Review
Cirrhosis and Liver Failure

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Cigarette smoking and liver diseases

David Marti-Aguado[1,2], Ana Clemente-Sanchez[2,3], Ramon Bataller[2,*]

Summary

Cigarette smoking is a preventable risk factor for premature morbidity and mortality. A history of smoking is observed in approximately 40% of patients with liver disease, while a growing number of studies are investigating the potential impact of smoking in chronic liver diseases. This review discusses the effects of smoking on liver diseases, at multiple levels, with a focus on its potential causal role. Clinical evidence indicates that cigarette smoking negatively impacts the incidence and severity of fatty liver disease, fibrosis progression, hepatocellular carcinoma development, and the outcomes of patients with advanced liver disease. The underlying mechanisms are complex and involve different pathophysiological pathways including oxidative stress and oncogenic signals. Importantly, smoking promotes cardiovascular disease and extrahepatic cancers in patients with steatohepatitis and in transplant recipients. We discuss how promoting smoking cessation could improve the rates of treatment response (in clinical trials) and fibrosis regression, while reducing the risk of hepatocellular carcinoma and improving liver transplant outcomes. Finally, we discuss current challenges such as the referral of smokers to specialised units for smoking cessation.

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Introduction

In 1958, Ronald A. Fisher, father of modern statistics and well-known inveterate pipe smoker, published papers in relevant journals such as *Nature* and *British Medical Journal* about cancer and smoking.[1,2] He claimed that the evidence purported to show that smoking caused lung cancer was flawed. His objections spurred a complex controversy around the differences between causal effect and statistical correlation. Fishers' objections were more about statistics (and derived conclusions) than the specific possibility that smoking caused cancer. Evidence started to mount and remarkably consistent connections between an increasing incidence of lung cancer and smoking were reasonably interpreted as an axiom. Although the debate around smoking is now over, causality has troubled scientific researchers and healthcare professionals for many years.[3]

Solid population-based epidemiological studies recognise that smoking is a preventable major risk factor for premature disability and mortality.[4] The worldwide prevalence of daily smoking is 30%, and has decreased in recent years.[5] Conversely, the burden of liver disease in Europe continues growing, mainly owing to alcohol consumption and obesity.[6] Although tobacco substances undergo first pass metabolism in the liver, hepatologists have traditionally paid scant attention to smoking-related diseases, perhaps blinded by the sheer number of other risk factors.[6,7] This may lead to the misled belief that smoking *per se* is not a causative agent in chronic liver disease. Current hepatologists usually recommend smoking cessation to patients with fatty liver diseases and in liver transplant recipients given the strong link with cardiovascular events and cancer.[8]

Mounting evidence supports the notion that smoking has a negative impact in chronic liver disease at multiple levels: i) *cell layer*: cigarette smoking promotes hepatocarcinogenesis; ii) *histologic layer*: smoking represents a hepatic fibrogenic stimulus; iii) *systemic layer*: smoking exacerbates metabolic fatty liver diseases; and iv) *clinical layer*: smoking negatively impacts liver-related outcomes. In this review, we have focused on the role of cigarette smoking in liver disease and discussed its potential implication in disease severity and clinical outcomes. To address this important issue, Austin Bradford Hill causality criteria (used to demonstrate the connection between cigarette smoking and lung cancer) have been used to critically appraise the correlation between smoking and liver disease (Table 1).[3]

Smoking and fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease, with an estimated worldwide prevalence of 25%.[9] The development and progression of NAFLD is determined by both genetic and environmental factors. Among the latter, an increasing body of evidence indicates that cigarette smoking negatively effects the progression of fatty liver disease. As both NAFLD and smoking are associated with the development of features of the metabolic syndrome, there has been increasing interest in testing the hypothesis that

[1]*Digestive Disease Department, Clinic University Hospital, INCLIVA Health Research Institute, Valencia, Spain;* [2]*Center for Liver Diseases, Division of Gastroenterology, Hepatology and Nutrition, Department of Medicine, Pittsburgh Liver Research Center, University of Pittsburgh Medical Center, Pittsburgh, PA, USA;* [3]*Liver Unit and Digestive Department, Hospital General Universitario Gregorio Marañon, CIBERehd, Instituto de Salud Carlos III, Madrid, Spain*

* Corresponding author. Address: Center of Liver Diseases, Division of Gastroenterology, Hepatology and Nutrition, Department of Medicine, University of Pittsburgh Medical Center, 201.19 Kaufmann Medical Building, 3471 Fifth Avenue, Pittsburgh, PA 15213, USA.

E-mail address: bataller@pitt.edu (R. Bataller).

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Table 1. Causal-relationship criteria supporting a deleterious effect of cigarette smoking in liver diseases.

Causality criteria	Definition	Example
Strength	Magnitude of the association	Current smokers attributable risk fraction for HCC [87]
Consistency	Reproducibility in different studies	Smoking history as a predisposing factor for PBC [61]
Specificity	One-to-one relationships	Liver metabolises tobacco chemicals into carcinogens [97]
Temporality	Exposure must precede the outcome	Tobacco smoking impacts liver transplantation outcomes [133]
Biological gradient	Dose-response curve and reversibility	Increased fibrosis severity in NAFLD and PBC [22,67]
Plausibility	Known bio-pathological mechanism	Induced AMPK inactivation involved in fatty acid synthesis [37]
Coherence	Consistent with existent knowledge	Profibrogenic effect of tobacco in different organs [71]
Experiment	Animal models experimental evidence	Cigarette smoking increases hepatic lipogenesis [41]
Analogy	Similarities with other associations	NAFLD and smoking are linked to metabolic syndrome features [10]

AMPK, AMP-activated protein kinase; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; PBC, primary biliary cholangitis.

NAFLD and smoking could be associated.[10,11] Furthermore, the links between smoking, insulin resistance, and visceral fat accumulation offer a pathological background that supports this idea.[12–14] In this context, numerous experimental and clinical studies have been performed to explore the impact of smoking on NAFLD.

Cross-sectional population-based studies have shown contradictory results regarding a possible association between smoking and NAFLD.[15–17] The inconsistency between these studies can be explained by: (i) different methods to determine smoking status (self-reported questionnaires *vs.* cotinine measured levels); (ii) NAFLD diagnosis based on ultrasound; (iii) different prevalence of overall current smokers (25% in the USA and Europe *vs.* 51% in China); and (iv) the lack of prospective databases that better reflect other lifestyle parameters such as physical activity, exercise, diet, alcohol intake, *etc.* To better elucidate the impact of smoking on NAFLD development, prospective longitudinal cohort studies have recently been published. These studies provide more robust evidence about the association between active smoking and incident NAFLD, after adjusting for time-changing cofounders (diet, physical activity, alcohol intake or socioeconomic factors).[18–20] Importantly, the risk association increased with the number of pack-years (10–19.9 pack-years: hazard ratio [HR] 1.25; 95% CI 1.21–1.29; ≥20 pack-years: HR 1.36; 95% CI 1.30–1.42, compared to 0 pack-years).[18] It is difficult to establish a definitive causal relationship between smoking and NAFLD if the role played by the intermediary effect of possible confounders is not overlooked. With this consideration, reviewed results suggest that smoking may contribute to the development of NAFLD. Similar studies to corroborate these findings in non-Asian populations are warranted.

