The risk of liver cancer in autoimmune liver diseases

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Abstract: Hepatocellular carcinoma (HCC), the dominant primary malignancy of the liver, has almost invariably a fatal outcome that can be averted only by early diagnosis and treatment. While the close association of HCC with chronic viral hepatitis and alcohol abuse has impacted favourably on screening and treatment of this deadly tumour, at the same time it has long obscured the etiologic role of autoimmune liver diseases. Recently, a systematic analysis of 25 published cohorts disclosed a 3.1 × 1000 patients/year incidence of HCC in autoimmune hepatitis patients that tripled in those with cirrhosis. HCC is also a sequela of primary biliary cholangitis, where the incidence is more relevant in males, those with advanced liver disease and nonresponders to ursodeoxycholic acid therapy. Cholangiocarcinoma (CCA), the second ranking primary cancer of the liver, is also on the rise with its intrahepatic pattern, in part reflecting an association with chronic liver diseases of diverse aetiology. In the USA and northern Europe, perihilar CCA is a frequent complication of primary sclerosing cholangitis, a cholestatic disorder thought to be immune mediated. International Guidelines clearly recommend HCC screening with abdominal ultrasonography every 6 months in autoimmune cirrhotic patients. While surveillance of patients with autoimmune liver disorders who are at risk of HCC affects both early diagnosis and radical therapy of this tumour, this is not the case for CCA, where early diagnosis is challenged by the lack of sensitive and accurate tests for screening.

Keywords: autoimmune hepatitis, autoimmune liver diseases, cholangiocarcinoma, hepatic cancer, hepatocellular carcinoma, primary biliary cholangitis, primary sclerosing cholangitis

Introduction

According to Global Disease Burden, in 2015 there were 854,000 incident cases of liver cancer and 810,000 deaths globally, contributing to 20,578,000 disability-adjusted life-years (DALYs).1 Liver cancer stands as the fourth leading cause of cancer death after lung, colorectal, and stomach cancer and, in the last three decades, its incidence has increased by 75%. Interestingly, half of cases can be explained by changing population age structures, one-third by population growth, and less than 10% by changing age-specific incidence rates. While chronic infection with hepatitis B virus accounted for one-third of liver cancer deaths, alcohol was implicated in another 30%, hepatitis C in 21%, and other causes in 16%.

Globally, hepatocellular carcinoma (HCC) represents the lion’s share of all liver cancers (90% of all cases), whereas cholangiocarcinoma (CCA) accounts for less than 10% of all primary malignant liver tumours. On a comparative analysis of cancer registries, HCC appears to be on the rise in northern and central Europe, North America and English-speaking Asia, due mainly to epidemics of viral hepatitis, alcohol abuse and metabolic syndrome. The incidence of this cancer is declining in several traditionally high-risk countries of Mediterranean Europe, Japan and Hong Kong following effective measures of sanitation, including vaccination against hepatitis B.

Autoimmune liver diseases (AILD) include autoimmune hepatitis (AIH) characterised by...
necro-inflammation, primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), the latter both characterised by progressive biliary damage and cholestasis. These all are rare diseases but, if untreated, they can lead to liver cirrhosis and result in significant morbidity and mortality. Although AIH and PBC are considered classic autoimmune diseases, the pathogenesis of both conditions is largely unknown. PSC is considered to be an immune-mediated disease, with immunogenetic features and a strong association with inflammatory bowel disease.

Owing to the fact that, globally, HCC risk is increasing in men, along with cirrhosis evolution, development of portal hypertension and decompen-sation (Table 1), AILDs likely play a minor role in liver carcinogenesis. However, as yet there has been no systematic effort to consolidate and critically evaluate the evidence regarding the risk of liver cancer in patients with AILD. Moreover, studies have reported different and inconsistent findings of determinants other than cirrhosis in increasing the risk for liver cancer.2-5

Herein, we propose a review to examine demographic, clinical, biochemical, and treatment-related factors associated with liver cancer in AILD.

**Autoimmune hepatitis**

AIH is a rare, nonresolving chronic liver disease that affects mainly women and is characterized by hypergammaglobulinemia, circulating autoantibodies, association with interface hepatitis on liver histology, and a favourable response to immunosuppression. The disease, if untreated, often leads to cirrhosis, liver failure and death.21 In the last decade, both the epidemiology and clinical presentation of AIH have changed, leading to the accumulation of males and seronegative patients without clear-cut clinical and histological markers of AIH.22,23

