

Review

# Sex and Gender Differences in Liver Fibrosis: Pathomechanisms and Clinical Outcomes

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**ABSTRACT:** The accumulation of extracellular matrix proteins is the hallmark of liver fibrosis associated with all chronic liver disease (CLD) types. Liver fibrosis results from repeated bouts of liver injury, which trigger the wound-healing response, ultimately disrupting the normal hepatic architecture. Over time, fibrosis can progress to cirrhosis, portal hypertension, liver failure, and hepatocellular carcinoma, worsening patient outcomes. Biological modifiers, such as sex and socio-cultural constructs like gender, influence the development of liver fibrosis through various genetic, hormonal, immunological, metabolic, and lifestyle-related factors, including alcohol consumption, diet, sedentary behavior, and hormonal therapy. Moreover, liver fibrosis is significantly modulated by age, reproductive status, and the etiology of CLD. This review aims to summarize the most well-characterized pathomechanisms underlying sex and gender differences in hepatic fibrogenesis as well as liver-related complications (cirrhosis, portal hypertension, hepatic encephalopathy, liver failure, and hepatocellular carcinoma) and extra-hepatic correlates of liver fibrosis (sarcopenia, cardiovascular disease, diabetes, chronic kidney disease, and dementia) across various types of CLD due to viral-related, autoimmune, drug-induced and metabolic etiologies. Understanding these disease modifiers and their mechanisms is crucial for developing innovative treatment strategies and precision medicine approaches in this field.

**Keywords:** Age; Cardiovascular disease; Chronic kidney disease; Dementia; Diabetes; Estrogen; Genetics; Hepatocellular carcinoma; Portal hypertension, Reproductive status; Sarcopenia; Testosterone



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## 1. Introduction

Liver fibrosis, characterized by the excessive accumulation of extracellular matrix proteins, is a hallmark of chronic liver diseases. The fibrogenic reaction results from repeated liver injury, the wound-healing response to such ongoing injury, and ultimately disrupts normal liver architecture and hepatic function [1]. Over time, liver fibrosis can advance to more severe stages such as cirrhosis, predisposing to liver failure, and hepatocellular carcinoma (HCC) development, all of which significantly worsen patient outcomes [2]. Recent research has expanded our understanding of liver fibrosis, revealing that its implications extend beyond liver-specific complications. Fibrosis is now recognized as a prognostic factor for a range of extra-hepatic conditions, including sarcopenia [3–6], cardiovascular disease (CVD) [7–14], chronic kidney disease (CKD) [15–18], and even cognitive decline [19], underscoring its systemic impact in broader health contexts.

A recent meta-analysis pinpoints that advanced liver fibrosis and cirrhosis are highly prevalent in the general worldwide population, with major geographic discrepancies. The prevalence rates are 3.3% (95% CI: 2.4–4.2) for advanced liver fibrosis and 1.3% (95% CI: 0.9–1.7) for cirrhosis, with a trend indicating an increase in prevalence after 2016 [20]. Male sex, viral hepatitis, diabetes, excessive alcohol intake, and obesity are the main risk factors for cirrhosis

[20]. Sex differences are a critical modifier of the development, progression, and outcomes of liver fibrosis [21]. Studies demonstrate that men and women exhibit different susceptibility to liver fibrosis [22]. However, the relationship between sex and liver fibrosis is complex and multifaceted and modulated by hormonal, genetic, as well as environmental factors [21]. For example, estrogen has a protective effect against fibrosis progression [23,24], potentially explaining the slower fibrosis rates observed in premenopausal women compared to men [25]. Additionally, sex differences in immune responses [26], fat distribution [27], and metabolic processes [28] also contribute to disparities in the risk of liver fibrosis development and progression among men and women.

In this review, we aim to summarize the current understanding of the pathomechanisms underlying sex and gender differences in liver fibrosis. We will also explore how these differences influence both intra- and extra-hepatic complications. By highlighting these differences, we hope to provide insights that could lead to more personalized strategies for managing liver fibrosis in both men and women.

