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Metabolism and Target Organ Damage

Review

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Metabolic primary liver cancer in adults: risk factors and pathogenic mechanisms

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Abstract

Primary liver cancer (PLC) is a heterogeneous group of disorders arising with the background of chronic liver disease (CLD) owing to varying etiologies. PLC carries a high lethality rate and a substantial epidemiological, clinical, and financial burden, which is projected to escalate. The two most common PLC histotypes in adults are hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC); the latter is sub-classified as either intrahepatic CC or extrahepatic CC. Over recent decades, there has been a decline of viral CLD accompanied by an increase in dysmetabolic CLD, resulting in PLC becoming relatively more common in Western countries. Metabolic co-morbidities are risk factors and co-factors for HCC and (increasingly) CC. Complex immunological, cellular, pro-inflammatory, molecular, and genetic processes in the systemic dysmetabolic milieu increase PLC risk. Improved understanding of these mechanisms requires close surveillance and early diagnosis of at-risk patients while paving the way for personalized medicine, chemoprevention, and innovative management of metabolic PLC.

Keywords: Cholangiocarcinoma, epidemiology, hepatocellular carcinoma, metabolic syndrome, NAFLD, pathogenesis

BACKGROUND

Definitions and burden

Primary liver cancer (PLC) is a highly lethal malignancy becoming more common worldwide[1,2] and

imposes substantial epidemiological, clinical, and financial burdens. PLC is the sixth or seventh most frequently occurring cancer globally, and the second to the fourth most common cause of cancer mortality; its incidence has been rising in many countries and is projected to continue rising[1,3]. PLC commonly arises with the background of underlying chronic liver disease (CLD), and (among those with CLD) PLC increases health care expenses while worsening quality of life[4].

Risk factors

Etiologically, PLC is a heterogeneous group of disorders. In adults, the two most common PLC histotypes are hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC); the latter is classified as either intrahepatic CC (ICC) or extrahepatic CC (ECC)[5]. The differences between ICC and ECC reflect varying epidemiological risk factors[6].

While HCC arises from hepatocytes, CC originates from cholangiocytes that line intrahepatic or extrahepatic bile ducts[1]. After HCC, CC is the second most common PLC characterized by late diagnosis and fatal outcomes[7]. Combined hepatocellular-cholangiocellular carcinomas (CHCs) exhibit mixed clinico-pathological and imaging features from HCC and CC[8]. CHCs are rare and account for fewer than 1% of all PLCs[5]; they are thought to derive from bipotent hepatic progenitor cells that possess the dual potential for differentiation (hepatocellular and cholangiocellular)[8]. However, histological features of PLC do not necessarily mirror its cell of origin, highlighting metaplasia and cell plasticity, i.e., trans-differentiation[9].

HCC

The most critical risk factor for HCC development is cirrhosis of any etiology, which is present in 70% to 90% of cases[10]; and HCC ranks as the leading cause of mortality in patients with cirrhosis[11]. The best-defined risk factors for HCC development include chronic viral hepatitis and lifestyle-related risk factors whose distribution varies regionally[12]. Viral hepatitis and the consumption of cereals contaminated with aflatoxin are responsible for most HCC cases in Asia and Africa[12]. These regions also exhibit robust sex disparities regarding lifestyle-related risk factors, particularly tobacco smoking[12]. Conversely, alcohol drinking and obesity account for a more significant percentage of cases in North America and Europe[12]. Cirrhosis-related HCC risk factors include genetic hemochromatosis (patients with cirrhosis occurring in the setting of hemochromatosis are exposed to a particularly elevated high risk of HCC, given that approximately one in two will develop HCC during their lives)[13]; autoimmune liver disease [i.e., primarybiliarycholangitis (PBC) and autoimmune hepatitis (AIH); hereditary tyrosinemia; alpha-1-antitrypsin deficiency; and non alcoholic fatty liver. In addition to transmissible and lifestyle-related risk factors, family occurrence and sex disparity are HCC typicalfeatures][14,15].

Cholangiocarcinoma

Similar to HCC, cirrhosis of various etiologies and chronic viral hepatitis due to either HCV (particularly in western countries) or HBV (especially in Asia) are risk factors for CC development (especially ICC)[5]. A recent diagnosis (i.e., one year) of PSC is a risk factor for CC development, particularly in younger individuals and elderly males with large-duct PSC and possibly concomitant ulcerative colitis, whereas the risk decreases after that[5,16]. Caroli's disease (with other bile duct disorders) is a risk factor for early-onset CC[5,7]. The CC high incidence in South-Eastern Asian countries has been attributed to the high circulation of hepatobiliary flukes (*Opisthorchis viverrini* and *Clonorchis sinensis*) and genetic predisposition[5]. CC risk factors include hepatolithiasis and bacterial cholangitides occurring after biliary-enteric drainage because of intestinal bacteria colonization and infections[5-7]. Finally, polymorphisms in genes encoding proteins participating in cell DNA repair, cellular protection against toxins, or immuno-surveillance have increased CC risk[6]. Diabetes and obesity have been examined as possible risk factors for CC, although data were

deemed preliminary in previous reviews[5,6].

CHC

CHC is a rare type of PLC, typically featuring dual hepatocytic and biliary differentiation within the same lesion and accounting for fewer than 5% of all PLCs[17-19]. Although CHC is a distinct PLC sub-type, it shares similar risk factors with other PLCs, including chronic viral hepatitis, cirrhosis, male sex, and flukes; this feature accounts for the geographical distribution of CHC[20].

CHC exhibits clinical and imaging features similar to classical HCC and CC[16,18]; i.e., it appears as an intrahepatic heterogeneous focal liver disease with imaging and contrast-enhancement behavior resembling either HCC or CC, depending on the prevalent subtype of the mass[17-19].

Because CHC diagnosis requires accurate evaluation of imaging characteristics and histological and immunohistochemical features, the quality of the liver biopsy sample is critical. This feature makes CHC diagnosis challenging before surgery, and disease prevalence is probably underestimated[17-19]. CHC is an aggressive disease that carries a poor outcome and worse survival rate than HCC[18,19]

Rationale and aim

In recent years, PLC research and practice have profoundly evolved due to the evolving CLD scenario. HBV infection has declined since the introduction of vaccination campaigns in many countries and oral nucleoside/nucleotide analogs for chronic HBV treatment[21,22]. Treating chronic hepatitis owing to HCV has become possible thanks to direct-acting antivirals (DAAs), while no vaccine against HCV yet exists[23]. Compared to interferon-based regimens, DAAs disrupt the HCV replication cycle and clear the infection in up to 90% of patients with shorter treatment duration, fewer adverse events, higher adherence rates, and improved liver-related and cardio-metabolic outcomes[24].

