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Association of MASLD Phenotypes With Liver Fibrosis in Hepatitis C: The Role of Cardiometabolic Risk Factors

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ABSTRACT

Steatotic liver disease is prevalent among people with hepatitis C virus (HCV). The new definition of metabolic dysfunction–associated steatotic liver disease (MASLD) emphasises the metabolic drivers of steatosis and recognises its frequent coexistence with other chronic liver diseases, including HCV. We aimed to evaluate the association of coexisting MASLD and HCV with liver fibrosis. Individuals with HCV who underwent transient elastography (TE) with associated controlled attenuation parameter (CAP) were included from two clinical centres. MASLD and significant liver fibrosis were defined as the presence of steatosis (CAP ≥ 275 dB/m) with at least one cardiometabolic risk factor, and liver stiffness measurement (LSM) ≥ 7.1 kPa measured by TE, respectively. Associated cofactors of significant liver fibrosis were determined using stepwise regression and cross-validation by LASSO models to select confounders. Among 590 participants, 31% were diagnosed with MASLD. The prevalence of significant liver fibrosis was the highest among people with MASLD (58%) followed by HCV-related steatosis (45%) and the non-steatosis group (39%). After adjusting for potential confounders, MASLD was associated with significant liver fibrosis (adjusted odds ratio [aOR] 2.29, 95% confidence interval [CI] 1.07–4.87). Furthermore, specific MASLD phenotypes including diabetes, hypertension and overweight were associated with significant liver fibrosis, with aORs of 4.76 (95% CI 2.16–10.49), 3.44 (95% CI 1.77–6.68) and 2.54 (95% CI 1.27–5.07), respectively. In conclusion, MASLD is associated with liver fibrosis in people with HCV, specifically the diabetes, overweight and hypertensive phenotypes. Beyond pursuing a virological cure, healthcare providers should prioritise managing metabolic conditions, particularly diabetes, hypertension and obesity.

1 | Introduction

Chronic hepatitis C remains a major public health concern, with 50 million people living with the hepatitis C virus (HCV) globally and approximately 1 million new infections annually [1]. HCV is a leading cause of liver cirrhosis and hepatocellular carcinoma, often requiring liver transplantation [2]. The advent of direct-acting antiviral agents (DAAs) has revolutionised HCV treatment, achieving sustained virologic response (SVR) rates as high as 98% [3, 4]. However, despite these excellent cure rates, unresolved clinically significant issues persist. Metabolic complications associated with HCV, both during chronic infection and post-SVR, remain a particular concern. Hepatic steatosis is a frequent condition linked to HCV, with a prevalence ranging from 40% to 86% [5]. The occurrence of steatosis in HCV patients can be attributed to either the direct viral effect on lipid metabolism, termed 'viral steatosis', or to the high incidence of metabolic syndrome features associated with HCV, known as 'metabolic steatosis' [6]. Several studies have shown that steatosis often persists after achieving SVR and is linked to an increased risk of liver fibrosis, especially in patients with pre-treatment metabolic conditions such as obesity, diabetes and dyslipidaemia [7, 8]. Thus, these findings highlight the critical role of metabolic factors in the development of liver fibrosis.

In June 2023, an international consensus panel introduced a revised nomenclature for fatty liver disease to more accurately reflect its underlying mechanisms. The term steatotic liver disease (SLD) was introduced as an umbrella category encompassing all causes of steatosis [9], while metabolic dysfunction–associated steatotic liver disease (MASLD) replaced nonalcoholic fatty liver disease (NAFLD). MASLD, which is now the second leading indication for liver transplantation after HCV [7], is defined as the presence of steatosis, either by histology or imaging, along with at least one cardiometabolic risk factor among obesity, prediabetes or diabetes, hypertension or lipid disturbances. This new nomenclature emphasises the metabolic mechanisms underlying steatosis, shifting away from potentially stigmatising terms like 'fatty' and 'alcoholic' [9]. Importantly, MASLD does not exclude the coexistence of other causes of steatosis, such as HCV.

The co-occurrence of MASLD and HCV-related metabolic complications, whether during chronic HCV infection or post-SVR, may contribute to a synergistic effect, exacerbating liver injury through steatosis, oxidative stress and cellular dysfunction. It remains uncertain whether steatosis alone is responsible for this effect or if other factors are involved. Therefore, we aimed to investigate whether the presence of MASLD was associated with a higher prevalence of significant liver fibrosis in individuals with a history of HCV infection (either active chronic infection or post-SVR). Additionally, we sought to identify which cardiometabolic risk factors within the MASLD phenotypes were associated with liver fibrosis.