In a meta-analysis of 25 studies (20 papers, 5 abstracts), out of 6528 patients with AIH, 118 were found to have developed HCC during a follow up of 3.3–16 years (median 8 years).16 In the face of an overall incidence of HCC of 3.1 cases per 1000 patients/year, the incidence of the tumour was more than threefold higher (10.1, range: 6.9–14.7 per 1000 patients/year) in those with cirrhosis, a complication of AIH that was present in 92 out of 93 patients with HCC and known cirrhosis status at diagnosis16 (Table 2). In addition to cirrhosis and higher age, male sex may be a factor associated with HCC development in AIH (incidence: women 3.13/1000 person-years; men: 4.65/1000 person-years); however, this difference was not found to be was not statistically significant, likely due to sample size limitations as only 1138 male AIH patients were included in the analysis. The strict association of HCC with development of cirrhosis was chronologically proven in two retrospective cohort studies published in London and Rochester. In the first

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**Table 1.** Incidence and risk factors for hepatocellular carcinoma.2–4 Almost 90% of HCCs are associated with a known underlying risk factor,5 with cirrhosis being the most important. Cirrhosis might be caused by chronic viral hepatitis, chronic alcohol abuse acquired, inherited metabolic diseases, NASH, and rare diseases like AILD. The presence of cirrhosis in any of these aetiologies significantly increases the risk of HCC.

| Liver disease | Liver status | % per year | References |
|---------------|--------------|------------|------------|
| HBV           | Noncirrhosis | 0.4–0.6    | Yang et al.6 |
|               | Cirrhosis    | 2.6–6.0    | Ioannou et al.7; Beasley et al.8 |
| HCV           | Noncirrhosis | 0.1        | Yoshida et al.9 |
|               | Cirrhosis    | 3.0–8.0    | Ioannou et al.7; Sangiovanni et al.10; Lok et al.11 |
| ALD           | Cirrhosis    | 2.6–6.8    | Mancebo et al.12; Nahon et al.13 |
| Haemochromatosis | Cirrhosis | 5.0        | Deugnier et al.14; Fracanzani et al.15 |
| AILD          | Cirrhosis    | 0.2–1.8    | Tansel et al.16; Trivedi et al.17 |
| NASH          | Cirrhosis    | 2.6        | Schlesinger et al.18; Calle et al.19; Younossi et al.20 |

AILD, autoimmune liver diseases; ALD, alcohol liver disease; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis.
A recent study from a large single centre in the USA confirmed that AIH is a rare cause (1.6%) for HCC in 1250 patients evaluated for HCC. They showed a decreasing trend of HCC occurrence in AIH over 14.5 years. Patients with prolonged duration of the disease and older age are at high risk to develop HCC. Only two AIH-HCC patients did not have cirrhosis at the time of HCC diagnosis, confirming that, in the AIH setting, HCC occurs mainly in cirrhotic patients. Another recent study from Japan reported a high risk of HCC in AIH patients. Whether the risk of HCC in AIH varies with race merits further study.

**Primary biliary cholangitis**

PBC is a rare liver disease characterised by chronic immune-mediated destruction of biliary epithelial cells that almost inexorably results in a slowly evolving cholestatic syndrome. Though the phenotype of PBC is diverse, if untreated, the disease slowly progresses toward cirrhosis with all the ensuing complications, including HCC. Treatment with ursodeoxycholic acid (UDCA) has been shown to improve outcome and prevent progression in patients with biochemical improvement upon initiation, whereas classic immunosuppressive therapies with steroids and thiopurines have been largely negative. Intriguingly, in recent decades, both the epidemiological pattern and clinical presentation of PBC have evolved towards a predominance of older age at diagnosis, with a worse prognosis being more frequently observed in nonresponders to UDCA therapy. In a systematic review of 17 studies, including 16,368 patients seen between 1984 and 2011, compared with the general population, PBC patients had a significantly higher risk of HCC (pooled RR, 18.80; 95% CI, 10.81–26.79), but not of other cancers. In most studies, the association between HCC and PBC was shown to be stronger in patients with advanced histological stage (stage 4 PBC), history of blood transfusion, and smoking or drinking habit, without a clear understanding whether these confounders were associated with increased probability for HCC development in PBC patients, or might be associated directly with PBC development. In a large retrospective study in 15 centres in the USA and Europe involving more than 4500 patients, HCC was more frequently detected in males than in females (6.7 versus 2.6 cases per 1000 years), patients with advanced liver disease (7.6 versus 1.3 cases per 1000 years), and nonresponders to UDCA, whatever score for a response was used (6.6 versus 1.4 cases per 1000 years with Paris 1). However, in a multivariable model, the lack of response to therapy according to Paris 1 was the only independent predictor of HCC development with an adjusted hazard ratio of 3.23 (range: 2.14–4.86). Not surprisingly, therefore, The European Association for the Study of the Liver (EASL) recommends 6 monthly screening.