The decline of viral CLD has been paralleled by an increase in CLD owing to common metabolic disorders such as metabolic syndrome (MetS) and its features: obesity, type 2 diabetes, arterial hypertension, and dyslipidemia[25]. The metabolic fatty liver syndromes (i.e., NAFLD/NASH) have a mutual and bi-directional association with the MetS, forming a cause-and-effect relationship[26]. As a result of these epidemiological evolutions, the etiology of CLD has dramatically changed, and NAFLD-HCC/NASH-HCC (the prototypic metabolic PLC) is becoming increasingly common in Western countries[9,27]. These evolving epidemiological patterns call for increased awareness regarding the role played by metabolic risk factors in PLC development. Therefore, the present review illustrates the epidemiological grounds and pathogenic mechanisms in metabolic PLC by covering topics relating to PLC occurring in association with common metabolic disorders.

Our review locates a broader scenario of escalating interest and concern regarding the association of various cancer types with metabolic disorders, which is "a preventable epidemic"[28-30]. We try to provide clinicians and researchers with a comprehensive overview while critically discussing the primary epidemiological, clinical, and pathogenic findings supporting the association of metabolic disorders with PLC (hence "metabolic PLC"). These data may pave the way for prevention, early diagnosis, and innovative treatment options.

EPIDEMIOLOGY OF PLC ASSOCIATED WITH METABOLIC RISK FACTORS

HCC

Principal studies: non-cirrhotic HCC vs. cirrhotic HCC

Epidemiological, etiological, molecular, histopathological, imaging and clinical features (namely presentation, management, and outcomes) of non-cirrhotic HCC *vs.* cirrhotic HCC are distinct; for example, while a higher tumor burden is typically found at diagnosis, non-cirrhotic HCCs carry better overall survival and disease-free survival than cirrhotic HCCs[31-37]. NAFLD-HCC is the most common etiology of non-cirrhotic HCC. Supporting this notion, a multi-center US study from 2000 to 2014 found non-cirrhotic HCCs in nearly 12% of 5,144 HCC patients and reported that NAFLD accounted for more than a quarter of non-cirrhotic HCCs[38]. Since 2018, two seminal studies have developed this topic. Stine *et al.* performed a systematic review with meta-analysis and reported that the prevalence of non-cirrhotic HCCs among those with NASH was significantly higher than among non-cirrhotic HCC owing to other etiologies (38.0% *vs.* 14.2%, $P < 0.001$)[39]; and that individuals with non-cirrhotic NASH had a higher risk of developing HCC than non-cirrhotic subjects with liver disease owing to other (i.e., non-NAFLD) etiologies (OR 2.61, 95%CI: 1.27-5.35, $P = 0.009$). Confirming these findings, Tarao *et al.* demonstrated that NASH was associated with the highest ratio of HCC incidence in the cirrhotic stage/non-cirrhotic stage (45.00-fold), compared to other etiologies of liver disease such as HBV (8.73-fold), HCV (7.07-fold), PBC (6.88-fold), and AIH (2.79-fold)[40]. Pinyopornpanish *et al.* studied 392,800 NAFLD patients, of whom 1,110 had HCC and 170 (15.3%) had no cirrhosis; the authors found that the following major risk factors: age > 65 years (adjusted OR 3.37, 95%CI: 2.47-4.59), elevated alanine aminotransferase (ALT) (2.69; 2.14-3.37), male sex (2.57; 1.88-3.49), smoking (1.75; 1.23-2.49), and diabetes mellitus (DM) (1.56; 1.15-2.11) were associated with non-cirrhotic NAFLD-HCC (all $P < 0.05$)[41]. The significant proportion of non-cirrhotic NAFLD-HCCs carries clinical implications that we discuss under section 4., devoted to surveillance.

In the US, the report by Davila *et al.* was the first population-based study demonstrating that DM was an independent risk factor for developing HCC[42]. Using the Surveillance Epidemiology and End-Results Program (SEER)-Medicare-linked database, the authors identified 2,061 HCC patients and 6,183 non-cancer controls. Multiple logistic regression analysis of data showed that DM was associated with a three-fold increased risk of HCC after adjusting for confounding factors (i.e., demographic characteristics, HCV, HBV, alcohol, and hemochromatosis). Subgroup analysis disclosed that, even in patients who were free of the above risk factors, the adjusted odds ratio (aOR) for DM remained significant (aOR 2.87; 95%CI: 2.49-3.30). A significant positive interaction between HCV and diabetes was also detected ($P < 0.0001$).

In their seminal study, Welzel *et al.* examined the association between MetS and the development of HCC and ICC in the SEER-Medicare database from 1993 to 2005 in 3,649 HCC cases, 743 ICC cases, and 195,953 controls residents in the same regions[43]. On adjusted multiple logistic regression analyses, MetS was associated with increased risk of both HCC (OR 2.13; 95%CI: 1.96-2.31, $P < 0.0001$) and ICC (OR 1.56; 95%CI: 1.32-1.83, $P < 0.0001$). In 2013, the authors used the same SEER-Medicare database to investigate the population-attributable fractions (PAF) of the principal HCC risk factors in the US[44]. To this end, 6,991 individuals with HCC were compared to 255,702 controls resident in SEER locations. The risk factors for HCC included HCV, HBV, alcohol, rare metabolic disorders, DM, and obesity. The PAF of all factors combined was 64.5%, highest among Asians (70.1%), and lowest among Blacks (52.4%). Interestingly, diabetes/obesity had the greatest PAF in either sex (men 36.4%; women 36.7%) among whites (38.9%) and Hispanics (38.1%).

Raff *et al.* performed a retrospective study of the impact of DM on the progression of NAFLD and alcohol-associated liver disease (ALD)[45]. Medical charts of patients with ALD (n = 73) or NAFLD (n = 307) managed at a tertiary referral center from 2004 to 2011 were retrospectively reviewed. Two-hundred patients with DM differed from non-diabetics for various demographic features (age, sex), MetS, and severity of liver disease (NAFLD, cirrhosis, and HCC). Over a three-year median follow-up, compared to non-diabetics, those with DM had a higher risk of developing cirrhosis and HCC (60% *vs.* 41%, P = 0.022, and 27% *vs.* 10%, respectively, P = 0.045).