2 | Methods

2.1 | Study Design and Population

This was a retrospective cross-sectional study conducted at the McGill University Health Centre (MUHC) and The Ottawa Hospital, Canada. A total of 2,401 individuals with a history of HCV infection were screened, including 1,557 participants from MUHC and 844 from the Ottawa Hospital. We included consecutive adults aged 18 years or older with a history of chronic hepatitis C (either with an active infection or who had achieved SVR following antiviral treatment) who underwent transient elastography (TE) with controlled attenuation parameter (CAP) between October 2015 and December 2023. Exclusion criteria were as follows: (a) excessive alcohol intake, defined by an Alcohol Use Disorders Identification Test (AUDIT-C) score ≥ 5 [10]; (b) positivity for hepatitis B virus (HBV) surface antigen or HIV antibody; (c) history of pre-existing liver disease (autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, haemochromatosis, Wilson's disease, alpha-1 antitrypsin); (d) failure to perform TE examination or acquisition of at least 10 valid measurements. The manuscript was prepared according to the STROBE Statement-checklist of items. The Research Ethics Board (REB) of the Research Institute of the MUHC (study code 14-026-GEN 2015-1134) and the Ottawa Hospital approved the study, which followed the principles of the Declaration of Helsinki. Given that the data were collected retrospectively, the REB waived the requirement for obtaining informed consent from patients.

2.2 | Clinical and Biomedical Parameters

Patient's records were reviewed retrospectively to extract clinical and biomedical parameters within 3 months of the TE examination. Collected parameters included platelets, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), total cholesterol, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), triglycerides and glycated haemoglobin (HbA1c). Additional information on age, sex, ethnicity, smoking habits (current, former, or never), alcohol consumption, presence of diabetes and/or hypertension and medication use (for type 2 diabetes, hypertension, dyslipidaemia and HCV infection) was also collected. Participants with AUDIT-C scores below 5 were considered to have non-hazardous alcohol consumption [10]. SVR was defined as either an undetectable qualitative polymerase chain reaction (e.g., Amplicor HCV Test v2.0) or a quantitative HCV viral load below the detection limit (e.g., Abbott Real Time HCV). We also collected data on liver-related events, defined as a history of any among classical hepatic decompensation, hepatocellular carcinoma and liver transplantation. Classical decompensation was defined as ascites, variceal bleeding or overt hepatic encephalopathy.

2.3 | Non-Invasive Diagnosis of Hepatic Steatosis and Liver Fibrosis

Liver stiffness measurement (LSM) by TE examination was performed using FibroScan (Echosens, Paris, France) on patients who had fasted for at least a 3 h, by experienced operators (> 500 examinations prior to this study). The standard M probe was used initially in all patients. The XL probe was used if BMI was ≥ 30 kg/m^2 or if the M probe failed. Valid examinations required a minimum of 10 valid measurements with an interquartile range (IQR) $< 30\%$ of the median [11, 12]. Steatosis was defined

as CAP ≥ 275 dB/m [13]. Significant liver fibrosis (stage ≥ F2 out of 4) was defined as LSM > 7.1 kPa [14].

2.4 | Definition of MASLD Phenotypes

MASLD phenotypes were determined by the presence of hepatic steatosis and at least one cardiometabolic risk factor, and were as follows:

- overweight MASLD: BMI ≥ 25 kg/m^2;
- hypertensive MASLD: blood pressure ≥ 130/85 mmHg or on antihypertensive medication;
- diabetic MASLD: prediabetes (fasting glucose levels 5.6–6.9 mmol/L, 2-h post-load glucose levels 7.8–11.0 mmol/L, or an HbA1c 5.7%–6.4%) or type 2 diabetes (fasting glucose levels > 6.9 mmol/L, 2-h post-load glucose levels > 11.0 mmol/L, or HbA1c > 6.4%) or receiving diabetes treatment;
- dyslipidaemic MASLD: triglycerides ≥ 1.70 mmol/L or HDL cholesterol < 1.0 mmol/L for men and < 1.3 mmol/L for women, or on lipid-lowering treatment [9].

These phenotypes were not mutually exclusive, and there could be overlap among individuals with multiple cardiometabolic risk factors.

2.5 | Outcome Measures

The primary study outcome was the association between MASLD and its phenotypes with significant liver fibrosis in individuals with a history of HCV infection. Additionally, we compared the prevalence of significant liver fibrosis in MASLD patients to those without steatosis and those with SLD without cardiometabolic conditions (HCV-related steatosis).

2.6 | Statistical Analysis

The chi-squared test or Fisher's exact test (for categorical variables), the unpaired Student's *t*-test (for normally distributed continuous variables) and the Mann–Whitney test (for non-normally distributed continuous variables) were used to compare study groups. Overlaps between MASLD phenotypes were visualised using an UpSet plot. Cofactors such as age, sex, ethnicity, smoking status, AST, ALT, platelets, total cholesterol, LDL cholesterol, genotype and detectable HCV viral load were examined using the change-in-estimate method, supported by stepwise regression. Only those cofactors that demonstrated significance through the change-in-estimate approach were included in the final models. All models were cross-validated by LASSO models (10-fold validation) to select confounders. Results were reported as adjusted odds ratios (aORs) with 95% confidence interval (CI). A complete case analysis was performed, as missing values for included variables were < 10%. All tests were two-tailed, with a significance level of $\alpha = 0.05$. Statistical analyses were conducted using STATA 17.2 (STATA Corp. LP, College Station, Texas, USA).