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### Table 2. Incidence and determinants of hepatocellular carcinoma in autoimmune hepatitis

| Study Size | 25 studies (20 papers, 5 abstracts) including 6528 AIH patients (118 with HCC) |
|------------|-----------------------------------------------------------------------------|
| Cohort     | Median size: 170 patients (25–1721) median follow-up: 8.0 years (3.3–16.0) |
| HCC Incidence Rate | AIH patients: $3.1 \times 1000$ patient/year [2.2–4.2]. patients with cirrhosis: $10.1$ per 1000 patient-year [6.9–14.7] |

AIH, autoimmune hepatitis; HCC, hepatocellular carcinoma.
with ultrasonography of PBC patients with suspected cirrhosis.\textsuperscript{35}

**Primary sclerosing cholangitis**

PSC is a chronic inflammatory syndrome involving the biliary tract, often accompanied by inflammatory bowel disease. This syndrome is a prototype disease linking chronic inflammation to carcinogenesis, being associated with an increased risk of cholangiocarcinoma (CCA), gallbladder cancer, HCC, and colorectal cancer. As the vast majority of CCA occur sporadically in patients without recognizable risk factors, the intrahepatic form of CCA (iCCA) is on the rise worldwide in comparison with extrahepatic CCA.\textsuperscript{34} In a landmark study at Mayo Clinic involving 2395 cases of CCA collected retrospectively, PSC stood as the dominant risk factor for CCA, with a relative risk of 171 compared with controls and in close association with the perihilar type with respect to intrahepatic or distal CCA. Non-PSC related cirrhosis and diabetes were also identified as strong risk factors (Table 3).\textsuperscript{35} The close association of CCA with PSC was confirmed in a multicentre study in Sweden that identified 31 hepatobiliary cancers (13.3\%) among 604 PSC patients who were followed up to 28 years (median 5.7 years).\textsuperscript{36} In that study too, PSC was associated with a skyrocketing risk (160-fold increase) of developing CCA with respect to control population, whereas hepatobiliary or colon cancer was the cause of death in 44\% of the patients compared with 37\% of liver diseases. As expected, hepatobiliary cancer dramatically attenuated the survival probabilities of the affected patients compared with those without hepatobiliary cancer.\textsuperscript{36} The preferential anatomical localization along the biliary tree is not the only distinctive feature of CCA arising in PSC, as this tumour shows a peculiar chronological synchronisation with the diagnosis of cholangitis, and is more frequent in patients with advanced portal hypertension. As CCA usually develops within a few years of diagnosis of PSC, the presence of a tumour should be suspected in every newly diagnosed PSC patient, as this may cause the presenting symptoms.\textsuperscript{37,38} In Mediterranean Europe, where CCA is also on the rise, PSC does not seem to represent a dominant risk factor for CCA as in the USA and northern Europe.\textsuperscript{39} However, more data are needed to confirm this observation.

As for most cancers, early diagnosis stands as the only hope for a surgical cure of CCA, and predictably can only be applied to patients known to be at risk. While PSC patients are known to be at risk of CCA, early diagnosis in these patients is often challenged by the poor predictive power of noninvasive diagnostic methods. EASL recommends that CCA should be suspected in any PSC patient with worsening cholestasis, weight loss, raised CA19-9 and/or new or progressive dominant stricture, particularly with enhancing mass lesion.\textsuperscript{40} While a raised serum CA19-9 may support the diagnosis of CCA, unfortunately this test has a poor specificity. Ductal sampling such as brush cytology and endobiliary

| Subtypes | Risk factors, OR | PSC | (pCCA>iCCA>dCCA) |
|----------|----------------|-----|------------------|
| iCCA 48.8\% | 171.2 | PSC |
| Perihilar (pCCA) 41.5\% | 12.1 | BTD (iCCA>pCCA) |
| Distal (dCCA) 9.6\% | 10.8 | Cirrhosis* (iCCA>pCCA>dCCA) |
| 2.8 | HBV (iCCA>pCCA>dCCA) |
| 2.8 | DTM (dCCA>pCCA>iCCA) |
| 1.3 | Smoke (dCCA>iCCA>pCCA) |
| 0.34 | Aspirin (dCCA<pCCA<iCCA) |

BTD, biliary tract diseases; dCCA, distal cholangiocarcinoma; DTM, Diabetes; iCCA, intrahepatic cholangiocarcinoma; PSC, primary sclerosing cholangitis.