The most convincing evidence supporting a link between smoking and NAFLD comes from large studies that included histological analysis of liver tissue. Ancillary studies from the non-alcoholic steatohepatitis (NASH) Clinical Research Network database have evaluated the association of smoking with the severity and progression of liver disease .[21,22] The prevalence of smoking among patients with NAFLD was around 20%.[21,22] Advanced fibrosis at diagnosis was independently associated with age, diabetes, and smoking history of ≥10 pack-years (odds ratio [OR] 1.6; 95% CI 1.2-2.2). The frequency of advanced fibrosis was higher among diabetics (regardless of smoking status) and smokers without diabetes than in non-diabetics without significant smoking history.[21] This suggests that smoking may enhance the progression of NAFLD, partly through its effect on insulin resistance, in an additive but non-synergistic association with diabetes. The histologic progression of NAFLD severity over time has also been evaluated with paired liver biopsies.[22] The likelihood of fibrosis regression was found to be lower among active smokers (proportion of regression: 4%; no change: 10%; fibrosis progression: 12%), corroborating the harmful effects of smoking from a histological perspective. Several studies showed an association between higher fibrosis severity and increasing cigarette pack-years, with lower fibrosis regression among smokers.[21–23] In contrast, the effect of smoking on the degree of steatohepatitis is less marked, with no differences in NASH resolution.[21–23] While the profibrogenic effects of smoking are well documented, 2 important methodological issues could explain these results. First, a selection bias by which healthier patients were over-represented (smoking activity can be underestimated by patient perception of negative attitudes to smoking). Second, NAFLD studies do not typically account for the potential contribution of low levels of alcohol use. In fact, modest alcohol consumption lowers the likelihood of NASH resolution and is associated with more severe steatosis but without a demonstrable association with fibrosis.[24]

Cardiovascular disease (CVD) is the main cause of mortality among patients with NAFLD.[25] This is largely sustained by the close association of NAFLD with traditional metabolic and cardiovascular risk factors that lead to CVD events. However, the independency and magnitude of the associations between NAFLD and CVD events is uncertain. Recently, Alexander *et al.* performed a population-based, retrospective, case-control study using electronic data from 4 European countries estimating the

Key point

All patients with liver disease who are active cigarette smokers should be advised and assisted to quit smoking.

incidence of major CVD events (acute myocardial infarction and stroke) in patients with NAFLD.[26] A recorded diagnosis of NAFLD was not independently associated with major CVD events. This remains a matter of debate that should be better addressed in prospective studies. Along these lines, a recent meta-analysis that included observational cohort studies with imaging-defined or biopsy-confirmed NAFLD showed that smoking is significantly associated with an increased risk of fatal and non-fatal cardiovascular events. However, these findings derive from observational studies and caution must be paid when concluding that NAFLD unequivocally causes CVD.[27] Importantly, recent studies have demonstrated that cigarette smoking increases the risk of CVD events among patients with NAFLD (OR 2.87; 95% CI 2.58–3.19).[28] Smoking was also associated with lower rates of fibrosis regression (Fig. 1).[29,30] Contrary to the non-synergistic association of smoking and diabetes on NASH-fibrosis, smoking and other metabolic risk factors (hypertension and dyslipidaemia) have a synergistic effect on the development of CVD.[31,32] Smoking and diabetes also have an additive effect on CVD incidence.[21,32] Thus, it is biologically plausible that steatosis and smoking could have a synergistic effect on CVD, as both conditions share several underlying mechanisms, including hepatic/systemic insulin resistance, atherogenic dyslipidaemia, hypertension and upregulation of pro-atherogenic, pro-coagulant and proinflammatory mediators.[25] Based on these observations, it is widely accepted that patients with NAFLD should abstain from cigarette smoking. Most tertiary centres have smoking cessation programmes that may be very useful for this endeavour. Surprisingly, a recent survey showed that less than 25% of hepatologists refer smokers to a specialised unit for counselling.[33] Hepatologists and gastroenterologists should be more active in identifying smoking as a risk factor of liver disease progression and in establishing strategies to promote smoking cessation among patients with NAFLD. It is important to bear in mind that smoking cessation has also been associated with NAFLD development due to weight gain, so patients should be closely monitored by a multidisciplinary team including dieticians.[34]

Patients with alcohol misuse are 3-fold more likely to smoke heavily than the general population. Likewise, the prevalence of alcohol abuse is about 4-fold higher among people with nicotine dependence than in the general population.[35] It is unclear if cigarette smoking aggravates the clinical course of alcohol-related liver disease (ALD). Smoking may exacerbate the pathogenic effects of alcohol on the

Key point

Smoking may negatively impact the incidence and severity of fatty liver disease.

