Hepatitis B virus-Associated Intrahepatic Cholangiocarcinoma Has Distinct Clinical, Pathological and Radiological Characteristics: A Systematic Review

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ABSTRACT

Intrahepatic cholangiocarcinoma (ICC) is a rare hepatic malignancy with a poor prognosis. It is known that Hepatitis B is both a risk factor and a prognosis factor for ICC. However, little is known about the clinical, pathological and radiological characteristics of ICC patients with hepatitis B virus (HBV) infection. A systematic review of relevant literature was performed using PubMed and EMBASE databases. HBV-associated ICC revealed several unique and interesting features, it was found to have higher alpha-fetoprotein (AFP), cancer antigen 19-9 (CA 19-9) levels, capsule formation and cirrhosis, but associated with lower lymph node metastasis. Radiologically, it was shown that some of the HBV-associated ICC tend to mimic atypical radiological features of HCC. Pathologically, it was found that *HBx* protein gene expression was associated with HBV-associated ICC, and that hepatic progenitor cells may be an alternative origin for HBV-associated ICC. In conclusion, HBV-associated ICC has distinct clinical, pathological and radiological characteristics, but further research is needed to further understand the pathogenesis of the disease.

Key words: hepatitis B virus, intrahepatic cholangiocarcinoma, clinical characteristics, radiological features, pathogenesis

Abbreviations:

ICC - Intrahepatic cholangiocarcinoma;
HBV - hepatitis B virus;
AFP - alpha-fetoprotein;
CA 19-9 - cancer antigen 19-9;
HR - hazard ratio;
CI - confidence interval;
OS - overall survival;
DFS - disease-free survival;
ALT - aminotransferase;
AST - aspartate aminotransferase;
GGT - gamma-glutamyl transferase;
AFP - alpha-fetoprotein;
CK19 - cytokeratin 19;
CEUS - contrast-enhanced ultrasound;
LI-RADS - Liver Imaging Reporting and Data System;
MAPK - mitogen-activated protein kinase;
HPCs - Hepatic progenitor cells;
ADC - apparent diffusion coefficient;
DWI - diffusion weighted imaging;
NCAM - neural cell adhesion molecule;
BCL-2 - B-cell lymphoma 2;

INTRODUCTION

Intrahepatic cholangiocarcinoma (ICC) is a rare but aggressive malignancy originating from the bile ducts inside the liver, representing 10-15% of all primary hepatic malignancies (1). As ICC is initially asymptomatic, there are challenges in obtaining an early diagnosis, resulting in a low resection rate and a poor prognosis, with a median survival of less than 24 months, and 1- and 2-year

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survival rates of 25% and 13%, respectively (2,3).

The liver flukes *Clonorchis sinensis* and *Opisthorchis viverrini*, as well as chronic biliary inflammation conditions such as primary sclerosing cholangitis, Caroli's disease, hepatolithiasis are established major risk factors of the disease (4,5). Other risk factors include biliary duct cysts, toxins such as thorotrast (thorium dioxide)(6).

Hepatitis B is a potentially life-threatening liver infection most prevalent in Asia Pacific and sub-Saharan African regions in the world (7). Hepatitis B virus (HBV) has been recently shown to be a significant risk factor for development of ICC. In a meta-analysis of studies evaluating the risk of HBV infection and ICC in 2012, the pooled risk ratio (2.66; 95%CI =1.97 to 2.60) was significantly higher for those individuals who were HBV-positive compared with those who were HBV-negative (8). In a recent large scale population based study in the United States, Hepatitis B was stated as a risk factor of ICC with an odds ratio of 2.97 (95%CI =1.97 to 4.46) (9).

It has been suggested that HBV-associated ICC may have unique features such as distinct clinical, pathological and radiological characteristics and HBV-associated ICC may have a different pathobiology when compared to the non-HBV-associated ICC. The literature is limited in this area, therefore, we performed a systematic review to better evaluate the clinical, pathological and the radiological characteristics of HBV-associated ICC.

METHODS

The study was performed in line with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (10).

Literature Search

We performed a systematic search of the pertinent literature, the databases of EMBASE and Medline were reviewed from Jan 1998 to Sept 2018 for relevant English language studies. The literature search used the following terms: Hepatitis B, cholangiocarcinoma and their synonyms and abbreviations (Table 1). We also examined the reference lists of published review articles and meta-analyses to identify other eligible studies.