3 | Results

After applying the exclusion criteria, 590 patients met the selection criteria and were included in the final analysis (Figure 1). The TE failure rate was 15%, consistent with previous studies [15]. The primary reason for TE failure was an unreliable result, including fewer than 10 valid measurements and/or an IQR > 30%. The XL probe was used in 36% of cases, while the standard M probe was applied for the remaining patients. The characteristics of the study population are summarised in Table 1. The overall median age was 53 years; 61% of the study population were male and 76% of White ethnicity. The mean duration of HCV infection was 10 years, and 74% of the study population achieved SVR. Significant liver fibrosis was present in 266 (45%) patients of the whole cohort. Patients with significant liver fibrosis were older, predominantly male, and had a higher body mass index (BMI). They also had lower platelets, higher liver transaminases and higher CAP. Hypertension and diabetes were significantly more prevalent among patients with significant liver fibrosis. We also reported on a history of liver-related events, acknowledging that the cross-sectional design of our study limited our ability to assess incidence rates or establish temporal relationships. A history of liver-related events, specifically hepatocellular carcinoma and variceal bleeding, was more frequent in patients with significant liver fibrosis compared to those without (Table 1).

3.1 | Prevalence of MASLD and Its Phenotypes, HCV-Related Steatosis and Liver Fibrosis

Among the 590 individuals with a history of HCV infection, 213 (36%) had SLD. Of these, 182 (31%) had steatosis with at least one cardiometabolic risk factor, meeting the criteria for MASLD, while 31 (5%) were classified as having HCV-related steatosis. To further categorise MASLD into its phenotypes, we used an UpSet plot to visualise overlapping MASLD phenotypes within the study population (Figure 2). The most frequent phenotypes were the intersection of overweight and hypertensive MASLD and hypertensive MASLD alone, both accounting for 30% of MASLD cases. The overweight MASLD alone was found in 12% of the cases. Other significant intersections include diabetic hypertensive MASLD, overweight diabetic hypertensive MASLD and overweight hypertensive dyslipidaemic MASLD, each present in 8% of the cases. More minor intersections represented

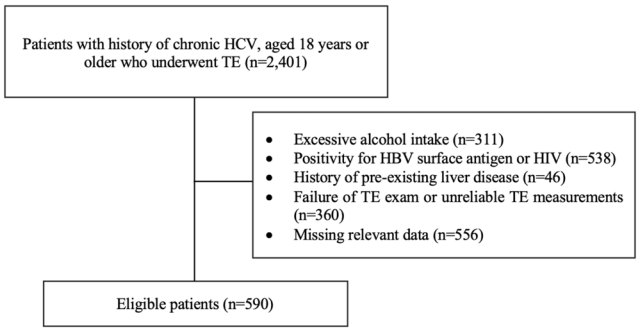

FIGURE 1 | Flow chart displaying the selection of the study participants.

TABLE 1 | Demographic, clinical, biochemical and virological characteristics of the study population and univariate analysis by significant liver fibrosis status ($n = 590$).

Variable	Total cohort ($n = 590$)	Significant liver fibrosis ($n = 266$)	No significant liver fibrosis ($n = 324$)	p
Age (median years, IQR)	53 (43–60)	54 (46–61)	51 (41–59)	**0.002**
Male sex (%)	359 (61)	181 (68)	178 (55)	**0.001**
Ethnicity (%)				
White	450 (76.2)	201 (76)	249 (77)	0.088
Black	32 (5.4)	11 (4)	21 (6)	
First Nation	20 (3.4)	14 (5)	6 (2)	
Others	88 (15)	40 (15)	58 (15)	
Smoking status (%)				
Never	242 (41)	100 (38)	142 (44)	**0.008**
Former	94 (16)	56 (21)	38 (12)	
Current	254 (43)	110 (41)	144 (44)	
Modality of HCV transmission (%)				
Intravenous drug use	105 (18)	56 (21)	49 (15)	0.061
Blood transfusion	36 (6)	14 (5)	22 (7)	0.066
Tattoos	19 (3.2)	7 (3)	12 (4)	0.493
Body piercing	8 (1.4)	5 (2)	3 (1)	0.319
Mixed	195 (33)	85 (32)	110 (34)	0.608
Unknown	227 (38.4)	99 (37)	128 (39)	0.570
ALT (median U/L, IQR)	49 (27–81)	64 (31–104)	41 (25–70)	**< 0.001**
AST (median U/L, IQR)	40 (26–63)	48 (29–81)	33 (23–48)	**< 0.001**
Platelet count (median 10^9/L, IQR)	215 (168–250)	193 (142–241)	228 (182–260)	**< 0.001**
CAP (median dB/m, IQR)	248 (204–292)	266 (224–307)	231 (1194–280)	**< 0.001**
MASLD (%)	182 (31)	106 (40)	76 (23)	**< 0.001**
BMI (median kg/m^2, IQR)	26 (23–32)	28 (24–34)	26 (22–30)	0.003
Diabetes mellitus or prediabetes (%)	145 (25)	83 (31)	62 (19)	0.001
Hypertension (%)	318 (54)	173 (65)	145 (45)	**< 0.001**
Blood glucose (median mmol/L, IQR)	5.2 (4.8–6.2)	5.4 (4.9–6.9)	5 (4.6–5.6)	**< 0.001**
HbA1c (median %, IQR)	5.6 (5.2–5.7)	5.7 (5.2–5.7)	5.5 (5.2–5.7)	0.139
Triglycerides (median mmol/L, IQR)	1.2 (0.8–1.5)	1.2 (0.8–1.5)	1.1 (0.8–1.6)	0.609
Total cholesterol (median mmol/L, IQR)	4.1 (3.6–4.9)	4.0 (3.4–4.6)	4.4 (3.7–5.3)	**< 0.001**
HDL-cholesterol (median mmol/L, IQR)	1.2 (1.0–1.6)	1.2 (1.0–1.6)	1.3 (1.0–1.6)	0.550
LDL-cholesterol (median mmol/L, IQR)	2.1 (1.6–2.8)	1.9 (1.4–2.5)	2.3 (1.8–3.1)	**< 0.001**
SVR (%)	379 (74)	155 (68)	224 (79)	**0.005**
Genotypes (%)				
Genotype-1	369 (63)	171 (64)	198 (61)	0.428