The association of DM with HCC is so robust that it may be evaluated with random plasma glucose (RPG) assessment. For example, Pang *et al.* utilized data from 503,993 adults from the prospective China Kadoorie Biobank database[46]. Over a 10-year follow-up, compared to non-diabetics, individuals with DM had adjusted HRs of 1.49 (95%CI: 1.30-1.70) for PLC and 1.81 (1.57-2.09) for cirrhosis. Among those without previously diagnosed diabetes, adjusted HRs per 1 mmol/L higher RPG were 1.04 (1.03-1.06) for liver cancer and 1.07 (1.05-1.09) for cirrhosis, and such associations did not vary according to HBV infection.

Cirrhosis is the most robust risk determinant of incident HCC: is NASH-cirrhosis associated with an increased risk of HCC? Yang *et al.* addressed this research question using the Mayo Clinic Rochester archive and the United Network for Organ Sharing (UNOS)/Organ Procurement and the Transplantation Registry[47]. Among 354 Mayo Clinic patients with NASH cirrhosis, followed for a median 47-month period, 30 individuals developed HCC. DM (with increasing age and decreasing albumin values but not body mass index (BMI), dyslipidemia, and arterial hypertension) was associated with an increased risk of developing HCC on multivariable analysis (HR 4.2; 95%CI: 1.2-14.2; P = 0.02). Among 6,630 UNOS NASH registrants, DM was associated with an increased risk of developing HCC on multivariable analysis (HR 1.3; 95%CI: 1.0-1.7; P = 0.03).

If DM is a potent factor for HCC development (as indicated above), it is logical to postulate that antidiabetic therapy protects from HCC, raising the possibility of personalized medicine approaches and chemoprevention of metabolic PLC. Kramer *et al.* retrospectively evaluated a cohort of 85,963 patients with NAFLD and DM diagnosed at the Veterans Administration facilities from 2004 to 2008 and followed them from diagnosis of NAFLD to HCC, death, or until or until 2018[48]. Overall, 524 patients developed HCC during a mean 10.3-year follow-up. Compared to no medication, metformin and adequate glycemic control were associated with a reduced risk of HCC (HR 0.80; 95%CI: 0.93-0.98; HR 0.69; 95%CI: 0.62-0.78, respectively), while insulin treatment *per se* did not affect HCC risk. However, combined therapy with insulin and other oral glucose-lowering drugs was associated with a 1.6-1.7-fold higher risk of HCC. The study concluded that glycemic control is a potential biomarker for stratifying the risk of HCC among those with NAFLD and DM[48].

Finally, DM differentially impacts HCC risk based on the variable etiologies of CLD. Doycheva *et al.* evaluated the UNOS database of all adults listed for liver transplantation from 2002 to 2017[49]. Compared to non-diabetic controls, comorbid DM was associated with an increased HCC risk only among those with NASH, cryptogenic cirrhosis, HCV, and ALD; however, DM was not associated with an increased risk of HCC among those with chronic hepatitis B or PBC. These data may be utilized to develop personalized medicine approaches for early diagnosis of metabolic PLC in individuals with CLD owing to various etiologies.

Metanalytic studies

Given the abundance of published studies on the role of metabolic risk factors in HCC, we specifically looked at meta-analytic reviews, traditionally deemed at the top of the pyramid of evidence-based medicine[50].

Over the last ten years, eight meta-analyses have addressed the impact of DM on HCC[51-57] [Table 1]. There are relatively few meta-analyses on obesity and MetS[58,59]. Studies in Table 1 support the notion that DM is a risk factor for the development of and mortality associated with HCC[57]. Interestingly, the association of DM and HCC is independent of sex, geographic location, alcohol consumption, history of cirrhosis, or chronic viral hepatitis[60]; however, the risk of developing HCC is affected by DM duration and type of antidiabetic treatment[57], and DM synergizes with HCV infection in increasing the risk of HCC[52]. This increased risk of developing HCC is also observed among those with DM following treatment with DAAs for HCV infection[53]. Metformin treatment appears to reduce the risk of incident HCC among those with DM successfully undergoing antiviral treatment[54,61] and is associated with significantly improved overall survival and recurrence-free survival among diabetic patients with HCC submitted to curative treatment options[55]. Limited meta-analytic evidence suggests that HCC, obesity, and the MetS are associated with the male sex in western populations[58,59]. Completing this picture, a recent study of 14.3 million individuals followed for a mean of 13.7 years demonstrated that overweight and obesity significantly increase the risk of HCC in Koreans and that this increase was mediated by ALT levels[62].To expand our review of published studies on the metabolic risk factors of HCC, we used the following research strategy: [risk factor (Title)] AND [hepatocellular carcinoma [(Title)]. We retrieved 171 results from 1985 until 27 December 2022. After excluding studies in non-English languages; case reports; reviews, and letters to the Editor, 22 of these 171 were retained based on the authors' agreement[63-84] [Supplementary Table 1].

With one exception[68], studies robustly and consistently indicated that obesity[63], steatosis[64,65], visceral fat[66], diabetes[67], obesity and diabetes[69], and MetS[76] were risk factors for HCC in selected cohorts (i.e., those with HCV infection, and those with recurrent HCC) and unselected population studies. The pathomechanisms sustaining this link include leptin[85], elevated insulin/insulin resistance[72,73], and sarcopenia[74]. Interestingly, metabolic factors, including steatosis, (visceral) obesity, and DM, also play a role in risk factors of HCC developing in the setting of alcoholic cirrhosis[71] and viral hepatitis[77-84], suggesting that these dysmetabolic traits are consistently associated with increased HCC risk across a broad spectrum of clinical scenarios.

As a result of the combined effect of the decreasing burden of chronic viral hepatitis and the increasing NAFLD and NASH incidence[86-90], NAFLD-HCC has overtaken viral hepatitis-HCC as the leading cause of HCC in many countries, particularly in the Western world[91]. The increasing epidemiological and clinical burden of NAFLD-HCC has impacted trends in liver transplantation[92]. In 2019, NASH was the fastest-growing cause of HCC among patients awaiting liver transplants in the US[93].

CC

We repeated our bibliographic study for CC using the following research strategy:[(riskfactors (Title)] and (cholangiocarcinoma (Title)] from 1985 until 1 February 2022. This research yielded 90 results and, after excluding studies in non-English languages, case reports, studies on disease recurrence, liver transplantation, reviews, and letters to the editor, 14 of these 90 were retained per authors' agreement[94-107] [Supplementary Table 2].