Study Selection

One investigator (HHN) performed the initial

searching, extraction of data, and quality assessment, which was subsequently reviewed by all other involved authors. Studies were assessed on the basis of their title or abstract and those studies which appeared to meet the eligibility criteria were selected for full text review. We sought studies reporting at least one of the following aspects of HBV-associated ICC: prognosis and clinical, radiological, and pathological characteristics. Small series assessing fewer than 20 patients, as well as studies without clinical, radiological or pathological data were excluded. Studies reporting on heterogeneous series of patients with intrahepatic and other types of cholangiocarcinoma (e.g., hilar cholangiocarcinoma, mixed cholangio-hepatocellular carcinoma) were also excluded. In addition, studies not differentiating between Hepatitis B or C virus were excluded. Previous systematic review and meta-analysis were reviewed, but not included in the final analysis. Conference abstracts that did not proceed to publication in peer-reviewed journals were not included in the review.

Data extraction

Relevant information from eligible publications were extracted. All publications included were reviewed by the senior author (SYL). For each study, the following data were captured: (1) authorship and year of publication; (2) the study population and size; (3) the study design; (4) the clinical parameters, including age, gender, clinical stage; (5) clinical characteristics (if applicable) including prognosis [hazard ratio (HR) and 95% confidence interval (CI) of HBV infection for overall survival (OS) and disease-free survival (DFS)]; (7) pathological characteristics (if applicable) including biomarkers; and (8) radiological characteristics (if applicable).

RESULTS

Literature Search and study characteristics

The publication search and selection process is illustrated in Fig. 1. 732 potentially eligible papers were retrieved in the initial search. After review of the titles and abstracts, 646 publications were excluded. 86 full articles were captured, among which 53 were finally

Table 1 - Terms used in literature search

Hepatitis B	Cholangiocarcinoma
HBV	bile duct neoplasms
CHB	ICC
	Biliary tract cancers

Figure 1 - PRISMA flow diagram on literature review strategy

excluded due to the insufficient information on HBV status, or lacking relevant data on clinical, pathological or radiological features. Finally, our review enrolled a total of 33 studies. Of these publications chosen for further assessment, 20 investigated the correlation of HBV-associated and non-HBV-associated ICC and their clinical characteristics, and 7 studied the relationship of HBV and its pathological features, and 10 correlated HBV virus status and the radiological features.

The main characteristics of each enrolled study are summarized in *Table 2*. The publications included in our study were published between 1991 and 2017. In total, 20 studies have reported clinical characteristics between HBV and non-HBV associated ICC. For clinical characteristics, 10 studies enrolled less than 100 cases, and 10 studies enrolled more than 100 cases. The mean age of the enrolled patients ranged from 51 to 62 years in these studies.

Clinical characteristics of HBV-associated ICC

Clinical characteristics of HBV-associated ICC has been established from multiple studies. Firstly, for biochemical markers, there was a study reporting HBV infection was associated with higher alanine aminotransferase (ALT) levels, and 2 studies with higher aspartate aminotransferase (AST) levels (11,12). One study has reported the HBV-associated group having lower gamma-glutamyl transferase (GGT) levels, but other studies showed no differences in GGT levels between HBV-associated and non-HBV-associated ICCs (11-14). The rest of the studies did not find any significant differences liver enzymes levels between the 2 groups (13-16). All studies that reported bilirubin levels has similar levels between HBV-associated and non-HBV-associated ICCs (11,12,14-16). All studies that reported alpha-fetoprotein (AFP) levels concluded that HBV-associated ICC is associated with

Table 2 - Main characteristics of all the studies included in the systematic review