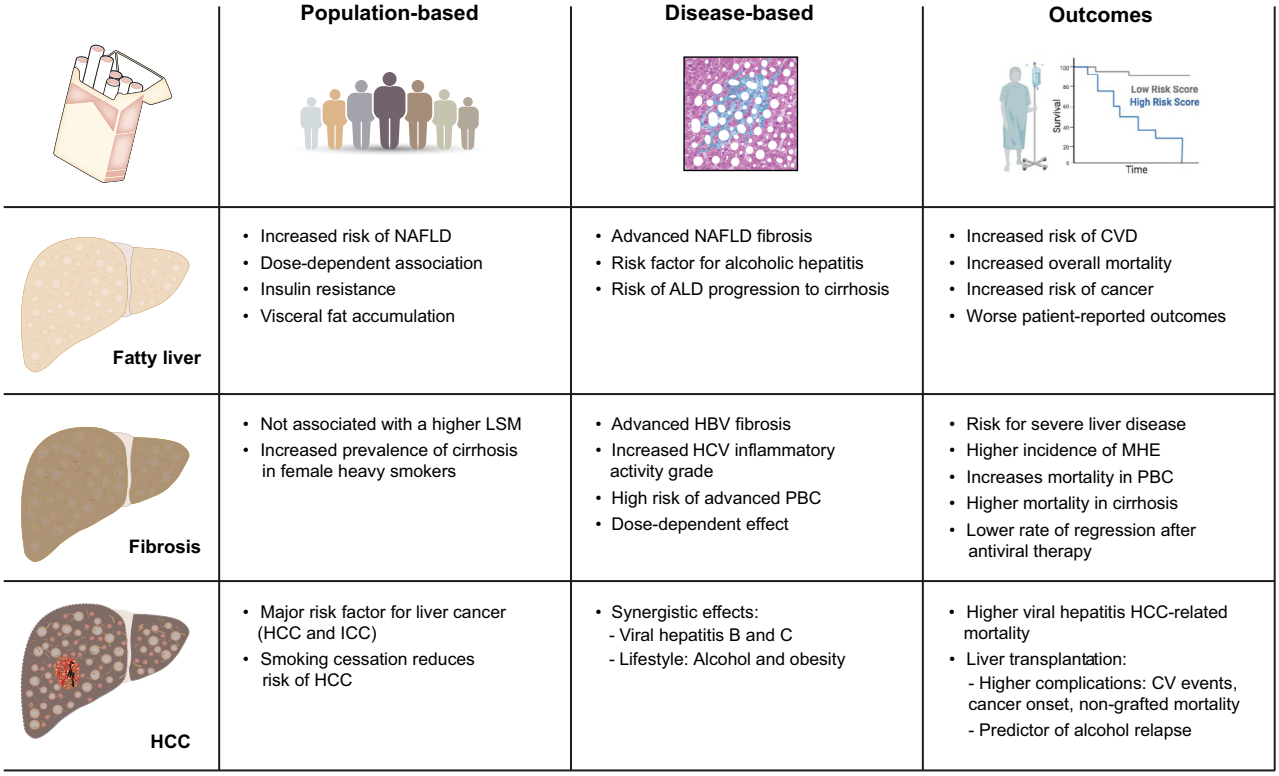


Fig. 1. Effects of cigarette smoking across the spectrum of liver disease reported in different investigation-related settings. Summary of cigarette smoking outcomes in particular disease groups (*e.g.* those with fatty liver disease, fibrosis and hepatocellular carcinoma, including liver transplant recipients). Evidence was evaluated from population-based, disease-based and longitudinal studies. AlcHep, alcoholic hepatitis; ALD, alcohol-related liver disease; CVD, cardiovascular disease; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; LSM, liver stiffness measurement; MHE, minimal hepatic encephalopathy; NAFLD, non-alcoholic fatty liver disease; PBC, primary biliary cholangitis.

liver and heavy cigarette smoking aggravates the deleterious effect of alcohol abuse in humans, suggesting that these factors may have a synergistic effect.[36] There is a clear need to perform both retrospective and prospective large cohort studies to explore this particular association. The impact of smoking in liver transplant recipients with ALD is discussed in a later section.

Experimental studies in mice have also investigated the underlaying mechanisms of NAFLD development and fibrosis progression (Fig. 2). Studies aimed at investigating the role of smoke exposure in standard diet-fed mice have shown: (i) an increase in hepatic lipogenesis through deregulation of genes involved in the modulation of 5′-AMP-activated protein kinase (AMPK) and sterol response element binding protein-1 activity, which are both critical in fatty acid synthesis, and (ii) a reduction of cholesterol clearance due to an imbalance in bile acid synthesis.[37–39] Nicotine exposure exacerbates diet-induced hepatic steatosis through AMPK inactivation and activation of its downstream target acetyl-coenzyme A-carboxylase.[40] In high-fat diet-fed rats, smoke exposure worsened the histological severity of NAFLD by increasing oxidative stress, hepatocellular apoptosis and ERK signalling.[41,42] Cigarette smoking increases *de novo* liver steatosis and further exacerbates NASH-related liver injury.[43] These experimental studies strongly suggest that smoking acts as a co-factor in NAFLD progression, modulating several pathways that regulate hepatocyte cell death and fibrogenesis. Importantly, the deleterious effect of smoking is higher in heavy smokers and is not observed after a short exposure in both animal and human studies, suggesting a dose-response.[41,42,44] Further research with standardised models is needed to elucidate the underlying mechanisms of smoking-induced NAFLD exacerbation.

In conclusion, mounting evidence suggests that smoking may negatively impact on the incidence and severity of NAFLD (Fig. 3). This evidence has implications for the design of future clinical trials in patients with NAFLD. Consensus recommendations (*i.e. Liver Forum*) for reporting standardised baseline parameters in NASH clinical trials should include current smoking as an important parameter to be recorded and evaluated.[45,46] Currently, few phase II clinical trials provide information on this essential lifestyle comorbidity (Fig. 4).[47] To ensure the reliability of clinical trials, an adequate stratification including comorbidities like smoking, alcohol consumption and metabolic factors seems mandatory.

Smoking in the progression of other chronic liver diseases

Hepatic fibrosis is a major determinant of morbidity and mortality in patients with chronic liver disease.[9,11,29] Understanding the individual risk of progression to fibrosis is crucial for personalised clinical management. Among the environmental factors that exacerbate liver fibrosis across all aetiologies, major evidence suggests that cigarette smoking could play a profibrogenic role. Well-designed studies are needed to unravel the specific role of smoking and distinguish it from

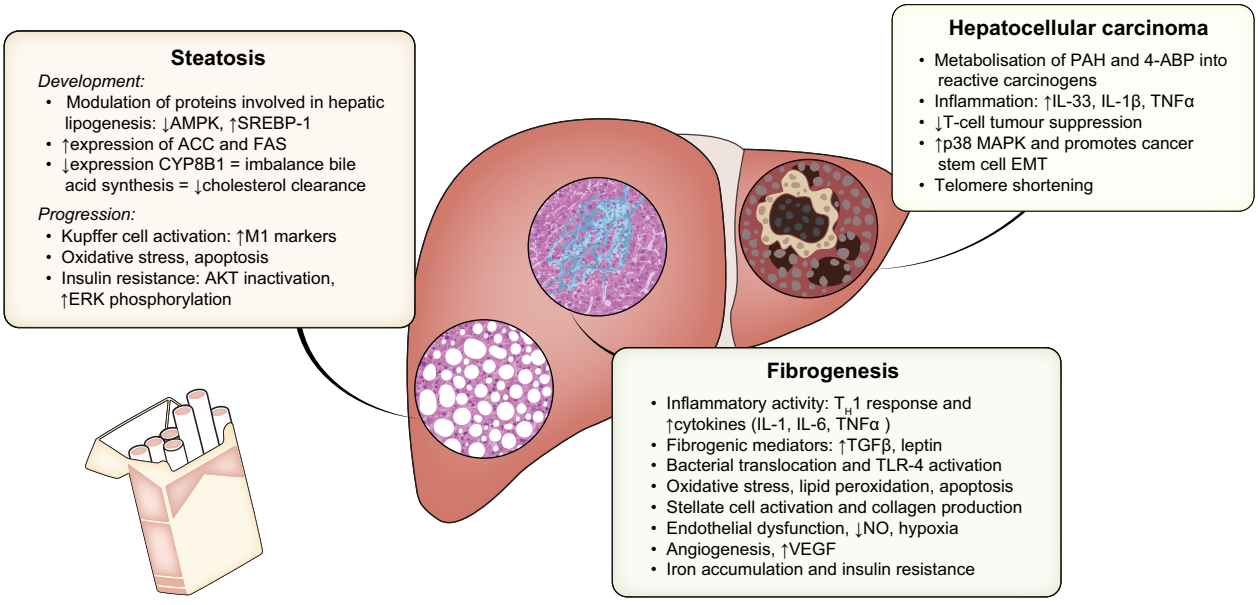


Fig. 2. Potential mechanisms of liver disease induced by cigarette smoke. The effect of cigarette smoking on postulated mechanisms for the development and progression of hepatic steatosis, fibrogenesis and hepatocarcinogenesis are schematically illustrated. 4-ABP, 4-aminobiphenyl; ACC, acetyl-coenzyme A-carboxylase; AKT, protein kinase B; AMPK, AMP-activated protein kinase; EMT, epithelial to mesenchymal transition; ERK, extracellular signal regulated kinase; FAS, fatty acid synthase; IL, interleukin; MAPK, mitogen-activated protein kinase; NO, nitric oxide; PAH, polycyclic aromatic hydrocarbons; SREBP, sterol response element binding protein; TGF, transforming growth factor; T_H1, T helper 1; TLR, toll-like receptor; TNF, tumour necrosis factor; VEGF vascular endothelial growth factor.

