Supplementary Table 1. Summary of study characteristics for included studies examining smoking-related liver outcomes.

Title	Author	Year	Study Type	Study Design	Population	Main Adjusted Effect	Follow-Up
Smoke Signals: Unraveling the Link between Cigarette Smoking and Serum Liver Markers	Amit Barapatre et al. [1].	2024	Cross-sectional study	Comparing serum liver enzyme levels between smokers (>20 cigarettes daily for >1 month) and non-smokers at a single time point.	60 male participants aged 18–35 years from Mumbai, India, divided into 30 smokers (>20 cigarettes daily for >1 month) and 30 non-smokers.	The study did not report adjusted effects. It reported unadjusted mean comparisons: • Smokers had significantly higher mean SGOT (29.63 vs 22.7 IU/L, *P*=0.002) • Smokers had significantly higher mean SGPT (30.75 vs 18.97 IU/L, *P*<0.0001) • Smokers had significantly higher mean ALP (178.3 vs 162.0 IU/L, *P*=0.003) • Smokers had significantly higher mean total bilirubin	Not applicable (cross-sectional study)

						(1.172 vs 0.78 mg/dl, *P*=0.0004) • No significant difference in direct bilirubin (*P*=0.191)	
Synergistic effect of smoking on alcohol consumption-associated liver disease: insights from a large Korean nationwide cohort database	Soobeen Lee et al. [2].	2024	Prospective Cohort Study	A prospective cohort study using the Korean National Health Insurance Service-Health Screening (NHIS-HEALs) database, following participants over time to investigate the association between smoking and alcohol consumption on the development of alcoholic liver disease (ALD), cirrhosis, and hepatocellular carcinoma (HCC).	Adults aged ≥20 years from a representative sample cohort (10% of the NHIS population, approximately 3.7–3.9 million individuals annually) who underwent health screenings between 2011 and 2017. Individuals with prior HCC or liver cirrhosis were excluded.	Multivariate Cox regression analysis adjusted for alcohol consumption, physical activity, age, gender, BMI, diabetes, HBV infection, and HCV infection: • Smoking significantly increased the risk of ALD (HR 1.325; 95% CI 1.293–1.357; $P < 0.001$) • Smoking significantly increased the risk of alcoholic cirrhosis	Up to 10 years for some analyses (Table 1); primary incidence outcomes were assessed over a 3-year follow-up period.

						(HR 1.534; 95% CI 1.457–1.615; P < 0.001) • Smoking significantly increased the risk of HCC (HR 1.532; 95% CI 1.411–1.664; P < 0.001)	
Cigarette smoking associates with lower chance of HBsAg seroclearance in chronic hepatitis B: A cohort study and mechanistic analysis	Cheuk-Fung Yip et al. [3].	2024	Combined retrospective cohort study and cross-sectional mechanistic study	Part 1 (Retrospective cohort study): Analysis of nucleoside analogue (NA)-treated chronic hepatitis B (CHB) patients from the Hong Kong CDARS database (2010–2021) to examine the association between smoking and HBsAg seroclearance. Part 2 (Cross-sectional mechanistic study): Phenotypic and functional analysis of peripheral blood lymphocytes from 27	Part 1: 7,833 NA-treated CHB patients (1,304 smokers, 6,529 non-smokers) from Hong Kong. Excluded patients with HIV/HCV coinfection, cirrhosis, HCC, liver transplantation, age <18 years, or missing laboratory data. Part 2: 27 non-cirrhotic CHB patients (14 with viral persistence	Part 1 (Multivariate Cox regression): After adjusting for age, sex, NA duration, bilirubin, albumin, and platelet count, smoking was associated with a significantly lower chance of achieving HBsAg seroclearance (adjusted hazard ratio [aHR] 0.70; 95% CI 0.57–0.87; *P* < 0.001). Additional adjustment for	Median follow-up of 5.0 years (interquartile range 2.2–9.4 years) for Part 1.