Table 1. Principal meta-analyses on the association of HCC and metabolic risk factors

Author [Ref.]	Method	Findings	Comment
		Diabetes	
Mrzljak *et al.*[51]	The following disease outcomes were explored: death, progressive disease after loco-regional therapies, and recurrence. PubMed and Cochrane Central Register of Controlled Trials Databases were utilized to this end (from 2000/01/01 to 2020/11/30) Data were also submitted to sub-analysis based on potentially curative (resection, transplantation, thermo-ablation) or non-curative therapies (all the other management options). 27 published studies (21 from Taiwan, China, and Japan) were selected	Data have shown that DM is associated with disease progression (OR 1.24; 95%CI: 1.09-1.41; *P* = 0.001) and recurrence (OR 1.30; 95%CI: 1.03-1.63; *P* = 0.03) as well as increased mortality (OR 3.60; 95%CI: 2.18-5.95; *P* < 0.001) independent of the management protocol adopted among patients with HCC submitted to either potentially curative or non-curative therapies	This study demonstrates that DM negatively impacts HCC outcomes independent of the curative *vs.* non-curative therapeutic strategy adopted. Confirmative studies, including Western countries, will have to further ascertain the effect of DM on HCC while also investigating the effects of antidiabetic pharmacotherapy
Yang *et al.*[52]	Literature was searched in PubMed, Scopus, Web of Science, and Cochrane Library as of January 2020 HBV - 22 articles (18 cohort studies and four case-control studies) were selected. 11 publications (eight cohort studies and three case-control studies) addressed the risk of HCC in Asian subjects with DM ad HBV HCV - 15 publications (13 cohort studies and 2 case-control studies) evaluated the risk of HCC among Asians with DM and HCV infection	HBV - Data yielded a cumulative RR of HCC among those HBV-infected = 1.37 (95%CI: 1.24-1.51; I2 = 27.8%) for cohort studies, and cumulative OR was 1.99 (95%CI: 0.73-5.48; I2 = 88.4%) for case-control studies HCV - Studies yielded a RR of HCC among those with HCV infection 1.76 (95% CI: 1.42-2.17; I2 = 62.8%) for cohort studies, and OR was 1.77 (95%CI: 1.18-2.64; I2 = 0.0%) for case-control studies	This metanalytic review supports the notion that both HBV and HCV synergize with DM in increasing the risks of incident HCC. However, this association is stronger among those with infection owing to HCV than to HBV
Váncsa *et al.*[53]	This metanalysis investigated the potential role of DM as a risk factor in the *de novo* development of HCC among HCV-infected patients previously submitted to DAAs Published studies were searched in four medical databases till November 2020 27 selected studies were subjected to this meta-analysis	Data have shown that patients with DM had an increased risk of HCC (AHR = 1.31, CI: 1.06-1.62), and such a risk was also increased in the subgroup analysis of those exhibiting either SVR (OR = 1.71, CI: 1.22-2.4; I 2 = 28.8%) or advanced hepatic fibrosis (AHR = 1.36, CI: 1.03-1.8)	Those with DM exhibit an increased risk of developing HCC following treatment with DAAs for HCV infection than DM-free individuals
Li *et al.*[54]	This metanalytic review investigated the possible association between metformin use and the risk of HCC among individuals with DM To this end, the PubMed and Web of Science databases were searched for relevant studies before April 2021. Those 24 selected studies (9 case-control studies and 15 cohort studies) totaled a global population of 1.4 million individuals	Data have shown that DM patients under metformin therapy exhibit a 41% decreased risk of HCC (OR/RR = 0.59, 95% CI: 0.51-0.68). Subgroup analysis has demonstrated that this protection from the risk of HCC occurs irrespective of ethnicity (Caucasian: OR/RR = 0.63, 95%CI: 0.52-0.77; Asian: OR/RR = 0.56, 95%CI: 0.47-0.67)	In DM patients, metformin use is associated with a significantly reduced risk of HCC
Zhou *et al.*[55]	This study evaluated the OS (primary outcome);	After curative treatment of HCC, compared to other antidiabetic drugs, metformin use	The use of metformin in HCC patients with DM

	the RFS and the PFS were also evaluated (secondary outcomes) Medline and EMBASE databases were searched until January 2019 to this end. Eight published studies, globally enrolling 13,985 patients, were included in this metanalytic review	was associated with significantly longer OS at 1, 3, and 5 years (all $P < 0.00001$) and RFS at 1 and 3 years (all $P < 0.00001$)	treated with curative options was associated with significantly improved OS and RFS
Tan *et al.*[56]	Medline and Embase databases were searched to identify studies published in English before February 2018 Seven studies were retrieved (5 cohort studies and 2 case-control studies), totaling 21,842 HBV chronically infected individuals	Compared to DM-free individuals, the DM population was prone to an increased incidence of HCC (pooled HR 1.77, 95%CI: 1.28-2.47; fixed effect) and higher overall mortality (pooled RR 1.93, 95%CI: 1.64-2.27; fixed effect)	Among individuals with chronic infection owing to HBV, DM is associated with increased HCC risk
Wang *et al.*[57]	PUBMED and MEDLINE databases were searched for studies published before February 2011 Overall, 17 case-control studies and 32 cohort-selected studies were included in the present meta-analysis	Data have shown a statistically significant increased prevalence of HCC among diabetic individuals (RR = 2.31, 95%CI: 1.87-2.84) The risk of HCC was decreased by metformin treatment and increased by DM duration and treatment with sulfonylureas or insulin Individuals with DM (compared to those DM-free) had a statistically significant increased risk of HCC mortality (RR = 2.43, 95%CI: 1.66-3.55)	DM is associated with a moderately increased risk of HCC prevalence and mortality
Wang *et al.*[60]	Studies published before 2010 were retrieved through a literature search of Medline from 1966 and EMBASE from January 1974. Overall, 25 cohort studies meeting inclusion and exclusion criteria were selected	Compared to non-diabetic controls, DM was associated with an increased incidence of HCC (SRRs = 2.01, 95%CI: 1.61-2.51), independent of confounding factors (i.e., geographic location, alcohol consumption, history of cirrhosis, or infections with either HBV or HCV) Moreover, DM was positively associated with HCC mortality (SRR = 1.56; 95%CI: 1.30-1.87)	This study supports the notion that T2D and HCC are strongly associated with either sex
Obesity			
Gupta *et al.*[58]	The following databases were searched: MEDLINE, MEDLINE InProcess, Embase, the Cochrane Database of Systematic Reviews, the Cochrane Database of Reviews of Effect, and the Cochrane Central Register of Controlled Trials before March 2016. Overall, 9 studies (8 regarding individual cohorts and 1 featuring global analysis from multiple cohorts) were included	Compared to normal-BMI individuals, obese subjects had higher mortality owing to HCC (aHR, 1.95; 95%CI: 1.46-2.46) and obese men (aHR, 2.50; 95% CI, 2.02-3.09; three studies) had a higher risk than obese women (aHR, 1.45; 95%CI: 1.08-1.97; two studies). Premorbid obesity was associated with HCC-related mortality among Western populations alone (aHR, 2.10; 95%CI: 1.77-2.48; four studies) but not in Asians	This meta-analytic review demonstrates that obese (but not overweight) individuals are exposed to an almost two-fold increased mortality risk owing to HCC, and this association is more pronounced in men and Western populations
Metabolic syndrome			
Li *et al.*[59]	PubMed, Ovid, Embase, Web of Science, and Cochrane Library databases were searched before September 2017 This meta-analysis included 10 studies (9 cohorts and 1 case-control)	MetS patients are significantly more likely to develop HCC (RR = 1.60, 95%CI: 1.12-2.28, $P = 0.01$). Limited to cohort studies, MetS was a potential risk factor for HCC occurrence (RR = 1.52, 95%CI: 1.01-2.30, $P = 0.05$). Male patients with MetS were at higher risk of developing HCC than women (RR = 1.91, 95%CI: 1.38-2.65, $P < 0.0001$ in males and RR = 2.1, 95CI: 0.69-6.37, $P = 0.19$ in female). Moreover, MetS was associated with an increased risk of HCC among the Euro-US populations (RR = 1.71, 95%CI: 1.09-2.67, $P = 0.02$)	MetS is associated with a high risk of HCC occurrence in male and Euro-US populations. However, no associations were found linking MetS with pathological disease characteristics and patient survival