Study	Study country	Patient number	Mean age	Gender (M/F)	Clinical staging	Characteristics	Study design
Zhou et al. (11)	China	317	53.1 ± 10.5	223/94	NA	Clinical	Retrospective
Zhou et al. (12)	China	155	55.0 ± 10.7 (27.0-76.0)	102/53	NA	Clinical, Pathological	Retrospective
Ahn et al. (15)	Korea	292	59±10	196/96	I-IV	Clinical	Retrospective
Tao et al. (13)	China	97	58.6 (37-78)	59/38	I-IV	Clinical	Retrospective
Wang et al. (16)	China	606	53.7 (44.5-62.3)	401/205	I-IV	Clinical	Retrospective
Wu et al. (14)	China	138	55	107/31	I-IV	Clinical	Retrospective
Peng et al. (17)	China	62	NA	NA	NA	Clinical	Retrospective
Jeong et al. (18)	China	106	60 (35-82)	62/44	I-IV	Clinical	Retrospective
Jiang et al. (19)	China	76	51.0 (40.0-60.0)	53/23	I-IV	Clinical	Retrospective
Liu et al. (20)	China	81	59.0 (30.0-76.0)	48/33	NA	Clinical	Retrospective
Zhang et al. (21)	China	40	56.0 (34.0-74.0)	24/16	I-IV	Clinical, Pathological	Retrospective
Luo et al. (22)	China	1333	54.1 ± 10.9	912/421	I-IV	Clinical	Retrospective
Pan et al. (23)	China	72	53.26 ± 11.05	29/43	I-III	Clinical	Retrospective
Asayama et al. (24)	Japan	67	62.0 (33.0-83.0)	36/31	NA	Clinical, Pathological	Retrospective
Zhang et al. (25)	USA, Europe, Australia, Asia	883	59 (45-69)	497/386	I-IV	Clinical	Retrospective
Zhang et al. (26)	China	127	55.5 ± 11.8	102/25	I-IV	Clinical	Retrospective
Uenishi et al. (27)	Japan	35	61.0 (35.0-83.0)	11/24	II-IV	Clinical	Retrospective
Horino et al. (28)	Japan	31	65(26-81)	21/13	NA	Clinical	Retrospective
Li et al. (29)	China	283	55.0 (18.0-79.0)	174/109	I-IV	Clinical	Prospective
Wang et al. (30)	China	110	NA	NA	NA	Pathological	Retrospective
Zhou et al. (31)	China	54	49(23-73)	36/18	NA	Pathological	Retrospective
Huang et al. (33)	China	71 (out of 612)	55(29-77)	51/20	NA	Radiological	Retrospective
Kang et al. (34)	China	50	62.3 (42-76)	41/9	NA	Radiological	Retrospective
Kim et al. (35)	Korea	26 (out of 105)	60.6 (40-75)	22/4	NA	Radiological	Retrospective
Li et al. (36)	China	84	50 (24-75)	66/18	NA	Radiological	Retrospective
Sheng et al. (37)	China	28 (out of 162)	60	19/9	NA	Radiological	Retrospective
Galassi et al. (40)	Italy	34	64.2 ± 8.4	16/8	NA	Radiological	Retrospective
Li et al.(41)	China	64	52.84±11.58	NA	NA	Radiological	Retrospective
Yuan et al. (42)	China	96	NA	NA	NA	Radiological	Retrospective
Iavarone et al. (38)	Italy	32	62 (45-81)	22/10	NA	Radiological	Retrospective
Rimola et al. (39)	Spain	25	62 (49-79)	17/8	NA	Radiological	Retrospective

higher AFP levels (11-14,16,17). All but one study that reported cancer antigen 19-9 (CA 19-9) levels reported that HBV-associated ICC is associated with relatively lower CA 19-9 levels compared to non-HBV-associated ICCs (11-17).

For tumour characteristics, among the 6 studies that reported cirrhosis status, 4 studies showed that there was a higher prevalence of liver cirrhosis amongst HBV-associated ICC patients (11-14,16,17). Three studies also stated that there were higher levels of capsule formation but Peng et al. reported no statistical significance between the 2 groups (11,12,14,17). For lymph node metastasis, 2 studies reported lower lymph node metastasis for HBV-associated ICC, but 6 other studies reported no statistical significance between the 2 groups (11-18). All studies reported no difference in

vascular invasion (11-18) or perineural invasion (11,12, 15) between the 2 groups. There was conflicting evidence for tumour differentiation. Zhou et al. reported that HBV-associated ICC was associated with poor differentiation, and Wu et al. reported non-HBV-associated ICC was associated with better differentiation, whereas all other studies reported no statistical significance between the 2 groups (11-18). Peng et al. also reported that HBV-associated ICC was associated with higher neutrophilic infiltration, but this finding was not reported in any other studies (17).

In addition, several studies evaluated the correlation between the presence of HBV infection and the prognosis of patients with ICC (*Table 3*). Some of these studies suggested HBV infection as a favourable prognostic factor in patients with ICC (12,14,16,19-24).