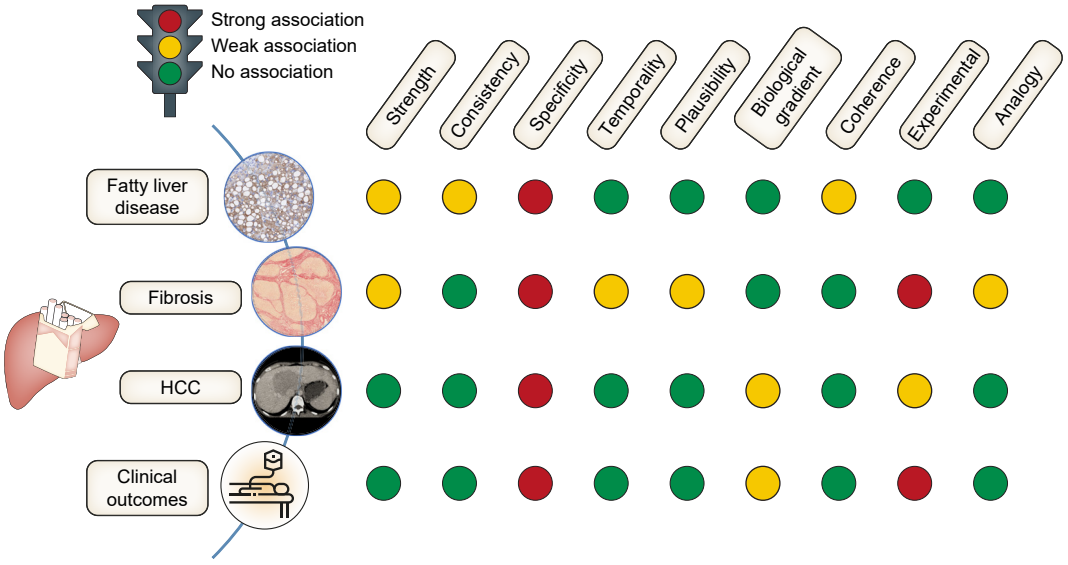


Fig. 3. Traffic light system to depict the magnitude of the association between cigarette smoking and liver disease according to each causal-relationship criterion. Association was critically appraised for fatty liver disease, advanced fibrosis, HCC and clinical outcomes. Green circles represent a strong association, yellow circles represent a weak association, and red circles represent absence of association. HCC, hepatocellular carcinoma.

other confounding factors (Fig. 3). There is a well-known association between smoking and alcohol consumption, another important profibrogenic habit. Therefore, it is feasible that the co-existence of both lifestyle habits could explain the different rates of fibrosis progression among patients with similar degrees of alcohol misuse.[48,49]

Population-based studies show that smoking prevalence is high, with important differences depending on the target population and geographic region (*e.g.*, 30% in young UK adults *vs.* 60% in middle-aged Danish adults from the general population).[50,51] Consequently, studies in patients with liver disease are difficult to compare, given the differences in population selection (age, underlying disease), fibrosis assessment (liver stiffness measurements [LSMs], ICD codes), smoking definition (dichotomised, categorised by dose) and covariables selected for adjustment. The prevalence of smoking history in patients with liver disease is high (around 40%) in most studies, suggesting that this is a clinically relevant issue. Smoking history is not associated with a higher LSM in "healthy individuals", but it is associated with an increase in cirrhosis prevalence in female heavy smokers (>10 cigarettes/day) and fibrosis degree in patients with underlying liver disease.[50–53] Epidemiological studies specifically aimed at evaluating the impact of cigarette smoking on liver fibrosis are summarised in Table 2. Earlier studies in this field focused on viral hepatitis with a retrospective and cross-sectional approach, while more recent studies targeting NAFLD have used prospective longitudinal assessments.

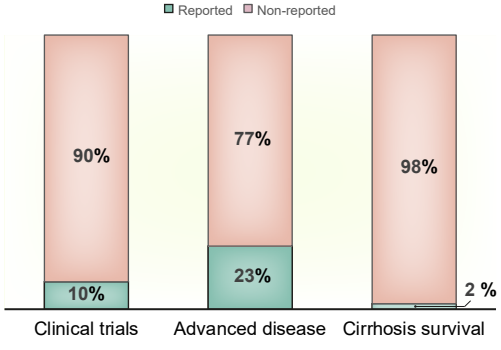


Fig. 4. Prevalence of reported smoking status in literature in different liver disease-related studies. Smoking data was only reported in 10% of the 10 reviewed clinical trials on NASH drugs,[47] 23% of the 13 reviewed studies on liver-related events in biopsy-confirmed NAFLD,[84] and 2% of the 118 reviewed studies on prognostic indicators of survival in viral and alcohol-related cirrhosis.[114] NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

Prospective studies performed in Asian patients with chronic hepatitis B (CHB) showed a deleterious effect of smoking on the progression to cirrhosis in heavy smokers (≥20 cigarettes/day), with a magnitude of effect that was even higher than alcohol consumption. The effect was particularly pronounced in regular alcohol consumers, suggesting a possible additive effect of cigarettes and alcohol. Recently, the impact of cigarette smoking on responses to antiviral therapy in patients with CHB has been explored in a longitudinal study from China. Smoking was associated with both an aggravation of liver fibrosis and a delay in fibrosis regression in patients under HBV antiviral therapy.[54] Also, smoking may contribute

Key point

Cigarette smoking is strongly associated with CVD events, the main cause of death in patients with NAFLD.

Table 2. Main clinical studies focused on the impact of cigarette smoking on liver fibrosis.