AHR: adjusted hazard ratio; CI: confidence interval; DAAs: direct-acting antivirals; DM: diabetes mellitus; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; MetS: Metabolic syndrome; OR: odds ratio; OS: overall survival; RFS: recurrence-free survival; PFS:- progression-free survival; RR: relative risk; SVR: sustained virologic response.

Based on disease anatomical topography, CC is classified as intrahepatic, perihilar, and distal; the intrahepatic subtype is split into large and small-duct types, and these differences are regarding clinical and histological features[108,109].

Although a substantial proportion of CC cases are not easily attributable to any known risk factors predisposing to their development, a *milieu* featuring chronic inflammation, fibrosis, and cytokine release offers a biological background facilitating the development of incident cancer[110]. This explains why, in clinical practice, many CC cases are associated with definite risk factors, the variable distribution of which accounts for global geographical disparities. In particular, the high prevalence of CC in Eastern countries mirrors the widespread presence of parasitic infections (e.g., *Opisthorchis viverrini* and *Clonorchis sinensis*). By contrast, primary sclerosing cholangitis (PSC) and liver cirrhosis are the principal risk factors of CC in Western countries[108,110,111].

Different and specific CLD types might predispose individuals to different CC subtypes. For example, the small-duct subtype is usually associated with advanced CLD, primarily owing to viral etiology[108,110,111].

Although a metabolic origin of CC is less robustly demonstrated than for HCC, several lines of evidence support the notion that obesity and NAFLD are major risk factors for CC[106]. Indeed, with the exceptions of some studies reporting negative findings on DM[94,104,105] and obesity[99], most studies consistently support diabetes[95-99,101] diabetes and obesity[100], obesity[102,103], and NAFLD[103] as potential risk factors for the development of CC. Of interest, two studies report a statistically significant inverse association with the use of metformin[101] and aspirin[106]. Conversely, large-duct subtype CC tends to develop in patients with chronic bile duct conditions, such as PSC, fluke infection, and gallstones[108,110,111].

PATHOGENIC PATHWAYS INVOLVED IN THE DEVELOPMENT OF PLC IN DYSMETABOLIC INDIVIDUALS

HCC

The molecular pathogenesis of HCC in individuals with NAFLD/NASH or disorders belongs to the domain of MetS through a complex, molecular, cellular, multi-step process involving genetic, viral, and immuno-metabolic determinants, cell microenvironment, and fibrosis stage of the underlying CLD[9]. These will be discussed in detail below.

Molecular pathogenesis and genetics

In HCC, mutations identified as cancer-driver genes with oncogenic or tumor-suppressive properties include, for example, telomerase activation, which occurs in ~80% of cases[9].

Telomerase activity is downregulated during early embryonic development and is not essential (and indeed absent) in the healthy adult liver, where most hepatocytes are quiescent[112,113]. However, low-rate telomerase activity restarts following proliferative signals such as liver injury/chronic liver diseases due to activation of oncogenes (such as mutations of Ras or amplification of c-Myc) or oncogenic protein expression[112].

Telomere shortening and reactivation of telomerase (TSRT) are described in aging and metabolic disorders[114] and across a broad range of human cancers, including PLC[112]. TSRT through TERT promoter mutations represents definite genetic risk factors for cirrhosis and PLC and is a potentially useful therapeutic target[113]. The role of telomere shortening and telomerase concerning NAFLD, cirrhosis, and HCC has been reviewed elsewhere[115].

NASH-HCCs belong to the so-called "non-proliferation class"[9]. These less aggressive cancers (compared to the HBV-related HCCs) exhibit moderate histological differentiation, lower serum alpha-fetoprotein (AFP) values, and less frequent vascular invasion[63,116]. According to the categorization recently proposed by Llovet *et al.*, this class has two distinct subsets: a) the WNT-β-catenin CTNNB1 subclass, which drives an immune-excluded phenotype with low immune infiltration, and b) the interferon sub-class featuring chromosomal stability, frequent TERT promoter mutations, a highly activated IL6-JAK-STAT signaling pathway, and a more markedly inflammatory tumoral micro-milieu[9].

Genes such as TP53, CTNNB1, AXIN1, and ARID1A frequently present mutations, which appear to play a role in cancer development[117,118]. CTNNB1-activating mutations contribute to the alteration of the Wnt/β-catenin signaling pathway, observed in more than 10% and up to 40% of PLCs. This type of mutation appears to be more frequent in non-Asiatic populations, where HBV infection is uncommon.