				CHB patients stratified by smoking status and HBsAg seroclearance.	[HBsAg+], 13 with HBsAg seroclearance), recruited from Queen Mary Hospital, Hong Kong.	concomitant steatotic liver disease yielded similar results (aHR 0.66; 95% CI 0.52–0.82). Propensity score matching confirmed the finding (aHR 0.68; 95% CI 0.53–0.88).	
Smoking Increases the Risk of Hepatocellular Carcinoma and Cardiovascular Disease in Patients with Metabolic-Associated Fatty Liver Disease	Jeong-Ju Yoo et al. [4].	2023	Retrospective Cohort Study	A retrospective cohort study using the Korean National Health Insurance Service (NHIS)-National Sample Cohort database (2002-2015) to investigate the association between smoking status and the incidence of hepatocellular carcinoma (HCC) and cardiovascular disease (CVD) in patients with metabolic-associated fatty liver disease	283,088 Korean adults aged ≥20 years who underwent health screening between 2002-2015, including 110,863 patients with MAFLD (defined by Fatty Liver Index ≥30 plus metabolic criteria) and 172,225 controls (FLI <30 without underlying liver disease). Subjects with missing smoking	Multivariate Cox regression adjusted for age, sex, alcohol consumption, exercise, BMI, diabetes, hypertension, dyslipidemia, and cirrhosis: • HCC risk in MAFLD patients: Current smokers had significantly higher HCC risk vs. non-smokers (aHR 1.24; 95% CI 1.08–1.41). Ex-smokers did not	Mean follow-up of 1,813 days (approximately 5.0 years) for HCC outcomes; mean follow-up of 1,758 days (approximately 4.8 years) for CVD outcomes.

		(MAFLD) compared to controls.	data, death in first follow-up year, prior HCC/CVD, or other liver diseases were excluded.	show significantly increased risk (aHR 1.04; 95% CI 0.91–1.19). • HCC risk in controls: Current smokers did not show significantly increased HCC risk (aHR 1.07; 95% CI 0.89–1.30). • CVD risk in MAFLD patients: Current smokers had significantly higher CVD risk vs. non-smokers (aHR 1.22; 95% CI 1.15–1.30). • CVD risk in controls: Current smokers had significantly higher CVD risk vs. non-smokers (aHR 1.21; 95% CI 1.13–1.29). • Sex-stratified

						analysis (MAFLD only): Smoking (ever vs. never) increased HCC risk in men (aHR 1.14; 95% CI 1.02–1.29) but not significantly in women (aHR 1.23; 95% CI 0.72–2.12). Smoking increased CVD risk in both men (aHR 1.08; 95% CI 1.02–1.14) and women (aHR 1.34; 95% CI 1.11–1.61).	
Tobacco Smoking and Risk of Autoimmune Hepatitis: A Population-Based Case-Control Study	Tea Lund Laursen et al. [5].	2023	Population-Based Case-Control Study	A population-based matched case-control study using data from the UK Clinical Practice Research Datalink (CPRD) and linked Hospital Episode Statistics (HES) to examine the association between tobacco smoking and the risk of	987 adult patients (≥18 years) with a first-time AIH diagnosis registered in primary or secondary care in England between 1 January 2005 and 31 July 2017, and 6,767 frequency-matched population controls.	Multiple logistic regression adjusted for matching variables (sex, age category, general practice, calendar time), age as a continuous variable, and socioeconomic status (Index of Multiple Deprivation	Not applicable (case-control study)

		developing autoimmune hepatitis (AIH). Cases with AIH diagnosed between 2005-2017 were matched with up to 10 population controls by sex, age category, general practice, and calendar year. Smoking status was ascertained from primary care records using a validated method.	Cases with alcoholic liver disease, viral hepatitis B/C, primary sclerosing cholangitis, or primary biliary cholangitis were excluded.	quintiles): • "Ever-smokers" (current or previous smokers) had a significantly higher odds of AIH compared to "never-smokers" in complete-case analysis (adjusted OR 1.19; 95% CI 1.02–1.38). • Multiple imputation analysis for missing smoking data yielded similar results (adjusted OR 1.20; 95% CI 1.03–1.40). • Stratified analyses suggested a stronger association in females (OR 1.24; 95% CI 1.05–1.47) compared to males (OR 1.03; 95% CI