*Non-PSC related cirrhosis.
biopsies are also recommended by professional societies. More recently, the usefulness of single-operator cholangioscopy (SpyGlass, Boston Scientific, Marlborough, MA, USA) in sampling of biliary strictures has been evaluated in patients with PSC and showed promising results. Further challenges in CCA diagnosis have been the reports of iCCA associated to chronic liver disease displaying a radiological wash in/wash out pattern leading to a misclassification with HCC and the fact that in some patients ductal changes are so extensive that the cholangiogram resembles a picture as seen in PSC. The societal recommendations for CCA surveillance in PSC are diverse. The American Association for the Study of Liver Disease (AASLD) provides no specific recommendation, arguing that inadequate information exists regarding the utility of screening for CCA in PSC, imaging studies plus a CA 19-9 test on annual intervals being, however, common practice. EASL recommends ERCP with brush cytology (and/or biopsy) when clinically indicated, and additional investigations such as cholangioscopy may be useful in selected cases.

Hepatobiliary malignancies in paediatric AILD

Paediatric HCC is the second most common type of liver cancer in children after hepatoblastoma; together they account for 0.5–1.5% of all paediatric malignancies and 4% of all liver transplantsations in children. Paediatric HCC differs from HCC developed in adults in the etiological predisposition (it is often associated with inherited liver disease), biological behaviour and lower frequency of cirrhosis. Perinatally acquired HBV is the most important risk factor, mainly in Asia, followed by congenic and genetic diseases (i.e. hepatorenal tyrosinemia, progressive familial intrahepatic cholestasis, glycogen storage disease (GSD), Alagille’s syndrome and congenital porto-systemic shunts). Gender difference, although reported, is not as significant as in adults and white children are equally predisposed to develop HCC as other genetic backgrounds. The Surveillance, Epidemiology, and End Results (SEER) database has shown a stable incidence of paediatric HCC in United States between 1973 and 1997. AILD are relatively common paediatric liver diseases; however, no solid data on HCC risk are available. Baumann and colleagues reported data on survival of children and adolescents that underwent Liver Transplant for HCC between 1985 and 2012 and were included in the large European Liver Transplant Registry; no PBC or AIH patients were included in the study and only one PSC patient was transplanted for HCC. Indeed, the main indication for liver transplantation in AILD children is acute liver failure, and HCC development seems to be a rare complication. Of note, paediatric cholestatic conditions, such as progressive familial intrahepatic cholestasis and biliary atresia, lead to HCC development and not CCA as observed in adults.

International Guidelines from the EASL and AASLD suggest surveillance with ultrasound every 6 months for all cirrhotic children and in noncirrhotic children with chronic HBV infection, GSD types 1, 3 and 4, alpha-1 antitrypsin deficiency, Wilson disease, autoimmune hepatitis, congenital porto-systemic shunts and hepatic venous outflow tract obstruction.

Surveillance, allocation and treatment of HCC in AILD patients

The usefulness and applicability of screening programs for early detection of liver cancer are influenced by several factors, including incidence of the disease in the target population, the availability of efficient tests and their cost, and the availability of treatments and their effectiveness. Indeed, the principal aim of surveillance of liver cancer in chronic liver disease, including AILD, is to reduce liver cancer-related mortality and morbidity. Although liver cirrhosis has been extensively demonstrated to underlay HCC development in up to 90% of cases, evidence on AILD is weaker than in other aetiologies given the rarity of these diseases. Importantly, cirrhosis is a progressive chronic disease that affects patient survival and hampers the application of tumour therapies.

Abdominal ultrasound is the recommended method for liver cancer surveillance in cirrhotic patients, and is often applied to also monitor the development of indirect signs of portal hypertension (i.e. splenomegaly, portal vein diameter), a common complication of liver cirrhosis. Ultrasound has an acceptable diagnostic accuracy when used as a surveillance test; however, it is less sensitive in the setting of hepatic steatosis which is a common problem. A meta-analysis showed that ultrasound surveillance detected the majority of HCC tumours before they presented clinically, with a pooled sensitivity of 94%. However, it was less effective for detecting early-stage HCC, with a
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sensitivity of only 63%.\textsuperscript{53} A 6-month interval has been established as the ideal interval of surveillance for HCC by both EASL and AASLD.