Similar to CTNNB1, TP53 mutations are frequently observed in PLC. TP53 is involved in cellular proliferation, regulation, and apoptosis. Therefore, a high-grade histological tumor (and worse outcomes) are usually associated with HCC with TP53 mutations[117-119].

AXIN1 mutations can be detected in HCC. AXIN1 negatively regulates the Wnt/β-catenin signaling pathway through activation and the consequent elevated expression of β-catenin[117,118].

In humans, single nucleotide polymorphisms in PNPLA3, TM6SF2, GCKR, and MBOAT7 have consistently been implicated in developing NAFLD-HCC, as recently reviewed elsewhere[120,121].

Immunological cells and cytokines

In healthy states,and compared to other organs, the liver is considerably more immunotolerant despite harboring a more significant number of immune cells[122]. This enables it to sustain the constant flux of pro-inflammatory signals of intestinal origin from portal blood[123]. This unique feature of the hepatic immune system is essential for the complex interaction between HCC and the hepatic immune reaction[124] and has potentially relevant therapeutic implications[122].

Approximately 90% of the HCC burden is associated with chronic hepatitis owing to exogenous (viral, alcoholic) or endogenous stimuli (NAFLD/NASH), implying that HCC is a prototypical inflammation-associated cancer[9]. However, the immune micro-environment serves a dual function: on the one hand, IL-6, lymphotoxin-α, and TNF accelerate tumorigenesis and enhance cancer aggressiveness[123]; on the other hand, lymphocytic infiltration predicts better outcomes[125].

Our understanding of the role of immunological cells and cytokines is based on animal studies, the relevance of which to the pathogenesis of human NAFLD-HCC remains to be proven. That said, the concurrence of the following cells and pathomechanisms simultaneously promote NAFLD-HCC: activated $CD8^+$ T cells; intrahepatic $CD4^+$ selective loss; B cells, Treg cells, natural killer cells, and different types of myeloid cells; intrahepatic recruitment of activated platelets; overexpressed hepatic IL-6 and TNF[9].

Patients with advanced HCCs may gain survival benefits from immune checkpoint inhibitors (ICIs) at the cost of tolerable adverse events[126]. Combined ICIs and antiangiogenic drugs in first-line systemic therapy of unresectable HCC may increase efficacy compared to ICI monotherapy[127,128]. However, at variance with findings observed with antiangiogenic drugs (where no differences related to etiology have been observed), non-viral HCC, notably NASH-HCC, is less responsive to immunotherapy than viral-related HCC[128-130]. To

understand these puzzling findings, we highlight that, in parallel with the demodulation of hepatic metabolism, NASH entails a wide-range reprogramming of various parenchymal and non-parenchymal liver cell types, including macrophages and intrahepatic T cells[131]. Intrahepatic T-cell reprogramming occurs in NASH, where various T-cell subtypes contribute to determining disease development/progression and the response to immunotherapy agents[131,132]. Supporting the notion of robust immunometabolic grounds underlying such phenomena, metformin treatment rescued the efficacy of anti-PD-1 therapy against liver tumors in several murine NASH models[133].

These findings suggest that NASH-associated HCC is enabled by inflammation-associated pro-tumorigenic mechanisms and insufficient immune surveillance[132]. These immunological pathomechanisms, while accounting for NASH development and progression, also explain why NASH-HCC is less responsive to immunotherapy, probably owing to NASH-related aberrant T-cell activation and impaired immune surveillance[129].

Liver-specific mechanisms

NAFLD exhibits distinctive patho-biochemical features resulting from the amount and (probably) the chemical structure and properties of accumulated lipid classes[134]. These NAFLD-specific distinctive features involve metabolic and oxidative stress, pathological lipophagy, increased reactive oxygen species production, and diminished reducing power (i.e., low NADH or NADPH levels); collectively, they represent an intrahepatic milieu favoring disease development and progression in the setting of fatty acid-overloaded hepatocytes[9].

Hepatic fibrosis

The activated hepatic stellate cell, via its capacity to synthesize collagen on the one hand and growth factors that promote neo-angiogenesis and fibrosis on the other hand, is fundamental to the response to chronic liver injury[135].

Cirrhosis *per se* is a risk factor for HCC, although some etiologies of cirrhosis are associated with an increased HCC risk[136,137]. Distortion of hepatic architecture in cirrhosis predisposes to portal hypertension[138] and creates the so-called "field effect", i.e., the immunologically permissive micro-environment favoring tumor development[9]. The field effect has been observed in various cancers and describes how tissue regions beyond tumor boundaries exhibit cancer-associated histological or molecular changes[139]. In the setting of NAFLD-HCC, $CD4^+$ lymphocytes and the interaction of the innate immune response with the gut microbiome interact to favor tumor development[140-142].

The pro-inflammatory and pro-fibrotic hepatic milieu favors HCC growth, metastasis, and sorafenib resistance through the activation of STAT3[143]. The tumor microenvironment plays a crucial role in the natural history of HCC, supporting the rationale of therapeutic strategy targeting the dynamic interconnections linking the hepatic immune system with hepatocytes[144]. However, it cannot be over-emphasized that the development of NAFLD-HCC is less cirrhosis-dependent than those HCCs associated with CLD owing to non-metabolic etiology, for example, viral and alcohol-related[27,136,137,145,146], such as is discussed in paragraph 2.1.1.

Metabolic causes of primary liver cancer

The same factors and cofactors (i.e., features of the MetS and lifestyle habits, respectively) that modulate the pathomechanics of organ dysfunction in NAFLD/NASH and MAFLD[147] also appear to be involved in the development of metabolic PLC.

Among the various components of the MetS, it is undoubted that "diabesity" is a risk factor for HCC development[148,149]. Innovative studies have highlighted that, over time (also in non-diabetic individuals), fluctuations of glycemic compensation and body weight changes (often mutually interconnected) are risk factors for HCC[150-154], suggesting that stable glucose metabolic control and stable body weight may reduce the risk of incident HCC.

Compared to *diabesity*, fewer data are available on other components of the MetS. That said, total cholesterol, potentially low-density lipoprotein cholesterol, and triglycerides are strongly and inversely associated with HCC risk among patients with CLD[155]. A general population study showing that ACE inhibitors were associated with a reduced incidence of HCC in a cohort of 12,327 Asians indirectly supports the notion that arterial hypertension is a risk factor for incident HCC[156].