## **2. Pathomechanisms Contributing to Sex Differences in Liver Fibrosis**

Sex differences in the prevalence, severity, and outcomes of liver fibrosis are well-documented. Understanding these differences is crucial for developing sex-specific therapeutic interventions and improving outcomes in patients with liver disease. Various factors contribute to sex differences in liver fibrosis, including genetics, hormonal influences, immune system responses, and lifestyle factors (Table 1). Research shows that females generally have a lower risk of liver fibrosis compared to males, particularly in conditions such as chronic hepatitis C and nonalcoholic fatty liver disease (NAFLD) [29,30], now renamed metabolic dysfunction-associated steatotic liver disease (MASLD). This susceptibility varies across different stages of reproductive life, including puberty, pregnancy, and menopause, highlighting the importance of considering sex differences in liver disease management [21].

**Table 1.** Factors contributing to sex differences in liver fibrosis \*.

	Author, Year [Ref.]		
Genetic Factors	Wu et al., 2024 [31]	<b>Sex chromosomes</b>	Males (XY) and females (XX) have different combinations of sex chromosomes, leading to varying gene expression. Genes on sex chromosomes, such as those involved in immune response and inflammation, can impact liver fibrosis development differently in males and females.
	Xu et al., 2004 [32]	<b>Hormone Receptors</b>	Estrogen and testosterone play significant roles in liver pathology. Estrogen receptors (ERs) can influence liver injury and fibrosis through proliferation, apoptosis, and inflammation pathways. Genetic variations in these receptors may affect hormone sensitivity and fibrotic response.
	Bernardi et al., 2020 [33]	<b>Inflammatory Pathways</b>	Genes in inflammatory signaling pathways, such as those encoding cytokines and receptors (e.g., IL-6, TNF- $\alpha$ ), may have sex-specific expression and activities, affecting the inflammatory response during liver injury and fibrosis progression.
	Athwal et al., 2017 [34]	<b>Fibrogenic Factors</b>	The expression of genes related to extracellular matrix (ECM) production (e.g., collagen genes) can differ between sexes. For example, the SRY-related HMG-box gene 9 (SOX9) transcription factor has been linked to sex-specific responses in liver fibrosis.
	Horn et al., 2024 [35]	<b>Metabolic Genes</b>	Genes related to lipid metabolism and insulin sensitivity may also show differences in expression or activity between sexes, potentially influencing liver damage and fibrosis progression, especially in metabolic liver diseases.
	Day, 2005 [36], Balcar et al., 2022 [37], and Wegermann et al., 2021 [38]	<b>Genetic Polymorphisms</b>	Specific genetic polymorphisms (SNPs) in genes related to liver function, drug and toxin metabolism, and fibrogenesis have been linked to variations in fibrotic progression between men and women. For instance, gene variations in <i>PNPLA3</i> , <i>IL1B</i> , <i>IL10</i> , <i>MMPs</i> and many other genes have sex-specific associations with liver disease.
Hormones	Nataraj et al., 2024 [39] and Milette et al., 2019 [40]	<b>Estrogen</b>	Estrogen is generally protective against liver fibrosis. It has anti-inflammatory effects, can modulate immune responses, and also influences the activity of hepatic stellate cells (HSCs), which are pivotal in developing fibrosis.
	Sarkar et al., 2021 [41]	<b>Testosterone</b>	Testosterone is often associated with a higher risk of developing liver fibrosis and cirrhosis, as it may promote the activation of HSCs and exacerbate fibrogenesis.
	Xu et al., 2022 [42]	<b>Progesterone</b>	Progesterone may also play a role, although its effects are less clearly defined compared to estrogen and testosterone. Progesterone can influence liver injury responses and may interact with other hormones to affect fibrosis.
	Targher et al., 2006 [43]	<b>Cortisol</b>	The stress hormone may affect liver fibrosis through its impact on the immune system and may interact with other sex hormones.
	Miyauchi et al., 2019 [44] and Wauthier et al., 2010 [45]	<b>Growth Hormone (GH) and Insulin-like Growth Factor 1 (IGF-1)</b>	These hormones are also implicated in liver regeneration and fibrosis with different effects in males and females, contributing to the disparity in fibrosis progression.
Immune System	Sayaf et al., 2023 [46]	<b>Cytokine Production</b>	There are notable differences in cytokine profiles between sexes. For instance, women often have higher levels of certain pro-inflammatory cytokines and a more robust Th2 response, which can influence the fibrosis process. The balance of cytokines like IL-6, TNF- $\alpha$ , and TGF- $\beta$ , which are involved in inflammatory and fibrogenic processes, can also differ between sexes.