Current EASL recommendations for HCC surveillance include cirrhotic patients, Child-Pugh stage A and B (strong recommendation besides the low available evidence low); cirrhotic patients, Child-Pugh stage C awaiting liver transplantation (evidence low; recommendation strong); noncirrhotic HBV patients at intermediate or high risk of HCC\textsuperscript{*} (according to PAGE-By classes for Caucasian subjects, respectively 10–17 and $\geq 18$ score points) (evidence low; recommendation weak); and (iv) noncirrhotic F3 patients, regardless of aetiology may be considered for surveillance based on an individual risk assessment (evidence low; recommendation weak).\textsuperscript{54} In the case of AILD, EASL clearly recommends 6-monthly screening with ultrasonography of PBC and PSC patients with suspected cirrhosis.\textsuperscript{33,40} However in the case of AIH, the strict association of HCC risk with cirrhosis led the AASLD to recommend 6-monthly screening with abdominal ultrasonography in AIH patients with evidence of cirrhosis, despite the fact that the HCC incidence rate was not found to be over 1.5% per year in this group, for HCC screening to be cost effective.\textsuperscript{55} EASL estimates that surveillance recommendations have not been validated in AIH and cirrhosis, but, as the HCC risk appears to be significant, liver ultrasonography every 6 months in patients with cirrhosis appears reasonable. Indeed, EASL recommends further research to establish whom, how often, and how to screen for liver cancer.\textsuperscript{21} Although the overall risk is low, it is, in our opinion, sufficient to undertake surveillance in those patients with cirrhosis who would be candidates for curative therapies.

Diagnosis, staging systems and treatment allocation of HCC in AILD follow the same criteria of any underlying aetiology. The Barcelona Clinic Liver Cancer (BCLC) staging system\textsuperscript{51} has been repeatedly validated and is recommended for prognostic prediction and treatment allocation of HCC in liver cirrhosis, including AILD.

\textbf{Conclusion}

While both HCC and iCCA are on the rise worldwide, recent evidence suggests that autoimmune disorders are also on the rise, possibly reflecting an enhanced interaction between environmental factors and predisposing genes. Importantly, epidemiological data on AILD are often limited and incomplete, and even more so regarding the risk of liver cancer in AILD. Studies have often small numbers of patients developing liver cancer (both HCC and CCA), and therefore the incidence rate estimates are not precise, especially in subgroup analyses. Further, most studies lack a comparison cohort and reported follow up is relatively short. Finally, the effects of HCC surveillance are not known since this information is not reported in most studies. There are, therefore, some critical issues that would require larger studies and need some consideration.

First, cirrhosis is confirmed to be a predominant risk factor for HCC in AILD, including AIH, PBC and PSC. Based on the fact that HCC development in noncirrhotic subjects is relatively rare, international guidelines do not recommend ultrasound surveillance in this population; however, most of the studies available are limited by the low inclusion of noncirrhotic patients. Second, AASLD guidelines suggest that HCC surveillance is cost-effective if the risk of HCC in the screened population is higher than 1.5% per year.\textsuperscript{56} Of note, most of the available studies report a borderline HCC risk in AIH\textsuperscript{16} and significantly lower in PBC,\textsuperscript{17} the incidence of HCC among patients with PSC is not known but likely low.\textsuperscript{57} There are, however, some special populations that deserve special attention and surveillance; indeed, male patients and nonresponders to treatment seem to be at higher risk of tumour development. Finally, PSC-associated CCA still remains the most challenging autoimmune condition for the hepatologist to deal with. CCA is a major threat to PSC patients, with a lifetime incidence of up to 20% and a reported 400-fold increased risk compared with the general population,\textsuperscript{58} and, unlike HCC, the presence of advanced fibrosis is not required for CCA development. Importantly, optimal biomarkers are lacking and current available biomarkers, that is, serum Ca19-9, have low positive predictive value and are inadequate for surveillance and the ability of serum CA 19-9 to detect asymptomatic or early-stage CCA has never been demonstrated. Similarly, instrumental surveillance with MRCP is not efficacious, since MRI imaging of a benign dominant stricture and ductal CCA remains extremely similar and no clear diagnostic criteria are available. Of note, AASL guidelines for PSC do not comment on cholangiocarcinoma screening. PSC-associated CCA needs therefore to be investigated further and larger cohorts of patients in order to define critical issues as CCA diagnosis, criteria to identify...
high-risk patients, and a rational approach to CCA surveillance.

Intriguingly, however, both the epidemiology and clinical presentation of liver cancer in autoimmune disorders are increasingly at variance with the past, often making diagnosis and management of these conditions a challenge that might require our schedule and approach to screening and management of neoplastic complications to be modified accordingly.