Table 3 - Studies showing survival outcomes in HBV-associated ICC

Study	No. of patients (n): HBV-ICC/non-HBV-ICC	OS HR (95% CI)*	Prognosis of HBV-ICC compared to non-HBV-ICC
Zhou et al. (12)	29/11	0.46 (0.19, 1.09)^	Favourable
Ahn et al. (15)	37/255	0.51(0.22,1.21)	No difference
Wang et al. (16)	519/87	0.37 (0.26,0.53)	Favourable
Wu et al. (14)	46/81	0.49(0.34,0.71)	Favourable
Jiang et al. (19)	34/42	0.88(0.72,1.04)^	Favourable
Liu et al. (20)	99/41	0.49(0.34,0.71)	Favourable
Zhang et al. (21)	29/11	0.46 (0.19, 1.09)^	Favourable
Luo et al. (22)	608/752	0.73 (0.63,0.85)	Favourable
Pan et al. (23)	34/38	0.426(0.232-0.785)	Favourable
Asayama et al. (24)	8/55	0.64(0.70,0.83)	Favourable
Zhang et al. (25)	201/682	Not significant when adjusted	No difference
Zhang et al. (26)	46/81	0.86(0.58,1.27)	No difference
Uenishi et al. (27)	3/29	0.70(0.22,2.24)	No difference
Horino et al. (28)	8/23	Not significant	No difference
Li et al. (29)	174/109	0.88 (0.59,1.290)	No difference

*if applicable; ^significant in univariate analysis

However, there were a few studies that reported HBV infection has no significant impact on the survival outcome of patients with ICC after hepatic resection, especially after propensity score matching (15,25-29).

Pathological characteristics of HBV-associated ICC

There has been postulation that *HBx* gene is key for the pathogenesis of ICC for HBV-associated cholangiocarcinoma. Wang et al. discovered the presence of HBx gene in different liver cancers, including cholangiocarcinoma (30). This has sparked the interest of how the gene is involved in the pathogenesis of the disease. Zhou et al. (31) reported that *HBx* expression was found in most of the cholangiocarcinoma tissues, and it was associated with elevated serum AFP. However, they also reported that only 33.3% of HBV-related ICCs exhibited p53 protein expression and it was not correlated with HBx gene expression (31).

Another study has shown that there was an increased co-expression of neural cell adhesion molecule (NCAM) and B-cell lymphoma 2 (BCL-2) in HBV-associated ICC (24). NCAM is a potential hepatic progenitor cell marker (32), which brings the speculation on a possible alternative origin of ICC. Two other studies also showed a lower cytokeratin 19 (CK19) expression on HBV-associated ICC (11,12).

Other prognosis markers have also been evaluated in some studies. In one study, HBV-associated ICC was associated with lower human epidermal growth factor receptor 2 (HER2) expression, where HEP1 and MUC1

expression was not associated with HBV positivity (16). These data suggested the potential role of such markers on carcinogenesis and possibly prognosis.

Radiological characteristics of HBV-associated ICC

The radiological characteristics of cholangiocarcinoma are well established. Mass forming cholangiocarcinoma are typically hypoattenuating relative to the normal liver tissues in pre-contrast scans, and heterogeneous peripheral early enhancement with gradual enhancement centrally in the postcontrast scans (33,34). This is in contrast to other primary liver cancers such as HCC, which typically show arterial phase hyperenhancement and washout in the portal venous and delayed phases.

However, the radiological characteristics of ICCs in patients with hepatitis B and cirrhosis are not clear, as there are no studies that directly compare the radiological characteristics of HBV-associated ICC and non-HBV-associated ICC (Table 4). However, multiple studies observed arterial enhancement with washout in the delayed phase in a small portion of ICC tumours (6-15.3%) on multiphase contrast Computed Tomography (CT) and Magnetic Resonance (MR) imaging, similar to the washout pattern of HCC (33-37) (Fig. 2). Most of the studies has associated this finding with liver cirrhosis in ICC, but HBV infection is present in most of the patients in these studies as well. They concluded that the arterial enhancement pattern of ICCs seems to be affected by the underlying liver disease, i.e.

Table 4 - Summary of the characteristics of HBV-associated ICC compared to non-HBV-associated ICC

	HBV-ICC	Non-HBV-ICC	Reference
<i>Biochemical markers:</i>			
ALT	↑ -	↓ -	(11) (12-16)
AST	↑ -	↓ -	(11, 12) (13-16)
GGT	↓ -	↑ -	(14) (11-13)
Bilirubin	-	-	(11, 12, 14-16)
AFP	↑	↓	(11-14, 16, 17)
CA 19-9	↓ -	↑ -	(11-14, 16, 17) (15)
<i>Tumour characteristics:</i>			
Cirrhosis	↑ -	↓ -	(11, 12, 14, 17) (13, 16)
Capsule formation	↑ -	↓ -	(11, 12, 14) (17)
Lymph Node Metastasis	↓ -	↑ -	(12, 14) (11, 13, 15-18)
Vascular Invasion	-	-	(11-18)
Perineural Invasion	-	-	(11, 12, 15)
Tumour differentiation	↓ ↑ -	↑ ↓ -	(12) (14) (11, 13, 15-18)
Neutrophilic infiltration	↑	↓	(17)
Prognosis	↑ -	↓ -	(12, 14, 16, 19-24) (15, 25-29)
<i>Pathological characteristics:</i>			
NCAM and bcl-2 co-expression	↑	↓	(24)
CK19 expression	↓	↑	(11, 12)
HER2 expression	↓	↑	(16)
HEP1 expression	-	-	(16)
MUC1 expression	-	-	(16)