						0.74–1.44), and in younger age groups (40-59 years: OR 1.49; 95% CI 1.06–2.11), though interaction tests were not statistically significant.	
A Mendelian randomization study on the causal effects of cigarette smoking on liver fibrosis and cirrhosis	Liwei Guo et al. [6].	2024	Mendelian Randomization Study	Two-sample Mendelian randomization analysis using summary statistics from genome-wide association studies (GWAS) to investigate the causal effects of cigarette smoking on liver fibrosis and cirrhosis. Genetic variants (SNPs) associated with six smoking-related exposures were used as instrumental variables, with MR-Egger,	Exposure data: European-ancestry participants from the MRC-IEU, Neale Lab, and GWAS and Sequencing Consortium of Alcohol and Nicotine use (sample sizes ranging from 142,387 to 461,066 depending on smoking phenotype). Outcome data: 1,602	Inverse variance weighted (IVW) method results: • Ever smoked was significantly associated with increased risk of liver fibrosis and cirrhosis (OR 5.704; 95% CI 1.166–27.910; *P*=0.032). • Previous smoking was significantly associated with increased risk (OR 99.783; 95% CI	Not applicable (Mendelian randomization study)

		weighted median, inverse variance weighted, simple mode, and weighted mode methods applied.	cases of liver fibrosis/cirrhosis and 332,951 controls from the FinnGen consortium (total N=334,553), all of European ancestry.	2.969–3,353; *P*=0.010). • Never smoking was significantly associated with decreased risk (OR 0.171; 95% CI 0.041–0.719; *P*=0.016). • Current smoking, pack years of smoking, and age of smoking initiation showed no significant associations with liver fibrosis/cirrhosis. No significant horizontal pleiotropy was detected (MR-Egger intercept *P*>0.05).

Tobacco, alcohol use and risk of hepatocellular carcinoma and intrahepatic cholangiocarcinoma: The Liver Cancer Pooling Project	Jessica L Petrick et al. [7].	2018	Pooled Analysis of Prospective Cohort Studies	Pooled analysis of individual-level data from 14 US-based prospective cohort studies participating in the Liver Cancer Pooling Project (LCPP). Harmonized data on tobacco smoking and alcohol consumption were analyzed using multivariable-adjusted Cox proportional hazards regression to estimate associations with hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) incidence.	1,518,741 individuals from 14 US cohorts, including 1,423 incident HCC cases and 410 incident ICC cases. Participants were predominantly white, older adults, with follow-up conducted through linkage to state cancer registries and medical records.	Multivariable-adjusted models included sex, age, race, cohort, BMI, diabetes, education, and the other exposure (smoking or alcohol) as appropriate: • Current smoking was associated with increased risk of HCC (HR 1.86; 95% CI 1.57–2.20) and ICC (HR 1.47; 95% CI 1.07–2.02). • Former smoking was associated with increased risk of HCC (HR 1.24; 95% CI 1.08–1.43) and ICC (HR 1.32; 95% CI 1.03–1.68). • Smoking cessation >30 years was associated with	Follow-up varied by cohort; participants were followed from baseline until incident liver cancer, death, loss to follow-up, or last date of follow-up (dates ranged by cohort, with follow-up through various years up to approximately 2011-2014 depending on the cohort).

			HCC risk similar to never smokers (HR 1.09; 95% CI 0.74–1.61); no significant trend for ICC. • Heavy alcohol consumption (≥7 drinks/day) was associated with increased HCC risk (HR 1.87; 95% CI 1.41–2.47). ≥5 drinks/day was associated with increased ICC risk (HR 1.68; 95% CI 0.99–2.86). • Light-to-moderate alcohol consumption (<3 drinks/day) was associated with decreased HCC risk (HRs ranging from 0.57 to 0.77), but not ICC. • Significant

				interaction between heavy alcohol consumption and diabetes on HCC risk (P=0.01), with greater risk in those with diabetes.