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**References**
1. Global Burden of Disease Cancer Collaboration; Fitzmaurice C, Akinyemiju TF, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2016: a systematic analysis for the global burden of disease study. *JAMA Oncol* 2018; 4: 1553–1568.
2. Bruix J and Sherman M; Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. *Hepatology* 2005; 42: 1208–1236.
3. Bruix J and Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology* 2011; 53: 1020–1022.
4. Ascha MS, Hanouneh IA, Lopez R, et al. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. *Hepatology* 2010; 51: 1972–1978.
5. Global Burden of Disease Liver Cancer Collaboration; Akinyemiju T, Abera S, et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the global burden of disease study 2015. *JAMA Oncol* 2017; 3: 1683–1691.
6. Yang HI, Lu SN, Liaw YF, et al. Hepatitis B e antigen and the risk of hepatocellular carcinoma. *N Engl J Med* 2002; 347: 168–174.
7. Ioannou GN, Splan MF, Weiss NS, et al. Incidence and predictors of hepatocellular carcinoma in patients with cirrhosis. *Clin Gastroenterol Hepatol* 2007; 5: 938–945, 945.e1–4.
8. Beasley RP, Hwang LV, Lin CC, et al. Hepatocellular carcinoma and hepatitis B virus. A prospective study of 22 707 men in Taiwan. *Lancet* 1981; 2: 1129–1133.
9. Yoshida H, Shiratori Y, Moriyama M, et al. Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. IHIT Study Group. Inhibition of hepatocarcinogenesis by interferon therapy. *Ann Intern Med* 1999; 131: 174–181.
10. Sangiovanni A, Prati GM, Fasani P, et al. The natural history of compensated cirrhosis due to hepatitis C virus: a 17-year cohort study of 214 patients. *Hepatology* 2006; 43: 1303–1310.
11. Lok AS, Seeff LB, Morgan TR, et al. Incidence of hepatocellular carcinoma and associated risk factors in hepatitis C-related advanced liver disease. *Gastroenterology* 2009; 136: 138–148.
12. Mancebo A, Gonzalez-Dieuguez ML, Cadahia V, et al. Annual incidence of hepatocellular carcinoma among patients with alcoholic cirrhosis and identification of risk groups. *Clin Gastroenterol Hepatol* 2013; 11: 95–101.
13. Nahon P, Sutton A, Rufat P, et al. Myeloperoxidase and superoxide dismutase 2 polymorphisms comodulate the risk of hepatocellular carcinoma and death in alcoholic cirrhosis. *Hepatology* 2009; 50: 1484–1493.
14. Deugnier YM, Guyader D, Cranotck L, et al. Primary liver cancer in genetic hemochromatosis: a clinical, pathological, and pathogenetic study of 54 cases. *Gastroenterology* 1993; 104: 228–234.
15. Fracanzani AL, Conte D, Fraquelli M, et al. Increased cancer risk in a cohort of 230 patients
with hereditary hemochromatosis in comparison to matched control patients with non-iron-related chronic liver disease. *Hepatology* 2001; 33: 647–651.

16. Tansel A, Katz LH, El-Serag HB, et al. Incidence and determinants of hepatocellular carcinoma in autoimmune hepatitis: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2017; 15: 1207–1217 e1204.

17. Trivedi PJ, Lammers WJ, van Buuren HR, et al. Stratification of hepatocellular carcinoma risk in primary biliary cirrhosis: a multicentre international study. *Gut* 2016; 65: 321–329.

18. Schlesinger S, Aleksandrova K, Pischon T, et al. Diabetes mellitus, insulin treatment, diabetes duration, and risk of biliary tract cancer and hepatocellular carcinoma in a European cohort. *Ann Oncol* 2013; 24: 2449–2455.

19. Calle EE, Rodriguez C, Walker-Thurmond K, et al. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med* 2003; 348: 1625–1638.

20. Younossi ZM, Ogoussen M, Henry L, et al. Association of nonalcoholic fatty liver disease (NAFLD) with hepatocellular carcinoma (HCC) in the United States from 2004 to 2009. *Hepatology* 2015; 62: 1723–1730.

21. European Association for the Study of the Liver. EASL clinical practice guidelines: autoimmune hepatitis. *J Hepatol* 2015; 63: 971–1004.

22. Jepsen P, Gronbaek L and Vilstrup H. Worldwide incidence of autoimmune liver disease. *Dig Dis* 2015; 33(Suppl. 2): 2–12.

23. de Boer YS, Gerussi A, van den Brand FF, et al. Association between black race and presentation and liver-related outcomes of patients with autoimmune hepatitis. *Clin Gastroenterol Hepatol* 2019; 17: 1616–1624.

24. Yeoman AD, Al-Chalabi T, Karani JB, et al. Evaluation of risk factors in the development of hepatocellular carcinoma in autoimmune hepatitis: implications for follow-up and screening. *Hepatology* 2008; 48: 863–870.

25. Park SZ, Nagorney DM and Czaja AJ. Hepatocellular carcinoma in autoimmune hepatitis. *Dig Dis Sci* 2000; 45: 1944–1948.