Legend: ↑ = increased/ better, ↓ = decreased/ worse, - = not significant difference and/or limited evidence, ALT = Alanine Aminotransferase, AST = Aspartate Aminotransferase, GGT = Gamma-Glutamyl Transferase, AFP = Alpha-Fetoprotein, CA 19-9 = Cancer Antigen 19-9, NCAM = Neural cell adhesion molecule, bcl-2 = B-cell lymphoma 2, HER2 = human epidermal growth factor receptor 2

cirrhosis and/or HBV positivity. Interestingly, two studies that had no ICC tumours displaying “HCC-like” washout pattern did not include any HBV-positive cases in their patient cohort (38,39). In fact, the aetiology of those patients having cirrhosis-related ICC were mostly due to Hepatitis C infection or alcohol consumption (38,39). It is possible to postulate that HBV-associated ICC displays radiological features less typical of non-HBV associated ICC, but this warrants further investigation.

For contrast-enhanced ultrasound (CEUS), there were a few studies that reported a significant portion of patients with HBV-associated ICC having heterogeneous hyperenhancement with early washout, which was then thought to mimic HCC (40-42). However, the recent CEUS LI-RADS (Liver Imaging Reporting and Data System) published by the American College of Radiologists has recognised early

washout on CEUS as being more typical for ICC than HCC which more typically show later and milder washout (43). The different washout behaviour between contrast agents for CT/MRI and that for CEUS is that the former accumulate in the interstitial spaces of tumours such as ICC in the late phase, whilst CEUS contrast stays only in the liver/tumour sinusoids resulting in marked and early washout (43). These earlier studies did not use the strict newer criteria of differentiation between HCC and ICC on CEUS, so their conclusions may not be accurate.

DISCUSSION

This is the first systematic review that explored the differences between clinical, pathological and radiological characteristics of ICC with and without HBV

Figure 2 - (Top) Contrast-enhanced CT scan of a non-HBV-associated ICC patient showing (a) hypoenhancing tumour with peripheral arterial enhancement on the arterial phase, and (b) progressive centripetal enhancement on the venous phase. (Bottom) In contrast, contrast-enhanced CT scan of a HBV-associated ICC patient showing (c) early arterial enhancement followed by (d) rapid washout on the portal venous phase

infection, whereas previous studies had only focused largely on prognosis and other characteristics. From the systematic review, it suggests that there are some clinical characteristics of HBV-associated ICC that may be distinct from non-HBV-associated ICC. Specifically, HBV-associated ICCs may have a higher AFP and CA 19-9 levels, tend to have tumour capsule formation, cirrhosis and a lower rate of lymph node metastasis. Two large meta-analyses have shown that HBV was associated with better prognosis, which is consistent with the majority of the studies included in this systematic review, but this association warrants further prospective investigation (44,45).

For pathological characteristics, it was demonstrated that *HBx* gene was expressed in cholangiocarcinoma tissues in HBV-positive patients (30). Additional research using in vivo zebrafish showed that the pSmad3L oncogenic pathway was activated in *HBx*-induced ICC (46). Moreover, phosphorylation of p38 mitogen-activated protein kinase (MAPK) and p44/42 mitogen-activated protein kinase (ERK1/2) was observed in the pathogenesis of ICC in the zebrafish model, indicating the association with transforming

growth factor beta 1 (TGF- β 1) signalling pathway in HBV-associated ICC. This is similar to HCC, where HBV would disrupt the TGF- β 1 signalling through different pathways and act as an oncogene (47-49).

Using a cell culture model, Zou et al. reported that *HBx* transfection induces human telomerase reverse transcriptase (hTERT) mRNA expression in human cholangiocytes in cell culture, causing cell immortality. These non-human studies provided additional information and suggested that *HBx* may directly be involved in the carcinogenesis of cholangiocytes, which acts as an alternative pathway (50).