Solid fuels for cooking and tobacco use and risk of major chronic liver disease mortality: a prospective cohort study of 0.5 million Chinese adults	Ka Hung Chan et al. [8].	2020	Prospective Cohort Study	Prospective cohort study using data from the China Kadoorie Biobank (CKB), recruiting ~0.5 million adults aged 30-79 years from 10 diverse areas across China between 2004-2008. Participants were followed through linkage to death registries to examine associations between self-reported long-term cooking fuel type and tobacco smoking with chronic liver disease (CLD) mortality.	501,104 adults aged 30-79 years from 10 regions in China, with no prior history of liver cirrhosis, hepatitis, or cancer at baseline. For cooking-related analyses, the sample was restricted to 350,349 participants who reported cooking regularly. During a median follow-up of 10.1 years, 2,461 CLD deaths were recorded (approximately 75% from liver cancer).	Multivariable Cox regression stratified by age-at-risk, sex, and study area, and adjusted for education, income, alcohol, BMI, diabetes, HBsAg status, cooking stove ventilation, heating fuel, and length of recall period: • Long-term solid fuel use for cooking was associated with increased CLD mortality risk (HR 1.26; 95% CI 1.02–1.56) compared to clean fuel users, with evidence of a dose-response relationship by duration (*Ptrend*=0.023). • Switching from solid to clean fuels	Median follow-up of 10.1 years (interquartile range 9.2–11.1 years)

			(median 14 years since switching) was not associated with excess risk (HR 1.07; 95% CI 0.90–1.29). • Current regular smoking was associated with increased CLD mortality risk (HR 1.28; 95% CI 1.13–1.44) compared to never-regular smokers. • Ex-regular smokers who quit for non-medical reasons (median 10 years since quitting) showed no significant excess risk (HR 1.16; 95% CI 0.95–1.43). • Joint effects: Compared to never-

				smoking clean fuel users, HRs were 1.41 (95% CI 1.10–1.82) for never-smoking solid fuel users, 1.55 (95% CI 1.17–2.06) for regular-smoking clean fuel users, and 1.71 (95% CI 1.32–2.20) for regular-smoking solid fuel users. No significant additive interaction was observed (RERI 0.11; 95% CI -0.30–0.52). • Stronger associations were observed in sensitivity analyses excluding those with poor health or early follow-up, and among HBsAg seronegative participants (HR

			1.39; 95% CI 1.08–1.78 for solid fuel use).

Smoking-related morbidity and mortality following liver transplantation	Joanna A. Leithead et al. [9].	2008	Retrospective Cohort Study	Single-center retrospective case-note study of consecutive patients who underwent elective liver transplantation between 1996-2000, examining associations between smoking status at transplant assessment and post-transplant morbidity and mortality.	132 patients who underwent elective liver transplantation at a single UK center between January 1, 1996 and December 31, 2000. Patients were categorized as active smokers (23%, n=31), ex-smokers (18%, n=24), or lifelong non-smokers (58%, n=77) based on documentation at transplant assessment. Patients with acute liver failure were excluded.	Multivariate Cox proportional hazards analysis adjusted for factors with $P<0.10$ on univariate analysis: • Active smoking at transplant assessment was independently associated with increased all-cause mortality (HR 2.23; 95% CI 1.08–4.61; $P=0.03$). Estimated 10-year survival: 54% for active smokers vs. 77% for non-smokers ($P=0.04$). • Cardiovascular-specific mortality: Active smoking was independently associated with increased risk (HR	Mean follow-up of 8.8 years (range 6.4–11.3 years)

			10.91; 95% CI 1.22–97.92; *P*=0.033). • Sepsis-specific mortality: Active smoking was independently associated with increased risk (HR 4.46; 95% CI 1.06–18.73; *P*=0.041). • Malignancy-related mortality: No significant association with active smoking (*P*=0.61). • Graft survival: No significant difference between active smokers and non-smokers (*P*=0.88). • Ex-smokers did not have significantly increased mortality risk compared to non-smokers

			(*P*=0.134). • Perioperative renal replacement therapy was also independently associated with all-cause mortality (HR 2.78; 95% CI 1.35–5.74; *P*=0.006).