26. van Meer S, van Erpecum KJ, Sprengers D, et al. Hepatocellular carcinoma in cirrhotic versus noncirrhotic livers: results from a large cohort in the Netherlands. *Eur J Gastroenterol Hepatol* 2016; 28: 352–359.

27. Dakhoul L, Jones KR, Gawrieh S, et al. Older age and disease duration are highly associated with hepatocellular carcinoma in patients with autoimmune hepatitis. *Dig Dis Sci* 2019; 64: 1705–1710.

28. Tarao K, Nozaki A, Ikeda T, et al. Real impact of liver cirrhosis on the development of hepatocellular carcinoma in various liver diseases-meta-analytic assessment. *Cancer Med* 2019; 8: 1054–1065.

29. Lammers WJ, van Buuren HR, Hirschfield GM, et al. Levels of alkaline phosphatase and bilirubin are surrogate end points of outcomes of patients with primary biliary cirrhosis: an international follow-up study. *Gastroenterology* 2014; 147: 1338–1349 e1335; quiz e1315.

30. Webb GJ, Rana A, Hodson J, et al. Twenty-year comparative analysis of patients with autoimmune liver diseases on transplant waitlists. *Clin Gastroenterol Hepatol* 2018; 16: 278–287 e277.

31. Murillo Perez CF, Goet JC, Lammers WJ, et al. Milder disease stage in patients with primary biliary cholangitis over a 44-year period: a changing natural history. *Hepatology* 2018; 67: 1920–1930.

32. Liang Y, Yang Z and Zhong R. Primary biliary cirrhosis and cancer risk: a systematic review and meta-analysis. *Hepatology* 2012; 56: 1409–1417.

33. European Association for the Study of the Liver. EASL clinical practice guidelines: the diagnosis and management of patients with primary biliary cholangitis. *J Hepatol* 2017; 67: 145–172.

34. Saha SK, Zhu AX, Fuchs CS, et al. Forty-year trends in cholangiocarcinoma incidence in the U.S.: intrahepatic disease on the rise. *Oncologist* 2016; 21: 594–599.

35. Choi J, Ghoz HM, Peeraphatdit T, et al. Aspirin use and the risk of cholangiocarcinoma. *Hepatology* 2016; 64: 785–796.

36. Bergquist A, Ekbom A, Olsson R, et al. Hepatic and extrahepatic malignancies in primary sclerosing cholangitis. *J Hepatol* 2002; 36: 321–327.

37. Lindor KD. Characteristics of primary sclerosing cholangitis in the USA. *Hepatol Res* 2017; 47(Suppl. 1): S75–S83.

38. Murillo Perez CF, Goet JC, Lammers WJ, et al. Milder disease stage in patients with primary biliary cholangitis over a 44-year period: a changing natural history. *Hepatology* 2018; 67: 1920–1930.

39. Choi J, Ghoz HM, Peeraphatdit T, et al. Aspirin use and the risk of cholangiocarcinoma. *Hepatology* 2016; 64: 785–796.

40. Bergquist A, Ekbom A, Olsson R, et al. Hepatic and extrahepatic malignancies in primary sclerosing cholangitis. *J Hepatol* 2002; 36: 321–327.

41. Lindor KD. Characteristics of primary sclerosing cholangitis in the USA. *Hepatol Res* 2017; 47(Suppl. 1): S75–S83.

42. Burak K, Angulo P, Pasha TM, et al. Real impact of liver cirrhosis on the development of hepatocellular carcinoma in various liver diseases-meta-analytic assessment. *Cancer Med* 2019; 8: 1054–1065.

43. Lammers WJ, van Buuren HR, Hirschfield GM, et al. Levels of alkaline phosphatase and bilirubin are surrogate end points of outcomes of patients with primary biliary cirrhosis: an international follow-up study. *Gastroenterology* 2014; 147: 1338–1349 e1335; quiz e1315.

44. Webb GJ, Rana A, Hodson J, et al. Twenty-year comparative analysis of patients with autoimmune liver diseases on transplant waitlists. *Clin Gastroenterol Hepatol* 2018; 16: 278–287 e277.

45. Murillo Perez CF, Goet JC, Lammers WJ, et al. Milder disease stage in patients with primary biliary cholangitis over a 44-year period: a changing natural history. *Hepatology* 2018; 67: 1920–1930.

46. Liang Y, Yang Z and Zhong R. Primary biliary cirrhosis and cancer risk: a systematic review and meta-analysis. *Hepatology* 2012; 56: 1409–1417.

47. European Association for the Study of the Liver. EASL clinical practice guidelines: the diagnosis and management of patients with primary biliary cholangitis. *J Hepatol* 2017; 67: 145–172.