Study	Patients, n (country)	Design	Smoking assessment	Smoking prevalence	Gold standard	Results
Kleiner DE, 2019[22]	446 with NAFLD (USA)	Prospective, NASH CRN longitudinal	Interview, grouping by status	9% active, 37% ever smoker	Histology	Current smoker ↓ fibrosis regression (p = 0.03)
Ou H, 2019[145]	225 with NAFLD (China)	Retrospective cross-sectional case-control	n.a., smoking index (no cig/day * duration of smoking)	44% smokers	Liver stiffness	Smoking index ↑ liver fibrosis (OR 1.3; 1.1–2.1)
Xiong M, 2019[54]	2,144 males with CHB (China)	Prospective, longitudinal cohort, propensity score matched	Interview, grouping by pack-years	47% smokers	Liver stiffness	Smokers ↑ advanced fibrosis (OR 1.5; 1.1–1.9), dose-response (≥10 pack-years ↓ fibrosis regression p = 0.02)
Mantaka A, 2018[124]	117 with PBC (Greece)	Retrospective cross-sectional case-control	Interview, grouping by status and pack-years	26% active, 30% ex-smoker	Histology	Smoking history ↑ advanced fibrosis (p = 0.04), dose-response (OR 3.2; 2.0–6.3)
Musterman ID, 2017[23]	56 with NAFLD (Netherlands)	Retrospective cross-sectional case-control	Chart review and interview	39% history of smoking	Histology	Smoking history ↑ fibrosis score (p = 0.04), dose-response (no of pack-years ↑ advanced fibrosis)
Dam MK, 2013[51]	18,479 from the general population (Denmark)	Population-based cohort	Interview, groups: ex, never, ≤ and >10 cig/day	56% ♀ 67% ♂	Hospital register: cirrhosis ICD code	Adjusted HR for >10 cig/day: ♀ 2.2; 1.4–3.4 ♂1.4; 0.9–2.2
Corpechot C, 2012 [67]	164 with PBC (France)	Prospective, cohort	Interview, grouping by pack-years	11% active smokers, 26% smoking history	Histology	Smoking history ↑ advanced fibrosis (OR 3.6; 1.5–8.5), dose-response (OR 1.2; 1.0–1.3)
Zein CO, 2011 [21]	1,091 with NAFLD (USA)	Prospective, NASH CRN cross-sectional studies	Interview, significant smoking: ≥10 pack-years	24% with significant smoking history	Histology	Significant smoking ↑ advanced fibrosis (OR 1.6; 1.2–2.2)
TsochatzisE, 2009 [60]	271 with CHB and CHC (Greece)	Prospective, cross-sectional case-control	Interview, groups: never, smoker, ≥20 pack-years	42% CHB 61% CHC smokers	Histology	No association with CH fibrosis. ≥20 pack-years ↑ CHC advanced fibrosis (OR 3.9; 1.4–11.3)
Dev A, 2006 [56]	244 with CHC (USA)	Retrospective, cross-sectional case-control	Medical records, grouping by no of cig/day	25% smokers	Histology	Smoking ↑ risk of fibrosis (OR 1.3; 1.0–1.8)
Zein CO, 2006 [57]	97 with PBC (USA)	Retrospective, cross-validated case-control	Interview, significant smoking: ≥10 pack-years	44% with significant smoking history	Histology	Smoking history ↑ advanced fibrosis (p <0.001), dose-response (≥10 pack-years: OR 13.3; 4.3–49.3)
Hézode C, 2003 [59]	244 with CHC (France)	Prospective, cross-sectional case-control	Interview, grouping by no of cig/day	44% smokers, 25% >15 cig/day	Histology	No association with fibrosis (p = 0.5), >15 cig/day ↑ activity grade (OR 3.6; 1.5-8.8)
Pessione F, 2001[58]	310 with CHC (France)	Retrospective, cross-sectional case-control	n.a., grouping by pack-years	57% smokers	Histology	Smoking ↑ fibrosis score (p = 0.03), dose-response (≥15 pack-years: OR 1.9; 1.1-3.6)
Yu MW, 1997[146]	1,506 with CHB (Taiwan)	Prospective, longitudinal	Interview, groups: 0, <20 and ≥20 cig/day	43% smokers	Ultrasound image of cirrhosis	≥20 cig/day ↑ risk of cirrhosis (OR 2.1; 1.2-3.7)

Included studies used logistic regression models to explore the association between smoking and fibrosis. OR with 95% confidence intervals determine the strength of statistical associations. p value <0.05 was considered to be statistically significance. CHB, chronic hepatitis B; CH, chronic hepatitis; CHC, chronic hepatitis C; HR, hazard ratio; NAFLD, non-alcoholic fatty liver disease, n.a., not available; NASH CRN: Non-Alcoholic Steatohepatitis Clinical Research Network; OR, odds ratio; PBC, primary biliary cholangitis.

to sustained high viral loads and have a greater effect on liver inflammation (alanine aminotransferase increase).[55] These studies strongly suggest that cigarette consumption influences the progression of liver injury in CHB. Regarding chronic hepatitis C (CHC), conflicting results have been observed. Retrospective studies showed that tobacco use was an independent predictor of fibrosis stage.[56,57] However, a weak relationship was seen on multivariate analysis, particularly when histologic inflammatory activity was taken into consideration.[58] Hezode *et al.* performed a prospective study and found no significant relationship between fibrosis stage and smoking history.[59] In contrast, smoking was independently and strongly associated with higher inflammatory activity (OR 3.6; 95% CI 1.5-8.8). Finally, Tsochatzis *et al.*, also in a prospective study, linked heavy smoking with steatosis and fibrosis severity in CHC but not in CHB.[60] Collectively, this data suggests that cigarette smoking may enhance fibrosis severity in viral hepatitis by increasing necroinflammatory grade and fat deposition.

History of smoking has traditionally been considered as a predisposing factor for primary biliary cholangitis (PBC).[61] Epidemiological and clinical studies have consistently demonstrated this association, which is likely to be due to the proinflammatory effects of smoking and a possible deleterious effect in biliary epithelial cells.[59–63] Smoking impacts both innate and adaptive immunity and plays dual roles in regulating immunity by either exacerbating pathogenic immune responses or attenuating defensive immunity.[64] This dual effect is central to the pathogenesis of autoimmune diseases and mechanisms linking cigarette smoking to autoimmune disorders are starting to be revealed. For instance, it has been shown that tobacco components may promote an adaptive T helper 1 (T_H1) immune cell response to autoantigens and disrupt regulatory T-cell function.[65] In patients with PBC, the predominant T cells infiltrating portal tracts are T_H1 cells.[66] This feature, together with autoantigen overload in individuals with impaired capacity for apoptotic cell removal, supports the potential role of smoking in inducing an immune-mediated bile duct injury.[67] In addition to an effect on PBC risk, 2 independent studies have shown that smoking history and level of tobacco consumption also impact on the degree of fibrosis.[57,67] Like the association of smoking with NAFLD-fibrosis but not NASH,[21–23] these PBC studies showed that necroinflammatory activity was not higher in smokers, cautiously suggesting that tobacco may exert profibrogenic effects through mechanisms that do not interfere with inflammation.[57,67] Possible mechanisms promoting fibrosis progression will be further discussed. The strong association between tobacco and PBC has not been seen in other autoimmune liver diseases, such as autoimmune hepatitis.[68] In patients with increased genetic susceptibility to autoimmune hepatitis, environmental factors such as pathogens, xenobiotics, or pollutants may trigger humoral and cellular autoimmune responses to liver autoantigens by molecular mimicry.[69] Whether toxic components of tobacco may precipitate autoimmune-mediated liver injury via this mechanism deserves further investigation. Table 3 summarises the prevalence of smoking in particular disease groups and stages, compared to the prevalence in the corresponding reference population.