(Continues)

TABLE 1 | (Continued)

Variable	Total cohort ($n=590$)	Significant liver fibrosis ($n=266$)	No significant liver fibrosis ($n=324$)	p
Genotype-2	31 (5)	17 (6)	14 (4)	0.272
Genotype-3	84 (14)	39 (15)	45 (14)	0.789
Others	41 (7)	14 (5)	27 (8)	0.193
Unknown	65 (11)	25 (9)	40 (12)	0.291
Time since HCV diagnosis (mean years, SD)	10.3 (9.1)	10.7 (9)	9.7 (9.4)	0.331
Liver-related events (%)				
Ascites	12 (2)	8 (3)	4 (1)	0.129
Variceal bleeding	9 (2)	8 (3)	1 (0.3)	**0.008**
Hepatic encephalopathy	3 (1)	3 (1)	0 (0)	0.055
Hepatocellular carcinoma	16 (3)	12 (5)	4 (1)	**0.015**

Note: Continuous variables are expressed as median (IQR) and categorical variables as frequency and percentage (%). The p values are based on the Student t-test, χ^2 test or Fisher's exact test between groups with and without significant liver fibrosis. Significant p-values ($p<0.05$) are presented in bold.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; HbA1c, glycated haemoglobin; HCV, hepatitis C virus; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; MASLD, metabolic dysfunction-associated steatotic liver disease; SVR, sustained virologic response.

fewer individuals, ranging from 0.5% to 6%. The prevalence of liver fibrosis was significantly higher in the MASLD group compared to the non-SLD group (58% vs. 39%, $p<0.001$). In contrast, no difference in fibrosis prevalence was observed between HCV-related steatosis and the no-SLD or MASLD groups (Figure 3a). When examining the SVR status in relation to the presence of significant liver fibrosis within the MASLD group, individuals with significant liver fibrosis were more likely to have achieved SVR compared to those without significant fibrosis (49.4% vs. 33.3%, $p=0.047$). To explore the association between the number of cardiometabolic risk factors and liver fibrosis, MASLD patients were stratified into three groups according to the number of cardiometabolic risk factors: 1, 2 or ≥ 3. The prevalence of significant liver fibrosis increased proportionally with the number of cardiometabolic risk factors (Figure 3b).

3.2 | Association of MASLD and Its Phenotypes With Significant Liver Fibrosis

In the univariate analysis, patients with MASLD were more likely to have significant liver fibrosis. After adjusting for potential confounders, MASLD was associated with a more than 2-fold increase in the odds of significant liver fibrosis (aOR 2.29, 95% CI 1.07–4.87). Other factors associated with liver fibrosis included sex, AST and platelet count (Table 2). However, the presence of a detectable HCV viral load was not found to be associated with significant liver fibrosis. In a sensitivity analysis, the association of MASLD with significant liver fibrosis was confirmed in both patients with and without SVR (Table S1). The duration of SVR was available only in a subset of 283 patients. When incorporated into the multivariate analysis, it did not show a significant association with significant liver fibrosis (data not shown). When evaluating specific MASLD phenotypes associated with significant liver fibrosis, diabetic MASLD (OR 4.76, 95% CI 2.16–10.49), overweight MASLD (OR 2.54, 95% CI 1.27–5.07) and hypertensive MASLD (OR 3.44, 95% CI 1.77–6.68) demonstrated significant associations with significant liver fibrosis (Table 3). In contrast, dyslipidaemic MASLD did not show a significant association with liver fibrosis (OR 1.69, 95% CI 0.94–3.03). In an exploratory analysis of the association between MASLD and liver-related events, we found that patients with MASLD had a higher prevalence of a history of variceal bleeding compared to those without MASLD (3.3% vs. 0.7%, $p=0.020$). No difference was observed for hepatocellular carcinoma, ascites or hepatic encephalopathy (data not shown).

