not been clearly shown in NAFLD patients. However, these NAFLD studies, including those conducted mostly on non-cirrhotic patients, mainly used crude categories of BMI (obesity vs. non-obesity) and possibly lacked statistical power to detect the true association.[25,59,64] Additionally, probably because cirrhosis is a main mechanism of NAFLD-related HCC, the association between obesity and HCC might not be apparent in NAFLD-LC patients.[20,23,24,59]

In summary, obesity may increase the risk of HCC in patients with CLD, but probably with a weaker effect size than that in the general population.[21,52,53] Liver damage caused by obesity and CLD itself may synergistically interact together and further facilitate the progression and/or development of HCC in patients with CLD. However, it should be noted that there is limited evidence even in NAFLD cases.

Central obesity

Compared to the lowest category, the highest waist circumference (WC) category had a 1.59 times higher risk of HCC development in a recent systematic review, mostly in the general population.[65] A recent Chinese study on chronic HBV patients reported that central obesity defined by waist-to-height ratio, not by WC and waist-hip ratio, was associated with an increased risk of HCC (HR, 1.63; 95% CI, 1.11–2.38) compared to non-central obesity. However, the risk of HCC with changes in the waist-to-height ratio was associated with an increased risk of HCC both with a decrease and an increase in the ratio.[66] In a small Korean study among 102 chronic HBV patients (seven HCC cases), central obesity, defined by WC, waist-hip ratio, and visceral fat area, was not associated with HCC risk.[67] Despite the potential, it is difficult to conclude whether central obesity is a better predictor and risk factor than general obesity in individuals with CLDs, due to the very small number of studies.

DYSLIPIDEMIA

General population

As each type of dyslipidemia may have different associations with HCC, we focused on studies reporting specific lipid profiles, such as total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglyceride (TG). Most studies revealed that low TC levels were strongly associated with an increased risk of HCC development.[6,68-74] In a Korean study that used the NHIS-HEALS, a nearly 50% reduced risk of HCC was observed for every 39 mg/dL (1 mmol/L) increase in TC (HR, 0.54; 95% CI, 0.51–0.58).[71] Only a few studies have examined the associations of other lipids with HCC. Low levels of LDL-C and TG were generally associated with a higher risk of HCC, while HDL-C showed unclear inverse associations.[69,70,74] Overall, TC and potentially LDL-C and TG, seemed to have clear inverse associations with HCC in the general population, whereas the dose-response association of HDL-C with HCC was unclear.

Patients with CLDs: TC

In patients with CLDs, like in the general population, TC levels were inversely associated with the risk of HCC. Higher TC levels were generally associated with a lower risk of HCC in individuals with viral hepatitis (including HBV and HCV), LC, and NAFLD (Table 4).[36,70,75-77] Compared to the studies on TC, a relatively small number of studies have reported associations between other lipid profiles and HCC.

While low TC levels may be a useful marker for HCC development in patients with CLD, the potential causal effects of low TC levels are uncertain. The presence of CLD leads to hepatic damage, which, in turn, is related to changes in lipid metabolism. Serum cholesterol levels in patients with HBV, HCV, and HCC were reported to be lower than those in the normal control group.[78-80] The decrement in cholesterol levels positively correlated with the severity of liver disease.[78,79,81-85] Statin affected lower levels of cholesterol levels were not associated with higher risk of HCC.[71] Low TC levels seemed to be more a strong predictor, but less a risk factor for HCC. Future studies are needed to clarify the role of lipid profiles, such as whether they have independent effects on HCC development.

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Table 4. Association between dyslipidemia and hepatocellular carcinoma

Study	Region	Etiology	Study design	Patients/HCC cases	Result (95% CI)	*P*-value
Lee et al.[36] (2017)	Taiwan	NAFLD	Population-based cohort study	18,080/41	HR, 0.41 (0.15–1.11)	0.08
Cho et al.[70] (2021)	Korea	LC	Large-population database study	6,399/561	HR, 0.78 (0.64–0.96); TC Q2*	
					HR, 0.65 (0.51–0.83); TC Q3	
					HR, 0.30 (0.21–0.44); TC Q4	
					HR, 0.78 (0.58–1.05); TG Q2	
					HR, 0.69 (0.44–1.07); TG Q3	
					HR, 0.47 (0.23–0.94); TG Q4	
					HR, 0.77 (0.63–0.94); LDL Q2	
					HR, 0.64 (0.51–0.81); LDL Q3	
					HR, 0.29 (0.21–0.40); LDL Q4	
					HR, 0.95 (0.75–1.20); HDL Q2	
					HR, 1.01 (0.80–1.28); HDL Q3	
					HR, 1.18 (0.94–1.49); HDL Q4	
		Viral hepatitis		86,368/806	HR, 0.69 (0.58–0.82); TC Q2*	
					HR, 0.50 (0.41–0.61); TC Q3	
					HR, 0.31 (0.24–0.39); TC Q4	
					HR, 0.78 (0.58–1.05); TG Q2	
					HR, 0.69 (0.44–1.07); TG Q3	
					HR, 0.47 (0.23–0.94); TG Q4	
					HR, 0.77 (0.63–0.94); LDL Q2	
					HR, 0.64 (0.51–0.81); LDL Q3	
					HR, 0.29 (0.21–0.40); LDL Q4	
					HR, 0.95 (0.75–1.20); HDL Q2	
					HR, 1.01 (0.80–1.28); HDL Q3	
					HR, 1.18 (0.94–1.49); HDL Q4	
Goh et al.[75] (2020)	Korea	HBV	Retrospective cohort study	7,713/702	HR, 0.77 (0.63–0.95); high TC	0.01
Wu et al.[76] (2014)	Taiwan	HBV	Population-based cohort study	43,190/5,446	HR, 0.87 (0.61–1.23)	0.43
Tan et al.[77] (2019)	Taiwan	HBV	Population-based cohort study	6,564/89	HR, 0.67 (0.39–1.16); high TG	0.15
					HR, 0.99 (0.54–1.83); low HDL	0.98