The mechanisms underlying the profibrogenic effect of cigarette smoking have been mostly explored at the experimental level. *In vivo* and *in vitro* studies showed that nicotine modulates fibroblast activation and enhances pro-fibrogenic mechanisms.[70] These effects have also been observed in other organs.[71] In the liver, mice models have shown that nicotine has a deleterious influence by aggravating the hepatotoxic effects of carbon tetrachloride.[72] It should be noted that experimental data on the direct hepatotoxic effects of tobacco components are more limited than data reported for other organs.[72,73] Overall, potential mechanisms of cigarette smoking-induced fibrogenesis include (Fig. 2):

- Release of transforming growth factor-β1 with activation and proliferation of resident fibrogenic cells. In response to injury, transforming growth factor-β1 stimulates the production of extracellular matrix proteins, mainly collagen synthesis by hepatic stellate cells (HSCs), and plays a key role in the regulation of fibrosis.[73]
- Increased production of proinflammatory cytokines (interleukin [IL]-1, IL-6 and tumour necrosis factor-α) and recruitment of inflammatory cells such as neutrophils and monocyte-macrophages.[74,75]
- Toll-like receptor 4 activation, a key pathway promoting fibrosis in steatohepatitis.[76] Cigarette smoking is associated with impaired intestinal barrier, increased permeability and bacterial translocation.[77] Toll-like receptor 4 is activated on the surface of HSCs by intestinal bacterial lipopolysaccharides derived from the gut, triggering cell activation and fibrogenesis.[78] This mechanism links fibrosis to the microbiome.
- Activation of reactive oxygen species (ROS) production by NADPH oxidase. Subsequent oxidative stress can lead to lipid peroxidation and hepatocellular damage.[79]
- Increase of carboxyhaemoglobin and decreased oxygen-carrying capacity of red blood cells which leads to tissue hypoxia. Induced erythropoietin production and secondary polycythaemia contribute to the accumulation of iron in macrophages and hepatocytes, enhancing liver injury and fibrosis.[80] In this line, an interaction between current smoking and haemoglobin

Key point

There is an increased risk of fibrosis progression to more advanced stages in smokers across the different liver disease aetiologies, with a higher impact on heavy smokers.

Table 3. Prevalence of smoking in particular liver disease groups and stages, compared to the prevalence in the corresponding reference population.

Disease, stage	Prevalence	Reference	Prevalence
NAFLD[19,21,22,50]			
Steatosis (S1-3)	Current S1: 29% Current S2: 32% Current S3: 28%	No steatosis (S0)	Current: 14-29%
NASH	Former: 38% Current: 9%	Simple steatosis	Former: 33% Current: 11%
F3-4	Former: 34% Current: 10% >10 pack-years: 43%	F0-2	Former: 9% Current: 9% >10 pack-years: 28%
ALD [35,51,115,122]			
Alcohol-related cirrhosis	Current: 60-78%	General population Other CLD cirrhosis	Current: 12% Current: 71%
CHB[54,60,146]			
F3-4	Current: 40-56% >20 pack-years: 28%	F0-2	Current: 42-44% >20 pack-years: 17%
Cirrhosis	Current: 59% >20 pack-years: 27%	No cirrhosis	Current: 42% >20 pack-years: 18%
CHC[58–60]			
F3-4	Former: 19% Current: 54-63% >20 pack-years: 43%	F0-2	Former: 18% Current: 57-61% >20 pack-years: 22%
A2-3	Current: 48%	A0-1	Current: 34%
S1-3	>20 pack-years: 32%	S0	>20 pack-years: 12%
PBC[57,67,124]			
F3-4	Current: 21-71% >10 pack-years: 71%	F0-2	Current: 19-33% >10 pack-years: 19%
A2-3	Former: 20-25% Current: 10-23%	A0-1	Former: 18% Current: 16%

A, necroinflammatory activity grade; ALD, alcohol-related liver disease; CHB, chronic hepatitis B; CHC, chronic hepatitis C; F, fibrosis stage; CLD, chronic liver disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cholangitis; S, steatosis grade.

levels and the risk of NAFLD-advanced fibrosis have been shown.[81]

- Changes in the microvasculature such as endothelial dysfunction, smooth muscle cell proliferation and vasoconstriction, leading to an impairment in nitric oxide delivery and tissue hypoxia.[82] In response to liver hypoxia, expression of vascular endothelial growth factor and type I collagen are increased in activated HSCs, enhancing fibrogenesis.[56,83]

In conclusion, there is mounting evidence from cross-sectional and retrospective studies that suggest that cigarette smoking has a deleterious effect on the progression of chronic viral hepatitis, PBC and NAFLD (Fig. 1). The mechanisms implicated are complex and involve different pathophysiological pathways. However, smoking status is not consistently reported in studies investigating fibrosis progression. A recent meta-analysis evaluating the association between fibrosis stage and outcomes of patients with NAFLD showed that only 3 out of 13 included studies accounted for this baseline prognostic characteristic (Fig. 4).[84] Given that reducing the number of pack-years or complete cessation of smoking can impact on relevant treatment outcomes like fibrosis regression after HCV clearance or NAFLD-fibrosis progression, special attention should be paid to identify and treat this deleterious lifestyle component in patients with liver disease.[22,85]

Smoking and hepatocellular carcinoma

Liver cancer is a major contributor to the worldwide cancer burden with an estimated global incidence rate of 9.3 per 100,000 person-years and a nearly equivalent mortality rate of 8.5.[86] It is responsible for 22% of cancer-related deaths worldwide.[4] In line with the carcinogenic properties of tobacco in several organs, a large number of studies indicate that cigarette smoking is associated with an increased incidence of hepatocellular carcinoma (HCC) in patients with cirrhosis.[87]

Several case-control and cohort studies have demonstrated that cigarette smoking is associated with an increased incidence of HCC. Relative risk variation can be explained by differences in the study design, the severity of smoking and the underlying disease.[36] This association has been confirmed by several well deigned meta-analyses.[87–89] Fig. 5 summarises the pooled risk ratios for HCC development from 3 large meta-analyses differentiating between former, current and heavy smokers, compared to never smokers.[87–89] The earliest meta-analysis published in 2009, included 38 cohort studies and 58 case-control studies. The observed adjusted relative risk for HCC was 1.12 (95% CI 0.78–1.60) for former smokers and 1.51 (95% CI 1.37–1.67) for current smokers.[88] In 2017, a meta-analysis including 81 epidemiological studies, showed an OR for HCC development of

1.39 (95% CI 1.26–1.52) for former smokers and 1.55 (95% CI 1.46–1.65) for current smokers.[89] Finally, the Liver Cancer Pooling Project consortium of 14 prospective cohort studies from the USA reported a HR for incident HCC of 1.24 (95% CI 1.08–1.43) for former smokers and 1.86 (95% CI 1.57–2.20) for current smokers.[87] Considering the high prevalence of smoking, the population attributable risk fraction for HCC seems to be relatively large despite the modest risk estimates. Tobacco accounts for 13% of HCC worldwide and its interaction with chronic viral hepatitis increases the risk of liver cancer.[90,91] There are no studies that have specifically examined the association between smoking and NAFLD-related HCC. However, tobacco and obesity may have a synergistic effect on HCC development (synergistic index: 2.9; 95% CI 1.8–3.5).[92] Alcohol and smoking also synergise as risk factors of HCC, but no interaction is seen in terms of HCC-related mortality.[92–94] Finally, even if there is relevant heterogeneity among different studies, a positive dose-response relationship between the number of cigarettes smoked has also been reported.[87,88,92,95] In patients particularly predisposed to HCC, such as those with chronic viral hepatitis, the association between smoking and liver cancers remained for current smokers but significantly reduced for former smokers.[88] In contrast, no interaction among smoking and HBsAg status has been seen in terms of HCC mortality.[94]