4 | Discussion

The present study demonstrates that MASLD is associated with significant liver fibrosis in individuals with a history of HCV infection. Interestingly, the prevalence of significant liver fibrosis varied across MASLD phenotypes, with individuals with diabetes, overweight and hypertensive MASLD showing higher figures. These findings suggest that specific metabolic abnormalities in these phenotypes may create a more pro-inflammatory environment, exacerbating hepatic fibrogenesis. In addition, the prevalence of significant liver fibrosis increased proportionally with the number of cardiometabolic risk factors.

MASLD is increasingly recognised as a key contributor to liver fibrosis progression. The meta-analysis by Singh et al. [16] highlighted that fibrosis in MASLD can advance rapidly, particularly in individuals with metabolic dysfunction-associated steatohepatitis (MASH) who progress by one stage every 7.1 years, compared to 14.3 years for those with less severe forms. The link between metabolic dysfunction, MASH and progression to advanced liver disease is well established [17]. In our study, MASLD represented 85% of patients with SLD, while only a small proportion was attributable to HCV-related steatosis. This underlines the relevance of metabolic factors in driving

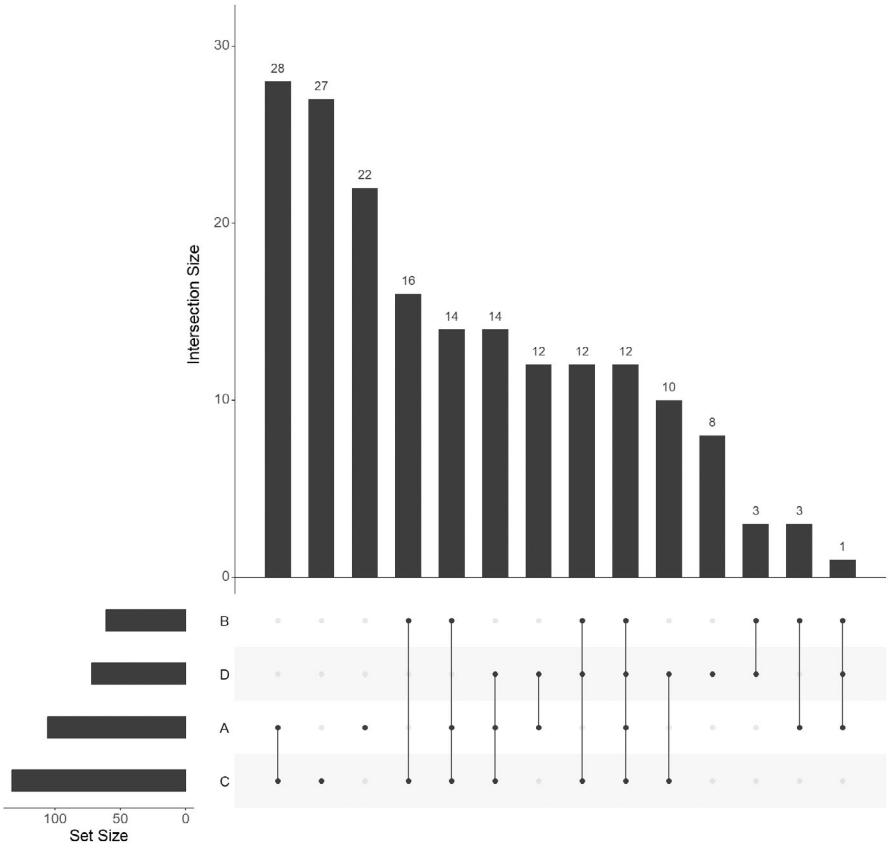

FIGURE 2 | UpSet plot showing the intersection of MASLD phenotypes. Phenotypes are represented by the sets A (overweight MASLD), B (diabetic MASLD), C (hypertensive MASLD) and D (dyslipidaemic MASLD).

SLD, even in the context of a history of HCV. Within the complex interplay of metabolic conditions contributing to MASLD, we identified a predominance of overweight and hypertensive MASLD phenotypes among individuals with a history of HCV. Additionally, there was a high prevalence of intersecting metabolic phenotypes, with hypertension and overweight being particularly common in HCV individuals with MASLD.