Regarding cofactors, such as diet and sedentary behavior, taken collectively, published studies suggest that an increased risk of PLC goes in parallel with an elevated dietary intake of saturated fatty acids[157]. Additionally, alcohol consumption adds to or multiplies by multiple folds the HCC risk inherent in BMI, and even consumption of modest amounts of alcohol is associated with an increased HCC risk among those with NAFLD[158]. The specific role of sedentary behavior in increasing the odds of incident HCC is documented by the finding that exercise blunts liver tumor development in a mouse model[159].

As to the specific biochemical pathways involved, altered oxidation of fatty acids coupled with the deranged metabolism of amino acids, lipids, and carbohydrates have all been involved. For example, a large European prospective cohort study utilized an untargeted nuclear magnetic resonance metabolomic approach for evaluating pre-diagnostic serum samples obtained from 114 HCC first incident cases and 222 matched controls[160]. Comparative analysis has identified a shift from glutamine to glutamate, compatible with impaired ammonium detoxification in HCC cases.

A previous study conducted in a more limited series of 36 individuals with cirrhosis, 39 HCC patients, and 63 controls found higher levels of aromatic amino acids to be associated with (liver cirrhosis and) HCC, together with lower levels of branched-chain amino acids, choline, and unsaturated lipids[161]. Finally, a recent study[30] including 290,888 UK Biobank adults who were followed for a median 3.87-year period has shown that, compared to the metabolically favorable subgroup, the subgroup featuring high BMI, C-reactive protein and cystatin C (a protease inhibitor connected to chronic kidney disease, and cardiovascular diseases, and inversely related to HDL cholesterol) was associated with PLC risk (HR 5.70; 95%CI: 3.57-9.11). This malignancy was also linked to testosterone (HR 2.49; 95%CI: 1.47-4.24) and several liver tests, notably including gamma-glutamyl transferase (GGT) (HR 2.40; 95%CI: 2.19-2.65). Interestingly, also CC was associated with higher GGT values (HR 1.76; 95%CI: 1.47-2.11); finally, the evaluation of additional 252 biomarkers yielded results consistent with those found for HCC[30]. Adiponectin, oxidative stress, fibroblast growth factor (FGF) 21, and hormonal factors are among the principal,though not the only, mediators linking metabolic derangement with hepatocarcinogenesis[30,160,162,163].

Molecular pathogenesis of CC

Activation of crucial signaling pathways driving the development and progression of cholangiocarcinogenesis results from genetic and epigenetic modifications in the setting of profoundly altered pro-inflammatory tumoral micro-*milieu*[164]. According to Fouassier *et al*., the signaling pathways involved in CC progression can be classified as (i) microenvironment and inflammation-related pathways; (ii) proliferation/ survival/death-related pathways; and (iii) development-related pathways[164].

Alterations of cancer micro-milieu and inflammation-associated pathways

The two principal pathogenic cascades include the pro-inflammatory interleukin (IL)-6/STAT3 pathway and the pro-fibrogenic transforming growth factor beta (TGFβ/SMAD pathway[164]. IL-6, a critical mediator of systemic inflammation and acute phase response following liver injury, is (in the context of CC) produced by several types and drives a circle of compensatory proliferation triggered by cell injury and inflammation[164-166]. IL-6 signaling is activated via its receptor and involves a complex cascade recruiting gp130, Janus kinases (JAK), signal transducers and activators of transcription (STAT), mitogen-activated protein kinases (MAPK), and phosphoinositide 3-kinase (PI3K)/AKT serine-threonine kinase (AKT) pathways to target the epithelial compartment[164)]. Interestingly, expression of some of these intermediate pathways (e.g., pSTAT3 staining) predicts worse outcomes in human CC[164].

The pro-fibrogenic TGFβ comprises a family of cytokines with multiple TGFβ receptors and co-receptors produced by many cell types[167]. In early CC, TGFβ can produce cytostatic effects[168]; however, in more advanced diseases, it may also promote tumor growth[169]. The role of TGFβ in CC pathogenesis is complex and varies according to the phase of the disease. Its signaling pathways may have prognostic significance, and TGFβ is also involved in hepatocyte-to-cholangiocyte conversion during liver regeneration and in intermediate HCC/CC phenotypes[164].

Pathways related to proliferation, survival, and death

Constitutive activation of receptor tyrosine kinases such as FGFR2 and ERBB receptors or components of downstream signaling modules, such as JAK/STAT, RAS/RAF/MEK/ERK, and PI3K is involved in CC pathogenesis[164].

FGFs and their receptors (FGFRs) represent a highly conserved signaling pathway playing critical roles in metabolic homeostasis and cell proliferation[170]. Accordingly, they are involved in embryonic development, fetal organogenesis, and tissue repair[171]. Structurally, they are single transmembrane receptor tyrosine kinases consisting of an extracellular ligand-binding domain and a cytoplasmic conserved tyrosine kinase domain; dysregulation of the latter contributes to cancer development and progression, evasion of immune responses, neo-angiogenesis, and resistance to anticancer pharmacotherapy[172,173]. Chromosomal translocation of FGFRs results in chimeric FGFR fusion proteins forming, leading to human cancer development and progression owing to aberrant signaling; therefore, this pathway is a promising therapeutic target for CC and other human cancers[173]. Clinical trials suggest that subsets of fusion-positive patients with hematological malignancies, intrahepatic CC, lung cancer, urothelial carcinoma, and glioblastoma respond to FGFR inhibitor therapies[173].

The erythroblastic leukemia viral oncogene homolog (ErBb) family, which comprises the receptor tyrosine kinases (RTK) epidermal growth factor receptor (EGFR; also called ERBB1), ERBB2, ERBB3, and ERBB4) regulates development, vascularization, growth, metastasis, and chemoresistance of CC via ligand-mediated activation of downstream targets and other transmembrane receptors[174]. The functional impact of those EGFR mutations identified in CC remains incompletely characterized, and the efficacy of EGFR inhibitors in CC is under investigation[174].

Secretin and histamine pathways are also involved in CC pathogenesis, though the pharmacological manipulation of such pathways has uncertain efficacy. Secretin can induce cell death and decrease CC cell proliferation and disease burden *in vitro* and *in vivo*[175]. It remains to be ascertained whether chronic H1/H2 HR blockade is a viable chemo-preventive option in human PSC, a precursor lesion of CC[164].

Several critical cell processes, such as proliferation, apoptosis, and cytoskeletal rearrangement, are regulated by the PI3K/AKT pathway[164]. Increased activation of the PI3K/AKT signaling pathway is associated with CC metastasis, and conversely, inhibition of the PI3K/mTOR axis represents a possible therapeutic strategy in this setting[176].