48. Saha SK, Zhu AX, Fuchs CS, et al. Forty-year trends in cholangiocarcinoma incidence in the U.S.: intrahepatic disease on the rise. *Oncologist* 2016; 21: 594–599.

49. Choi J, Ghoz HM, Peeraphatdit T, et al. Aspirin use and the risk of cholangiocarcinoma. *Hepatology* 2016; 64: 785–796.

50. Bergquist A, Ekbom A, Olsson R, et al. Hepatic and extrahepatic malignancies in primary sclerosing cholangitis. *J Hepatol* 2002; 36: 321–327.

51. Lindor KD. Characteristics of primary sclerosing cholangitis in the USA. *Hepatol Res* 2017; 47(Suppl. 1): S75–S83.

52. Burak K, Angulo P, Pasha TM, et al. Real impact of liver cirrhosis on the development of hepatocellular carcinoma in various liver diseases-meta-analytic assessment. *Cancer Med* 2019; 8: 1054–1065.
of cholestatic liver diseases. *J Hepatol* 2009; 51: 237–267.

41. Chapman R, Fevery J, Kalloo A, *et al.* Diagnosis and management of primary sclerosing cholangitis. *Hepatology* 2010; 51: 660–678.

42. Arnelo U, von Seth E and Bergquist A. Prospective evaluation of the clinical utility of single-operator peroral cholangioscopy in patients with primary sclerosing cholangitis. *Endoscopy* 2015; 47: 696–702.

43. Sapisochin G, Facciuto M, Rubbia-Brandt L, *et al.* Liver transplantation for “very early” intrahepatic cholangiocarcinoma: international retrospective study supporting a prospective assessment. *Hepatology* 2016; 64: 1178–1188.

44. Li R, Cai P, Ma KS, *et al.* Dynamic enhancement patterns of intrahepatic cholangiocarcinoma in cirrhosis on contrast-enhanced computed tomography: risk of misdiagnosis as hepatocellular carcinoma. *Sci Rep* 2016; 6: 26772.

45. European Society of Gastrointestinal Endoscopy; European Association for the Study of the Liver. Role of endoscopy in primary sclerosing cholangitis: European Society of Gastrointestinal Endoscopy (ESGE) and European Association for the Study of the Liver (EASL) Clinical Guideline. *J Hepatol* 2017; 66: 1265–1281.

46. Hadzic N and Finegold MJ. Liver neoplasia in children. *Clin Liver Dis* 2011; 15: 443–462, vii-x.

47. Katzenstein HM, Kralio MD, Malogolowkin MH, *et al.* Hepatocellular carcinoma in children and adolescents: results from the pediatric oncology group and the children's cancer group intergroup study. *J Clin Oncol* 2002; 20: 2789–2797.

48. Darbari A, Sabin KM, Shapiro CN, *et al.* Epidemiology of primary hepatic malignancies in U.S. children. *Hepatology* 2003; 38: 560–566.

49. Baumann U, Adam R, Duvoux C, *et al.* Survival of children after liver transplantation for hepatocellular carcinoma. *Liver Transpl* 2018; 24: 246–255.

50. Yoon HJ, Jeon TY, Yoo SY, *et al.* Hepatic tumours in children with biliary atresia: single-centre experience in 13 cases and review of the literature. *Clin Radiol* 2014; 69: e113–119.

51. Forner A, Reig M and Bruix J. Hepatocellular carcinoma. *Lancet* 2018; 391: 1301–1314.

52. Bolondi L. Screening for hepatocellular carcinoma in cirrhosis. *J Hepatol* 2003; 39: 1076–1084.

53. Singal A, Volk ML, Waljee A, *et al.* Meta-analysis: surveillance with ultrasound for early-stage hepatocellular carcinoma in patients with cirrhosis. *Aliment Pharmacol Ther* 2009; 30: 37–47.

54. European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2018; 69: 182–236.

55. Manns MP, Czaja AJ, Gorham JD, *et al.* Diagnosis and management of autoimmune hepatitis. *Hepatology* 2010; 51: 2193–2213.

56. Sarasin FP, Giostra E and Hadengue A. Cost-effectiveness of screening for detection of small hepatocellular carcinoma in Western patients with child-pugh class A cirrhosis. *Am J Med* 1996; 101: 422–434.

57. Zenouzi R, Weismuller TJ, Hubener P, *et al.* Low risk of hepatocellular carcinoma in patients with primary sclerosing cholangitis with cirrhosis. *Clin Gastroenterol Hepatol* 2014; 12: 1733–1738.

58. Eaton JE, Talwalkar JA, Lazaridis KN, *et al.* Pathogenesis of primary sclerosing cholangitis and advances in diagnosis and management. *Gastroenterology* 2013; 145: 521–536.