Table 4. Continued

Study	Region	Etiology	Study design	Patients/HCC cases	Result (95% CI)	*P*-value
Choe et al.[86] (2021)	Korea	HBV	Large-population database study	1,504,880/29,412	HR, 0.46 (0.45-0.47); high TG HR, 0.68 (0.66-0.70); low HDL	
Kanwal et al.[25] (2020)	USA	NAFLD	Retrospective cohort study	271,906/253	HR, 1.31 (0.84–2.04); high TG and/or low HDL-cholesterol	

HCC, hepatocellular carcinoma; CI, confidence interval; NAFLD, non-alcoholic fatty liver disease; HR, hazard ratio; LC, liver cirrhosis; TC, total cholesterol; Q, quartile; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HBV, hepatitis B virus.
*Quartile 1 (Q1, lowest), Q2, Q3, and Q4 (highest). The reference was Q1.

Patients with CLDs: other lipid profile

The association between LDL-cholesterol and HCC was similar to that between TC and HCC.[70,77] A recent population-based Korean study on HBV patients showed that HCC was negatively associated with increased TG levels.[86] In a large-scale Korean study, TG showed inverse associations and low HDL-cholesterol (L-curve) levels were associated with a higher risk of HCC in individuals with chronic viral hepatitis or LC, whereas a smaller study (89 HCC cases) reported that high TG levels, but not low HDL-cholesterol levels, were associated with a higher risk of HCC in patients with HBV.[70,77] Dyslipidemia, defined by high TG and/or low HDL-cholesterol levels, was not associated with a higher risk of HCC in American patients with NAFLD.[25] Overall, similar to the results in the general population, TC, potentially LDL-cholesterol and TG, seemed to have inverse associations with HCC in individuals with CLDs, whereas the association of low HDL-cholesterol with HCC was unclear.

Statin therapy in CLDs

In several observational studies, statin therapy has generally been associated with a reduced risk of HCC development in patients with CLDs (Table 5). Statin use was associated with a materially lower risk of HCC in patients with HBV, HCV, and NAFLD.[17,33,36,75,76,87-94] A recent meta-analysis of studies on CLD reported that statin use was associated with an HR of 0.57 for HCC development.[94]

Caution should be exercised when interpreting the beneficial effects of statins on HCC based on evidence from observational studies. The higher the cholesterol level, the higher the possibility of statin use. The natural low cholesterol level, not the attained level after statin use, is an important predictor and a potential risk factor for HCC.[71] Therefore, when the association between statin use and HCC risk is examined in observational studies, only patients newly initiated on statin treatment should be enrolled as statin users and their natural cholesterol levels before statin use should be measured. The preventive effect of statins disappeared in such studies on the general population.[71,95] Importantly, in the ad hoc analysis of randomized controlled trials for cardiovascular disease prevention, statins had no effect in preventing HCC (HR, 1.06 for statin use/more use compared with non-use/less use).[96,97] Overall, whether statins have a preventive effect against HCC

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Table 5. Association between statin use and hepatocellular carcinoma