Regarding the underlying mechanisms, it is biologically plausible that smoking plays an important role in HCC. Several chemicals present in tobacco smoke, including 4-aminobiphenyl and polycyclic aromatic hydrocarbons, can be metabolised into reactive carcinogenic agents in the liver.[96,97] These molecules induce histopathological changes such as liver parenchyma degeneration in animal models.[98] Different tobacco components such as nitrosamines and benzenes can be activated into procarcinogens by CYP2E1.[99] This enzyme is the most important in the microsomal ethanol oxidising system, an alternate pathway of ethanol metabolism. Chronic ethanol consumption induces the activity of this system, which biotransforms ethanol into acetaldehyde, a highly toxic and carcinogenic metabolite.[99] In patients with advanced ALD, carcinogenesis can be triggered by acetaldehyde and ROS, which promote mutagenesis and interfere with DNA methylation, synthesis, and repair.[100] It is likely that the simultaneous consumption of alcohol and tobacco contributes to the development of HCC via common metabolic pathways.[101] Experimental data revealed that inflammation plays a critic role in generating a tumourigenic microenvironment (Fig. 2). Tobacco smoke exposure leads to the release of proinflammatory cytokines, such as IL-33, IL-1β and TNFα.[102,103] IL-33 regulates liver inflammation through the activation of p38 MAPK. Increased expression of hepatic cancer stem cells and epithelial to mesenchymal transition, both major determinants of HCC development, were shown to be induced by smoke exposure.[104] Moreover, peripheral blood studies have associated smoking with immunosuppression and telomere dysfunction, both of which are early events in cancer development.[105,106] In line with these findings, hepatocarcinogenesis is promoted by reduced immune surveillance and telomere attrition in mouse models and liver tissue.[107,108] These key features were related to NASH, aging, fibrosis and alcohol, all of which are closely related to smoking.

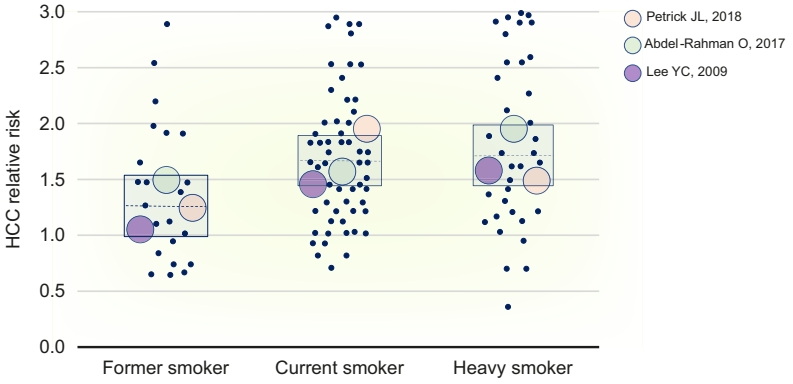


Fig. 5. Relative risk for HCC development stratified by smoking status. Small dark blue dots represent the reported HCC risk for individual case-control and cohort studies. Each circle represents the reported HCC risk in 3 large meta-analysis: Petrick *et al.* study[87] (orange circle, 14 studies); Abdel-Rahman *et al.* study[89] (green circle, 81 studies), Lee *et al.* study[88] (purple circle, 66 studies). Light blue boxes represent the median value for the risk ratio (dashed line) and 95% confidence intervals. HCC, hepatocellular carcinoma.

Key point

Cigarette smoking has been clearly identified as a risk factor for HCC in chronic liver disease.

Fig. 3 depicts the cause-effect relationship between cigarette smoking and HCC and the potential underlying mechanisms. Importantly, smoking cessation is inversely associated with HCC risk. There is data suggesting that individuals who quit smoking more than 20 years ago have a near equivalent risk to never smokers.[87] Given that smoking has been associated with steatosis, NAFLD-fibrosis and HCC, best practice advice from the American Gastroenterology Association expert review states that patients with cirrhosis due to NAFLD should be counselled to abstain from smoking.[109] Similar to NASH clinical trials and meta-analyses of fibrosis-related events, many HCC risk models in NAFLD-related cirrhosis do not include smoking as an important environmental factor.[47,84,110] Among risk factors of early and late recurrence after HCC resection, most studies do not include detailed exposome data regarding history of cigarette smoking.[111,112] The inclusion of environmental data in future studies is strongly recommended and supported by the potential impact of the exposome on liver-related outcomes.[113] In sum, given that smoking is not only associated with a higher risk but also lower survival rates in HCC, there is an urgent need for increased awareness and more resources to address this important

factor in patients with either HCC or those at high risk of developing it (Fig. 1).

Impact of smoking on clinical outcomes in patients with liver disease

In 2015, 6.4 million deaths were attributable to smoking worldwide, representing a 4.7% increase in smoking-attributable deaths since 2005 and ranking cigarette smoking as the second-leading risk factor for attributable mortality just behind high-systolic blood pressure .[5] With this scenario and the bio-pathological background that smoking is associated with chronic liver disease and advanced fibrosis, it seems pertinent to review the evidence for its impact on liver-related clinical outcomes (Fig. 3).

Key point

Smoking has a negative impact on the outcomes of patients with cirrhosis and HCC and may have deleterious effects in patients after liver transplantation.

Modern personalised medicine entails detecting individuals that are at high risk of developing advanced/decompensated liver disease, in order to target a more intense diagnostic liver work-up, possible specific treatment and closer follow-up. A systemic review on predictors of mortality in cirrhosis, beyond the Child-Pugh and MELD (model for end-stage liver disease) score, was performed by Gennaro D'Amico.[114] Smoking was only assessed in 2 of the 118 included studies (46% ALD, 46% chronic viral hepatitis) and it was shown to be an independent predictive factor for survival (Fig. 4). Smoking was highly prevalent in alcohol-related cirrhosis (60-78%) and increased mortality independently of abstinence, with 5-year survival rates in smokers and non-smokers of 42% and 73% in patients <55 years, and 17% and 43% in patients >55 years, respectively.[51,115] The impact of smoking on the natural history of NAFLD has been investigated in prospective population-based studies. Analysis from the USA and Thai National Health Examination Surveys revealed that smoking consistently leads to a 2-fold increase in mortality among patients with NAFLD (HR 2.33; 95% CI 1.66-3.27).[116–118] Differences were stronger among heavy smoking women (HR for ≥10 pack-years: 5.40; 95% CI 2.19–13.4).[118] Adjusted by sex, the magnitude of increase in mortality differed from the non-NAFLD population if fatty liver was diagnosed with biochemical tests (hepatic steatosis index) but not if it was based on ultrasound.[116,117] The most common cause of death among patients with NAFLD was CVD, but smoking also had an impact on non-cardiovascular mortality (HR 2.79).[117] In patients with biopsy-proven NAFLD, current smoking has been associated with mortality or need for liver transplantation (HR 2.62; 95% CI 1.67–4.10).[119] The magnitude of this association was higher than diabetes and age.[6] Smoking also impacts survival rates in viral hepatitis-related HCC (HR 2.99; 95% CI 1.7–5.23).[94,120,121] It remains unclear if this is attributable to a faster progression of cirrhosis or other factors that may play a major role, such as a direct effect on HCC, related lifestyle factors or poor compliance. However, smoking cessation does reduce HCC-specific mortality, with a significant survival benefit after 10 years of abstinence (HR 0.77; 95% CI 0.61–0.97).[94] In the setting of advanced liver disease, smoking is only a faint risk factor for first hospital admission due to a decompensation and a weak predictor of 180-day mortality after discharge.[122,123] In the presence of other well-known stronger risk factors, any possible impact of tobacco may be easily masked. Considering the changing trends in liver disease aetiology in the current metabolic-era, new studies on larger patient series should be performed. Regarding PBC aetiology, mortality is increased in smokers with advanced disease (bridging fibrosis and cirrhosis) at presentation .[124] Collectively, this data strongly suggest that smoking negatively impacts the outcome of patients with advanced chronic liver disease, including cirrhosis and HCC, further reinforcing the need to identify and treat this significant lifestyle factor.