Our study reported that diabetic MASLD had the highest probability of significant liver fibrosis. There is a bidirectional relationship between MASLD and diabetes: MASLD can predict the onset of diabetes, and diabetes accelerates the progression of MASLD [18–26]. A European MASLD registry corroborated this, showing that type 2 diabetes mellitus was associated with significant liver fibrosis (aOR 6.25, 95% CI 1.88–20) [27]. Furthermore, these findings align with the outcomes of a biopsy-proven MASLD cohort, which demonstrated an elevated risk of liver-related mortality (adjusted hazard ratio [aHR] 2.19, 95% CI 1–4.81) and overall mortality (aHR 2.09, 95% CI 1.39–3.14) in individuals with diabetes [28]. Insulin resistance (IR), a hallmark of diabetic MASLD, plays a critical role in the development and progression of liver fibrosis [29, 30]. It has also been identified as a pivotal factor in the intricate pathogenic mechanisms underlying MASH [29, 31]. In addition, studies show that persistent hyperglycemia, arising from poorly controlled diabetes, promotes chronic glucotoxicity, thereby facilitating the progression of hepatic steatosis, necroinflammation and hepatocellular dysfunction [29, 32–40]. Our study found a 25% prevalence of prediabetes and diabetes in the HCV population, higher than that reported in the general population [41]. Numerous studies have shown that HCV infection increases the risk of IR and type 2 diabetes, which in turn exacerbate liver steatosis and fibrosis progression [42–44]. One longitudinal study has demonstrated that individuals with HCV had an 11.5 times higher risk of incident type 2 diabetes compared to the general population [45]. Several studies have consistently confirmed a positive association between HCV and IR [42, 43, 46, 47]. Moreover, IR can occur in non-obese, non-diabetic individuals with HCV, suggesting an independent role of HCV in inducing IR [48]. A meta-analysis by Patel and colleagues further links the incidence of IR in HCV-infected patients with the degree of liver fibrosis induced by HCV [49]. Patients with both HCV and type 2 diabetes are at a risk of developing steatosis and progressive liver disease, leading to severe clinical outcomes including hepatic decompensation, hepatocellular carcinoma and elevated risk of liver failure and mortality [38–40].

Our study also demonstrated that hypertensive MASLD was associated with significant liver fibrosis. Although the relationship between MASLD and hypertension is not fully understood, potential mechanisms include systemic IR, gut dysbiosis, fibrinolytic dysfunction via increased plasminogen activator inhibitor-1 levels, altered adipokine profile, chronic inflammation, oxidative stress and endothelial dysfunction [50–52]. Previous studies have shown a direct link between hypertension and liver fibrosis, especially in MASLD [53–55]. However, the relationship between hypertension and fibrosis seems to be complex in hepatitis C [56]. A recent study has shown that individuals