Hepatic progenitor cells (HPCs) are bipotential cells residing in normal liver. They possess the potential to differentiate toward the hepatocytic or biliary phenotype. As reservoir cells, HPCs were shown to be activated in a wide range of liver diseases and in conditions such as submassive necrosis, chronic viral hepatitis, and fatty liver disease (51-55). Cancer progression is thus often accompanied by HPC activation, but mechanisms initiated by injured hepatocytes remain still elusive.

Traditionally, it has been thought that ICC was

caused by intrahepatic biliary epithelial cells. However, recently it has been debated that ICC could originate from multiple cell types. Some studies have shown that cholangiocarcinoma can originate from HPCs in some animal models (56,57). Moreover, in some recent transcriptomic profiling analyses for liver cancers, it has been reported that some ICC subtypes with poor prognosis would present with hepatic stem-like gene signatures (58).

However, the proportion of ICC cases with a stem cell origin remains unclear. For Hepatitis B, increased expression of NCAM in human HBV-associated ICC tumours suggested that hepatic progenitor cells play an important role in the pathogenesis of the cancer (24). In a study focusing on cholangiocellular carcinoma, a subset of intrahepatic cholangiocarcinoma, a high level of expression of NCAM was reported in HBV-associated ICC, and thus some have postulated HPCs as a possible origin of ICC (59).

Studies have also investigated on the genome sequencing of ICC. The tumour pathogenesis of ICC is often heterogeneous, with multiple overlapping and lower-penetrance driver genes and a diverse signalling pathway. In a recent genetic study on ICC, it was found that KRAS mutation was predominately enriched in HBV-negative ICCs compared to HBV-positive cases (60). The same study also suggested that KRAS mutation was associated with poorer prognosis, thus the association of HBV-associated ICC with better prognosis could be due to the difference in mutation signatures.

In addition, a separate study has postulated a p53-mediated pathway being a main contributor to the tumour genesis of ICC if the patient is viral hepatitis positive (61). HBV-associated hepatocellular carcinoma (HCC) has also a similar inactivation of p53-mediated cell cycle pathway for a substantial number of patients, which may arise on non-cirrhotic livers (62,63). Some other studies have shown increased expression of N-cadherin and cholangiocellular differentiation in viral hepatitis, but N-cadherin expression did not appear to be correlated with prognosis in ICC.

Changes of the tumour immune microenvironment is important in the pathogenesis of cancer, especially in virus-mediated cancers such as HCC, lymphoma and ICC. Current studies indicate that the neutrophil to lymphocyte ratio (NLR) may be a useful biomarker of long-term outcomes in patients with cholangiocarcinoma (64-66), but not much is known about how HBV affects the tumour immune microenvironment in ICC. Studies have shown that the HBV-associated HCC immune microenvironment was more immunosuppressive

and exhausted than the non-HBV-associated HCC microenvironment, but not much is known for the immunological microenvironment in HBV-associated ICCs (67). The chronic inflammation and changes in immunological microenvironment induced by HBV infection may be important in the pathogenesis for HBV-associated ICC, and further research is needed in exploring such hypotheses.

Early radiological diagnosis is important for the management for ICC. Misdiagnosis is not ideal as treatment between HCC and ICC can be very different. Some patients with HBV-associated ICC have arterial enhancement with washout in the delayed phase in CT/MR imaging, which is not seen in non-HBV-associated ICCs (*Fig. 2*). This phenomenon would be attributable to the changes in circulatory patterns due to portal hypertension, but there is limited information available on these possible changes in the literature. One way to differentiate between HBV-positive ICCs and HCCs is the use of apparent diffusion coefficient (ADC) derived from a mono-exponential model using diffusion weighted imaging (DWI) in MRI, but this method requires specific DWI imaging and is subject to further validation (68). Further research is needed to understand more on distinct radiological patterns on ICC tumours under the influence of HBV infection and cirrhosis.

CONCLUSION

In conclusion, we have shown that HBV-associated ICC has potentially distinct clinical, pathological and radiological characteristics compared to non-HBV-associated ICC as their pathobiology may be diverse. Moreover, multiple studies showed a possible origin of hepatic progenitor cells specific to HBV-associated ICC, thus it is plausible that ICC and HCC may hold common disease process for carcinogenesis under the effects of HBV (59). Future biological studies, especially focusing on the tumour microenvironment and radiological patterns are warranted to better understand biological mechanisms and behaviours of HBV-associated ICC, so as to improve diagnosis and help the establishment of specific subtype-targeting treatments.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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