Key point

The prevalence of e-cigarette use has rapidly increased worldwide, especially among adolescents who are not fully aware of its potential harmful effects, including liver injury.

Besides mortality, smoking is an identifiable risk factor for other liver-related outcomes. In severe metabolic-associated liver disease, cigarette smoking increases the risk of liver-related events (*e.g.* hospital admission, cirrhosis, liver cancer or decompensation) in addition to other metabolic syndrome components.[125,126] In patients with NAFLD, smoking not only has an impact on CVD events or cancer development, but also on patient-reported outcomes.[127,128] Factors independently associated with poorer patient-reported outcomes included cirrhosis, female sex, history of smoking, and metabolic comorbidities.[128] In a cross-sectional nationwide study from India evaluating patients with cirrhosis (mainly alcohol and viral aetiology), smoking was significantly associated with the presence of minimal hepatic encephalopathy, a well-known factor that impacts the quality of life and leads to increased hospitalisations.[129]

Finally, liver transplantation significantly improves the survival and quality of life of patients with end-stage liver disease. Tobacco smoking has been shown to negatively impact liver transplantation outcomes (Fig. 1). Among complications related to cigarette smoking, there are 3 main factors to be highlighted: i) increased risk of vascular complications such as hepatic artery thrombosis, a potential cause of graft loss[130]; ii) development of *de novo* tumours[131,132]; iii) increased rate of non-graft-related mortality, mostly due to CVD events.[133,134] Cardiovascular events and cancer are mainly seen among liver transplant recipients for ALD, the second most frequent indication for liver transplantation.[8] The International Liver Transplant Society guidelines on Liver Transplantation for Alcoholic Liver Disease strongly recommend promoting smoking cessation in alcoholic liver transplant recipients in order to improve overall health and patient outcomes.[8] Many liver transplant programmes and health insurance plans do not offer/cover liver transplantation in patients who are current smokers. A cessation period of

at least 2 months prior to liver transplantation may lead to a significant reduction in the risk of vascular complications.[130] The benefits of smoking cessation should be discussed at every office visit, and accordingly, medical assistance should be offered to promote smoking cessation prior to listing a patient for liver transplant.

Electronic cigarette exposure and liver disease

Electronic nicotine delivery systems, also known as e-cigarettes, are battery powered inhalation devices resembling a cigarette that deliver nicotine to users without burning tobacco. E-cigarette and other vaping devices such as waterpipe smoking are rapidly gaining popularity, especially among younger populations .[135] The misconception of representing a healthier alternative to cigarette smoking may be a key factor.[136] Like the cigarette smoking debate in the era of Ronald A. Fisher, e-cigarettes and other vaping devices have become the subject of public health disputes driven by the scarce data on this issue.[137] As e-cigarettes are a relatively new product, studies are needed to determine their long-term detrimental effects, some of which may be similar to nicotine exposure.

Like conventional cigarettes, e-cigarettes and other vaping devices contain multiple substances with potentially harmful effects on human health. Components such as nicotine, nitrosamines, polycyclic aromatic hydrocarbons, metals, and carbon monoxide, among others, have been shown to have toxic effects and potentially induce inflammation, mental disorders, acute lung and subclinical CVD, metabolic disease, and certain cancers (oral and lung).[138–140] The impact of e-cigarettes on health has recently been studied in other disciplines, mainly in lung and cardiovascular diseases.[139,140] However, only a few studies have explored the impact of vaping devices on liver function. Some *in vitro* and *in vivo* studies suggest that exposure to the smoke and components of e-cigarettes may induce liver injury through different mechanisms. Mice on a western diet (NASH model) exposed to e-cigarettes exhibited a marked increase in hepatic lipid accumulation and hepatocyte apoptosis compared with control mice.[141] Contrary to cigarette smoking, the detrimental effects of e-cigarettes on hepatic steatosis were associated with oxidative stress independent of AMPK signalling. In this mouse model of NASH, hepatic RNA sequencing analysis also showed a significant differential expression in more than 400 genes compared to controls not exposed to e-cigarettes, especially those associated with lipid metabolism and cholesterol biosynthesis.[141] These results suggest that e-cigarettes may contribute to liver injury and lipogenesis disturbances in the context of NAFLD. Other mechanisms such as direct DNA damage and mitochondrial dysfunction have been proposed to play a role in this setting.[142] Finally, the flavouring chemicals used for e-cigarettes may induce hepatocyte injury independently of smoke and nicotine. The exposure of HepG2 cells to flavouring chemicals significantly reduces cell viability in a dose-dependent way.[143]

These data provide the basis for expanding our knowledge on e-cigarette-induced liver injury. The mechanisms behind the development of liver disease associated with these devices are probably multiple and complex. There are studies supporting the idea that the use of e-cigarettes plays an important role in inducing endothelial dysfunction and subsequent CVD.[139,140] It is well-known that endothelial dysfunction is a critical event involved in the interplay between liver injury, fibrosis progression and haemodynamic derangement.[144] Therefore, as in CVD, it could be speculated that liver endothelial damage triggered by toxic compounds in e-cigarettes could significantly contribute to the development of liver injury. More translational and clinical studies are warranted to unravel the mechanisms involved and set the basis for evidence-based recommendations in clinical practice.

Conclusions

Increasing evidence indicates that smoking is associated with the development and progression of liver disease, HCC development and poorer clinical outcomes. The magnitude of the associations should increase the awareness of hepatologists about its deleterious effects and prompt strategies to encourage and assist patients to stop smoking. Although most providers are aware of this situation, referral to smoking cessation programmes is not routinely performed in clinical practice. Active smoking should be considered as a potential confounding factor in NAFLD, fibrosis, and HCC clinical trials.[33,47,109] Finally, due to the deleterious effects of smoking in patients undergoing liver transplantation, an increased number of centres should make smoking cessation an explicit requirement to be listed. Future studies should evaluate the association between objective smoking measurements, including urinary nicotine levels, and liver-related outcomes.

Abbreviations

ALD, alcohol-related liver disease; AMPK, AMP-activated protein kinase; CHB, chronic hepatitis B; CHC, chronic hepatitis C; CVD, cardiovascular disease; FLD, fatty liver disease; HCC, hepatocellular carcinoma; HR, hazard ratio; HSCs, hepatic stellate cells; IL, interleukin; LSM, liver stiffness measurement; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NASH CRN, Non-Alcoholic Steatohepatitis Clinical Research Network; PBC, primary biliary cholangitis; ROS, reactive oxygen species; T_H1, T helper 1.

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Conflict of interest

The authors declare no conflicts of interests.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

All of the authors performed the research, writing, and review of all of the drafts of this paper and approved the final version.

Supplementary data

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Author names in bold designate shared co-first authorship

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