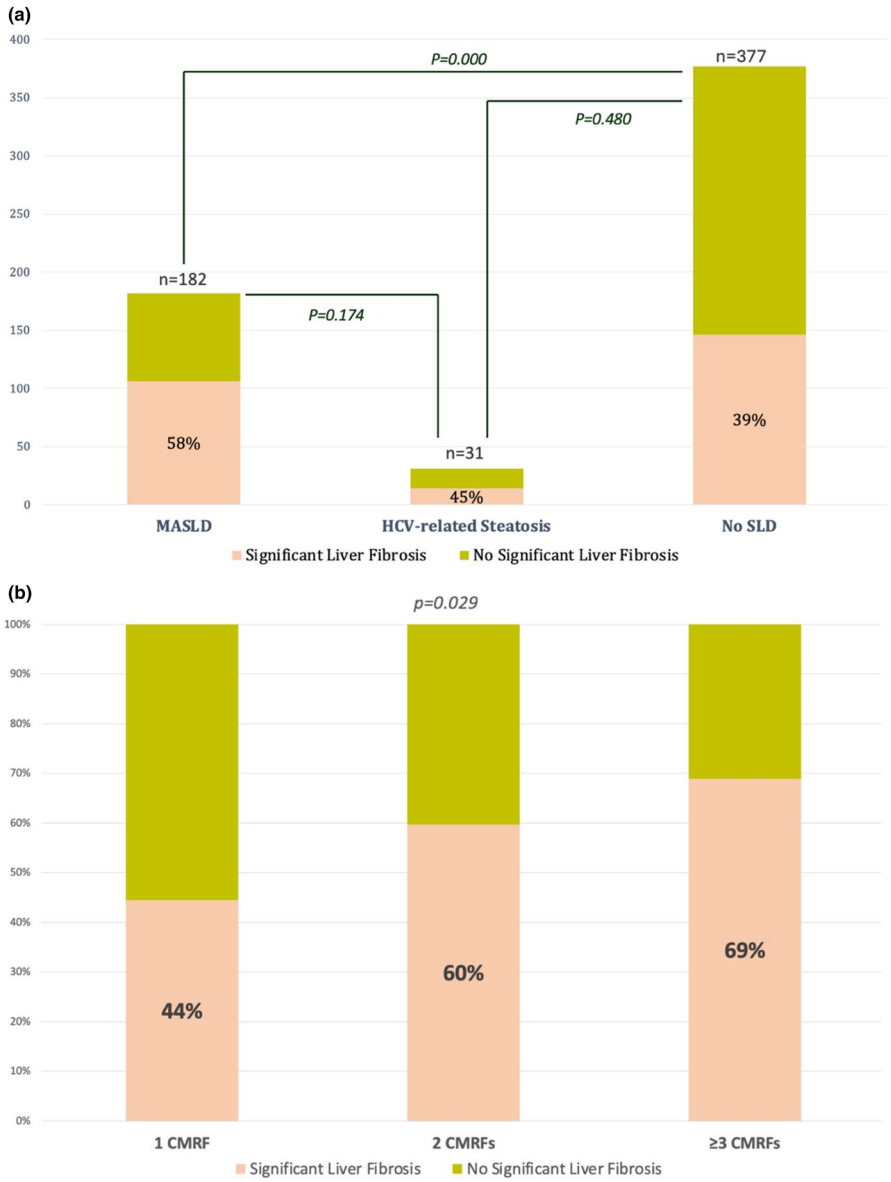

FIGURE 3 | Prevalence of significant liver fibrosis according to: (a) category of steatotic liver disease in the study population; (b) the number of cardiometabolic risk factors (CMRF).

with hepatitis C caused by HCV genotypes 1 and 4 have a higher prevalence of hypertension than those with HCV genotype 3 [57]. Chronic HCV infection induces a systemic inflammatory state that can lead to endothelial dysfunction, a precursor of hypertension [58, 59]. Several studies have shown a direct correlation between hypertension and the development of liver fibrosis [53, 60]. In a meta-analysis including 411 patients with biopsy-proven MASLD, hypertension was associated with fibrosis progression [16]. However, while our study supports the association between hypertensive MASLD and significant liver fibrosis, conflicting data exist. In a cross-sectional analysis of the National Health and Nutrition Examination Survey data, Ciardullo et al. [61] found that, while obesity and diabetes were associated with both steatosis and fibrosis, there was no association between hypertension and liver fibrosis. This discrepancy may be due to differences in study populations, inclusion criteria and methodologies.

In our study, overweight MASLD was also associated with significant liver fibrosis. Obesity has long been recognised as an independent risk factor for fibrosis in MASLD [62, 63]. Furthermore, obesity seems to have a more detrimental effect than other metabolic abnormalities on the severity of advanced fibrosis [64]. The mechanism underlying this relationship is multifaceted. Adipose tissue acts as hormonally active by releasing pro-inflammatory cytokines like tumour necrosis factor-alpha and interleukin-6 contributing to liver inflammation and fibrosis. Moreover, obesity alters adipokine profiles and gut microbiota, further promoting fibrogenesis [65]. Similar mechanisms have been observed in patients with HCV infection [37, 66, 67]. Indeed, elevated BMI is associated with steatosis progression in patients with chronic HCV infection [68]. Notably, weight reduction in chronic HCV infection has been shown to improve not only steatosis and liver enzymes but also fibrosis, despite ongoing viral infection [69].

TABLE 2 | Univariate and multivariate analyses of cofactors associated with significant liver fibrosis.

	OR	95% CI	*p*	aOR	95% CI	*p*
MASLD	**2.16**	(1.51–3.08)	**<0.001**	**2.29**	(1.07–4.87)	**0.031**
Female				0.42	(0.21–0.85)	**0.016**
AST				1.01	(1.00–1.02)	**<0.001**
Platelet				0.99	(0.99–1.00)	**0.032**

Note: Odds ratios and 95% confidence intervals are shown for each variable analysed in univariate and multivariate logistic regression analyses. Significant *p*-values ($p < 0.05$) are presented in bold.
Abbreviations: aOR, adjusted odds ratio; AST, aspartate aminotransferase; CI, confidence interval; MASLD, metabolic dysfunction–associated steatotic liver disease.

TABLE 3 | Univariate and multivariate analyses exploring the association of each MASLD phenotype with significant liver fibrosis.

	MASLD phenotypes							
	Overweight		Diabetic		Hypertensive		Dyslipidaemic	
	OR (95% CI)	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Univariate	1.81 (1.18–2.77)	0.006	3.57 (1.99–6.42)	<0.001	2.48 (1.66–3.69)	<0.001	1.97 (1.18–3.28)	0.010
	aOR (95% CI)	***p***	**aOR (95% CI)**	***p***	**aOR (95% CI)**	***p***	**aOR (95% CI)**	***p***
Multivariate	2.54 (1.27–5.07)	**0.008**	4.76 (2.16–10.49)	**<0.001**	3.44 (1.77–6.68)	**<0.001**	1.69 (0.94–3.03)	0.078
Age							1.02 (1.00–1.04)	**0.004**
Female					0.43 (0.24–0.76)	**0.004**	0.53 (0.36–0.80)	**0.002**
AST	1.01 (1.00–1.02)	**<0.001**	1.01 (1.00–1.02)	**0.001**	1.01 (1.00–1.02)	**<0.001**	1.01 (1.00–1.01)	**<0.001**
Platelets	0.99 (0.98–1.00)	**<0.001**	0.99 (0.98–0.99)	**<0.001**	0.99 (0.98–0.99)	**<0.001**		
Genotype-3	0.80 (0.29–2.20)	0.667						
Total cholesterol			0.73 (0.61–0.87)	**<0.001**				
LDL cholesterol	0.68 (0.45–1.00)	**0.009**			0.71 (0.53–0.95)	**0.024**		