Pathways related to development

The Notch pathway

The hepatoblast, embryologically derived from the ventral foregut endoderm, is the bi-potent shared common progenitor of hepatocytes and cholangiocytes[177]. Experimental and clinical evidence suggests that Notch signaling, activated through cell-cell contacts, is implicated in the cholangiocyte differentiation of hepatoblasts and the formation of bile ducts[164,177,178]. Activation of Notch signaling determines cell fates, while Notch pathway dysfunction accounts for embryonic development defects and, among postnatal diseases, CC[164]. Notch signaling may affect a biologically aggressive CC form, and pharmacological manipulation of Notch signaling holds promise as a therapeutic target[179,180].

The Wnt/β-catenin pathway

Compared to HCC, a lower proportion of CC patients display mutations of genes involved in the Wnt-β-catenin cascade, which, potentially, could be a target for treating and reversing multi-drug resistance[164,181,182].

Additional genetic and epigenetic pathways associated with CC

In human cancer, hotspot gain-of-function of isocitrate dehydrogenase (IDH) genes IDH1 and IDH2 are the most often mutated metabolic genes resulting in the IDH enzyme aberrantly generating high levels of the oncometabolite R-2-hydroxyglutarate. This molecule competitively inhibits enzymes that, among other cellular processes, govern epigenetics, DNA repair, and metabolic features[183]. The biology and clinical implication of mutant IDH genes in ICC have recently been discussed elsewhere[164,183,184].

Chromatin remodeling, regulated by specific geneses called "chromatin remodelers", defines the dynamic process in which the cell DNA mass can be modified through either transcriptional activation or transcriptional silencing[185]. This is a critical epigenetic mechanism of normal cell biology and a pathomechanism involved in cancer biology often altered in different human cancer types[185].

Among PLC types, CC (particularly ICC) will often exhibit loss of function mutations or epigenetic modifications in genes encoding proteins involved in regulating chromatin organization, including ARID1A, PBRM1, and BAP1[164,186]. These gene modifications have been reported in ICC with a ductal plate malformation pattern occurring in chronic hepatitis owing to either HBV or alcohol[187]; therefore, the relevance of these factors to "metabolic" CC is worth investigating.

SURVEILLANCE

According to the AASLD updated guidelines and the EASL Clinical Practice Guidelines[136,188], given that individuals with NAFLD-cirrhosis exhibit an awaited HCC incidence rate approximating 1.5% per year, they should adhere to the screening guidelines for cirrhosis owing to all etiologies, namely, hepatic ultrasound scanning with or without AFP semi-annually. This approach's points of strength, technical limitations, and predicted development lines have recently been addressed elsewhere[37,189]. The AGA Clinical Practice 2020 update recognizes that individuals with earlier stages of NAFLD (compared to NAFLD-free controls) have a higher risk of developing HCC; nevertheless, the guidelines state that unless

advanced hepatic fibrosis is present, NAFLD patients should not be routinely considered for protocols of HCC surveillance[190]. Experts agree that the true incidence and risk modifiers of HCC remain insufficiently defined and are likely to fall below the threshold to justify routine screening of non-cirrhotic and non-advanced fibrosis NAFLD patients[190-193].

Along the same lines: should surveillance practices be conducted for HCC and CC? Based on the AGA Clinical Practice Update[194], surveillance for CC (and gallbladder cancer) should be performed among adults with PSC using imaging techniques (ultrasonography, computed tomography, or magnetic resonance imaging), with or without serum carbohydrate antigen 19-9. Screening should occur annually or semi-annually, irrespective of disease stage, particularly in the first year following PSC diagnosis, among those with ulcerative colitis and individuals diagnosed at older ages. However, individuals with small-duct PSCs or aged < 20 years should not undergo surveillance for CC. It is noteworthy that these guidelines fail to mention any metabolic risk factors. Compared to the more commonly occurring HCC, little is known regarding surveillance aimed at early diagnosis of the comparatively rarer CC. However, some provinces of Thailand are plagued by CC, with prevalence rates nearly 100-fold higher than those registered in Western countries[195], supporting the rationale of experimental protocols of ultrasound surveillance for CC. Siripongsakun *et al.* conducted one such study on a surveillance population-based cohort of 4,225 adult inhabitants of Northern Thailand who volunteered to enter a semi-annual ultrasonographic surveillance protocol for 5-years[196]. In contrast, the non-surveillance control cohort was recruited among CC patients diagnosed in the hospital. Surveillance was independently associated with decreased mortality (HR = 0.41; $P = 0.012$), supporting that ultrasound surveillance is a logical option to reduce CC mortality in hyperendemic regions[196]. While such an approach in western countries would not be justifiable owing to the different CC prevalence rates discussed above, the possibility remains that CC might be incidentally detected among those submitted to surveillance for HCC. Confirming this notion, Tovoli *et al.* reported that cirrhotic patients with ICC were under a surveillance program for HCC in approximately 50% of cases and, at diagnosis, had smaller ICCs, higher chances of receiving surgery, and, consistently, better prognostic characteristics than non-surveyed cirrhotic patients, even considering a possible lead-time bias[197].

CONCLUSIONS

HCC and CC are the most common histological types of PLC. The incidence of PLC has increased in recent years, generating a considerable clinical and economic impact. Pre-existing CLD is often associated with PLC development. Chronic hepatitis owing to HBV and HCV is increasingly better treated; therefore, full-blown MetS and its features are the primary causes of CLD, especially in Western countries. Moreover, metabolic comorbidities, particularly *diabesity*, increased visceral fat, and MetS, are consistent risk factors for HCC development in patients with CLDs of various etiology. However, the association between metabolic comorbidities and CC is comparatively less robust, although diabetes and obesity are notable risk factors for CC development.

Pathogenic mechanisms involve metabolic PLC development, including complex immunological, cellular, pro-inflammatory, molecular, and genetic processes.

In conclusion, considering the escalating prevalence of metabolic dysfunction, it is necessary to increase awareness that metabolic liver disease is a factor or a cofactor in the development and progression of many PLC cases. This notion supports the definition of metabolic PLC as a novel disease entity. Improved understanding of pathomechanisms underlying the association of PLC with metabolic disorders calls for close surveillance and early diagnosis of at-risk patients while laying the groundwork for chemoprevention and novel drug management approaches of metabolic PLC.

DECLARATIONS

Authors' contributions

Conceived the study design and wrote the first draft of the article: Lugari S, Lonardo A
All the authors contributed to refining the first draft and to addressing Reviewers' concerns.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

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Consent for publication

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