Smoking and outcomes in candidates for liver transplantation: Analysis of the Pulmonary Vascular Complications of Liver Disease 2 (PVCLD2)	Colleen R Cecil et al. [10].	2024	Prospective Cohort Study	Multicenter prospective cohort study of patients with advanced liver disease undergoing evaluation for liver transplantation (LT) at three US centers (2013-2017). Patients were classified by self-reported smoking status as nonsmokers, past smokers, or current smokers. Associations with mortality were assessed using Cox proportional hazards models and Fine-Gray models with LT as a competing risk.	410 patients with portal hypertension undergoing initial LT evaluation. Excluded patients with portopulmonary hypertension not being considered for LT. Mean age 56.5 years, 65% male. Smoking status: 39% nonsmokers, 45% past smokers, 16% current smokers. Common liver disease etiologies: alcohol (39%), hepatitis C (39%), NAFLD (23%).	Multivariable models adjusted for age, sex, BMI, MELD-Na score, race/ethnicity, family income, and liver disease etiology: • Current smokers had significantly increased risk of death compared to nonsmokers (HR 2.17; 95% CI 1.12–4.18; *P*=0.02). • Every 5 pack-year increase in smoking history was associated with 7% increased risk of death (HR 1.07; 95% CI 1.01–1.13; *P*=0.02). • With LT as competing risk: Current smokers had increased	Median follow-up of 23 months (IQR 14–33 months) after initial LT evaluation

					subdistributional HR for death (2.45; 95% CI 1.31–4.60; *P*=0.005); past smokers showed a non-significant increase (1.58; 95% CI 0.91–2.72; *P*=0.10). • With LT as time-varying covariate: Current smokers had increased risk of death (HR 2.26; 95% CI 1.17–4.37; *P*=0.02). • The association between pack-years and death weakened with increasing time since quitting among past smokers, and strengthened with increasing MELD-Na score.

Reference：

1 Barapatre, A., et al. Smoke Signals: Unraveling the Link between Cigarette Smoking and Serum Liver Markers. 2024. https://doi.org/10.9734/ajbgmb/2024/v16i3363

2 Lee, S., et al. Synergistic effect of smoking on alcohol consumption-associated liver disease: insights from a large Korean nationwide cohort database. 2024.

3 Yip, C.F., et al. Cigarette smoking associates with lower chance of HBsAg seroclearance in chronic hepatitis B: A cohort study and mechanistic analysis. 2024.

4 Yoo, J.J., et al. Smoking Increases the Risk of Hepatocellular Carcinoma and Cardiovascular Disease in Patients with Metabolic-Associated Fatty Liver Disease. 2023. https://doi.org/10.3390/jcm12093336

5 Laursen, T.L., et al. Tobacco Smoking and Risk of Autoimmune Hepatitis: A Population-Based Case-Control Study. 2023.

6 Guo, L., et al. A Mendelian randomization study on the causal effects of cigarette smoking on liver fibrosis and cirrhosis. 2024. https://doi.org/10.3389/fmed.2024.1390049

7 Petrick, J.L., et al. Tobacco, alcohol use and risk of hepatocellular carcinoma and intrahepatic cholangiocarcinoma: The Liver Cancer Pooling Project. 2018. https://doi.org/10.1038/s41416-018-0007-z

8 Chan, K.H., et al. Solid fuels for cooking and tobacco use and risk of major chronic liver disease mortality: a prospective cohort study of 0.5 million Chinese adults. 2020. https://doi.org/10.1093/ije/dyz216

9 Leithead, J.A., et al. Smoking-related morbidity and mortality following liver transplantation. 2008. https://doi.org/10.1002/lt.21471

10 Cecil, C.R., et al. Smoking and outcomes in candidates for liver transplantation: Analysis of the Pulmonary Vascular Complications of Liver Disease 2 (PVCLD2). 2024. https://doi.org/10.1097/LVT.0000000000000485