Note: Odds ratios and 95% confidence intervals are shown for each variable analysed in univariate and multivariate logistic regression analyses. Significant *p*-values ($p < 0.05$) are presented in bold.
Abbreviations: aOR, adjusted odds ratio; AST, aspartate aminotransferase; CI, confidence interval; LDL, low-density lipoprotein; MASLD, metabolic dysfunction–associated steatotic liver disease.

While previous studies have demonstrated a link between dyslipidaemia and liver fibrosis [70–72], our study found that dyslipidaemic MASLD does not exhibit an association with significant liver fibrosis in HCV infection. This may be partly due to the absence of data on lipid-lowering medications, such as statins, which have been shown to have anti-inflammatory and potentially anti-fibrotic effects [73].

In line with our findings, Yamamura et al. reported that the number of metabolic abnormalities is a key determinant of liver fibrosis progression in patients with SLD. We also observed a higher prevalence of significant liver fibrosis in MASLD patients compared to those with no SLD or HCV-related steatosis, suggesting that metabolic abnormalities, rather than steatosis per se, may drive fibrosis progression in HCV patients. This supports the superiority of the MASLD definition over NAFLD in identifying individuals at risk of fibrosis.

This study has several limitations. Its retrospective design restricts data availability, particularly for key metabolic parameters like homeostatic model assessment for insulin resistance, an important marker of IR and a major driver of fibrosis [74]. Additionally, we lacked data on the use of lipid-lowering agents, which may have influenced the relationship between dyslipidaemia and fibrosis [73]. Moreover, we were unable to account for the duration of MASLD and SVR, which may have influenced our findings. The

cross-sectional nature of the study also limits our ability to establish causality and/or assess the temporal progression of fibrosis. Despite these limitations, our study has several strengths. It is one of the first to explore the association between MASLD phenotypes and liver fibrosis in individuals with a history of HCV infection. Additionally, the relatively large sample size and focus on HCV monoinfection enhance the robustness of our findings.

In conclusion, our findings underscore the importance of a comprehensive approach to managing patients with HCV, even after viral eradication. Early identification and management of metabolic risk factors, especially diabetes and hypertension, could potentially reduce the risk of fibrosis progression, improving long-term outcomes. Furthermore, the differential impact of MASLD phenotypes highlights the need for personalised care, where interventions are tailored based on individual risk profiles to prevent or slow the progression of liver disease. Further longitudinal studies are needed to evaluate the joint effects of HCV and MASLD on liver fibrosis and on the incidence of liver-related events.

Author Contributions

Wesal Elgretli contributed to the study concept and design, acquisition of data, interpretation of data and critical revision of the manuscript. Mohamed Shengir, Solomon Sasson, Luz Esther Ramos Ballestreros, Marc Deschenes, Phil Wong, Tianyan Chen, Nadine Kronfli, Alexa Keeshan and Saniya Tandon were involved in the acquisition of data and critical revision of the manuscript. Sahar Saeed and Agnihotram V. Ramanakumar were involved in statistical analysis, interpretation of data and critical revision of the manuscript. Curtis Cooper was involved in the acquisition and interpretation of data, critical revision of the manuscript and overall study supervision. Giada Sebastiani was involved in the study concept and design, acquisition and interpretation of data, analysis and drafting of the manuscript, critical revision of the manuscript and overall study supervision. All the authors declare they have participated in the preparation of the manuscript and have seen and approved the final version.

Conflicts of Interest

Marc Deschenes has served as an advisory board member for Merck, Janssen and Gilead. Phil Wong has acted as a consultant for BMS, Gilead, Merck and Novartis. Nadine Kronfli reports research funding from Gilead Sciences, advisory fees from Gilead Sciences, ViiV Healthcare, Merck and Abbvie, and speaker fees from Gilead Sciences, Abbvie and Merck. Sahar Saeed served as an advisory board member for Novo Nordisk. Curtis Cooper is a consultant and speaker for AbbVie and Gilead. Giada Sebastiani has acted as a speaker for Merck, Gilead, Abbvie, Eli Lilly and Novo Nordisk, and served as an advisory board member for Merck, Gilead, GlaxoSmithKline and Novo Nordisk. Wesal Elgretli, Mohamed Shengir, Solomon Sasson, Agnihotram V. Ramanakumar, Felice Cinque, Luz Esther Ramos Ballestreros, Tianyan Chen, Alexa Keeshan and Saniya Tandon declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.