Study	Region	Etiology	Study design	Patients/HCC cases	Result (95% CI)	*P*-value
Campbell et al.[17] (2020)		HBV	Meta-analysis	40 studies (536,456)	HR, 0.36 (0.19–0.68) to HR, 0.81 (0.73–0.90)	
Chen et al.[33] (2015)	Taiwan	HBV	Population-based cohort study	71,824/1,735	HR, 0.34 (0.27–0.42)	<0.001
Goh et al.[75] (2020)	Korea	HBV	Retrospective cohort study	7,713/702	HR, 0.36 (0.19–0.68)	0.002
Wu et al.[76] (2014)	Taiwan	HBV	Population-based cohort study	43,190/5,446	HR, 0.55 (0.47–0.63)	<0.001
Tsan et al.[87] (2012)	Taiwan	HBV	Population-based cohort study	33,413/1,021	HR, 0.47 (0.36–0.61)	<0.001
Hsiang et al.[88] (2015)	China	HBV	Cohort study	73,499/6,883	HR, 0.68 (0.48–0.97)	0.033
Tsan et al.[89] (2013)	Taiwan	HCV	Population-based cohort study	260,864/27,883	HR, 0.53 (0.49–0.58)	<0.001
Butt et al.[90] (2015)	USA	HCV	Cohort study	7,248	HR, 0.52 (0.35–0.78)	<0.001
Mohanty et al.[91] (2016)	USA	HCV	Retrospective cohort study	2,747/173	HR, 0.42 (0.27–0.64)	<0.001
Simon et al.[92] (2016)	USA	HCV	Cohort study	9,135/239	HR, 0.85 (0.47–1.53)	0.580
Li et al.[93] (2020)		HBV, HCV	Meta-analysis	13 studies (519,707)	RR, 0.54 (0.44–0.66)	<0.001
Wong et al.[94] (2021)		HBV, HCV, LC	Meta-analysis	13 studies (1,742,260)	HR, 0.57 (0.52–0.62)	0.060
Lee et al.[36] (2017)	Taiwan	NAFLD	Population-based cohort study	18,080/41	HR, 0.29 (0.12–0.68)	0.005

HCC, hepatocellular carcinoma; CI, confidence interval; HBV, hepatitis B virus; HR, hazard ratio; HCV, hepatitis C virus; LC, liver cirrhosis; RR, risk ratio; NAFLD, non-alcoholic fatty liver disease.

remains unclear. In the meantime, for the prevention of cardiovascular diseases, there is no need to apply different criteria for starting statins in patients with CLD and the general population.

SYNERGISTIC EFFECTS OF METABOLIC FACTORS

Several studies have examined whether metabolic factors have a synergistic effect on the development of HCC in patients with CLDs. In a study on patients with cirrhosis, the HR for obesity alone was 2.1, and the HR for DM alone was 1.4. The coexistence of obesity and DM (compared to BMI <25 kg/m^2 and no diabetes) increased the risk of HCC by >6 times.[60] However, this study only adjusted for age, sex, and a cirrhosis etiology. In a Taiwanese study on patients with HBV, a single metabolic factor did not increase the risk of HCC; however, the coexistence of three or more metabolic factors increased the risk of HCC.[98] In a retrospective study on 271,906 patients with NAFLD in the USA, obesity, hypertension, diabetes, and dyslipidemia had no clear synergistic effects on the composite occurrence of HCC and LC.[25] In a recent study on Korean patients with HBV, a higher number of metabolic syndrome components was negatively associated with the risk of liver cancer.[86] Overall, the evidence of a synergistic interaction among metabolic factors is insufficient. Further studies are needed to elucidate this issue.

LIMITATION

First, only a limited number of studies are available on the association between lipids other than TC and anti-diabetic agents and HCC development, although the number of studies conducted on patients with CLDs is increasing. Second, statistical models seemed to adjust for potential mediators of the effects of metabolic factors in most studies that included information on the associations between metabolic factors and HCC. For example, it is inadequate to adjust for diabetes, blood pressure, and cholesterol when examining the association between obesity and cardiovascular disease/mortality because these factors are considered as mediators of the effects of obesity.[99] Although this is understandable, since most of the studies were not specifically examining metabolic factors. Nonetheless, these studies may not accurately capture the specific associations of metabolic factors. Third, it is difficult to compare potential regional differences (such as between Western and Eastern populations) in this association. For example, most studies on HBV have been conducted in East Asia, while NAFLD and non-viral LC have been mainly studied in the Western population. Finally, most of the previous studies reviewed were retrospective studies, which are more prone to bias than prospective studies. More prospective, large-scale studies are needed to better capture these associations.

CONCLUSION

Comorbid DM increases the risk of HCC in patients with CLD. However, at least some of the effects of DM on HCC reflect the underlying severity of CLDs (reverse causality), especially for HCV and NAFLD. Obesity may increase the risk of HCC in patients with CLD, although the magnitude of the effect is weaker than that in the general population. Although obesity increases the risk of NAFLD, there is limited evidence on whether obesity increases the HCC risk in patients with NAFLD. Low lipid levels, especially TC, and perhaps LDL-C and TG, rather than dyslipidemia, are associated with an increased risk of HCC. TC levels may be used as a marker of liver disease severity associated with the risk of HCC. Whether statins or anti-diabetic agents have a preventive effect against HCC in patients with CLD remains unclear.

Authors' contribution

Study concept and design: Baek Gyu Jun and Sang-Wook Yi; Data analysis and interpretation: Baek Gyu Jun, Hwang Sik Shin, and Sang-Wook Yi; Wrote the paper: Baek Gyu Jun, Sang-Wook Yi, and Hwang Sik Shin; All authors have read and approved the final version of the manuscript.

Conflicts of Interest

The authors have no conflicts to disclose.

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