	Scotland et al., 2011 [47]	<b>Immune Cell Composition</b>	The composition and activation status of immune cells (such as macrophages, T cells, and dendritic cells) can vary by sex. For example, females tend to have a higher proportion of regulatory T cells, which may contribute to a more controlled inflammatory response, while males may exhibit a more aggressive fibrotic response characterized by different macrophage polarizations.
	Saboo et al., 2021 [48] and Shi et al., 2021 [49]	<b>Microbiome Differences</b>	There are known differences in gut microbiota composition between sexes, which can indirectly influence liver fibrosis via modulation of immune responses and systemic inflammation.
	Yang et al., 2014 [25]	<b>Age and Menopausal Status</b>	Age and hormonal changes, such as those occurring during menopause in women, can influence the immune response and alter the pathogenesis of liver fibrosis. The transition can shift immune profiles and exacerbate fibrosis-development mechanisms.
	Glass et al., 2019 [50]	<b>Inflammatory Response and Comorbidities</b>	As people age, the likelihood of developing comorbid conditions increases, which can complicate the pathogenesis of liver fibrosis. The impact of these comorbidities may be sex-dependent. Furthermore, aging is associated with increased levels of systemic inflammation, which can exacerbate liver injury. The immune responses can be different between sexes, affecting the fibrotic response.
<b>Lifestyle Factors</b>	Kezer et al., 2021 [51]	<b>Alcohol Consumption</b>	Males typically consume higher levels of alcohol compared to females, which can lead to an increased risk of alcohol-related liver disease and fibrosis.
	Yabe et al., 2021 [52]	<b>Dietary Habits</b>	Differences in dietary choices, such as the intake of high-calorie diets, sugar, and fats (which can contribute to non-alcoholic fatty liver disease), often vary by sex. Males might have diets higher in fats and proteins, while females may consume more fruits and vegetables.
	Yabe et al., 2021 [52]	<b>Physical Activity</b>	Physical activity levels can vary by sex, with males often engaging in different types or intensities of exercise compared to females. Physical inactivity is a risk factor for obesity, which is linked to liver fibrosis.
	Rinaldi et al., 2024 [53]	<b>Obesity</b>	While obesity can affect both sexes, the distribution of fat (visceral vs. subcutaneous) and the rates of obesity can differ, influencing the development of conditions like non-alcoholic fatty liver disease (NAFLD) and subsequent fibrosis.
	Shi et al., 2021 [49]	<b>Smoking</b>	Tobacco use can differ by sex and has been associated with an increased risk of liver fibrosis. Smoking can exacerbate liver injury and fibrosis progression.
	Para et al., 2018 [54]	<b>Medication Use</b>	Differences in how males and females respond to medications, including their metabolism and side effects, may also play a role in liver health, especially with medications that may be hepatotoxic.
	Straw et al., 2022 [55] and Kardashian et al., 2023 [56]	<b>Healthcare Access and Utilization</b>	Males and females may differ in their healthcare-seeking behavior and access to medical care, possibly leading to disparities in the diagnosis and management of liver diseases.

\* For discussions and references on specific points, please refer to the text.

## 2.1. Genetic Factors

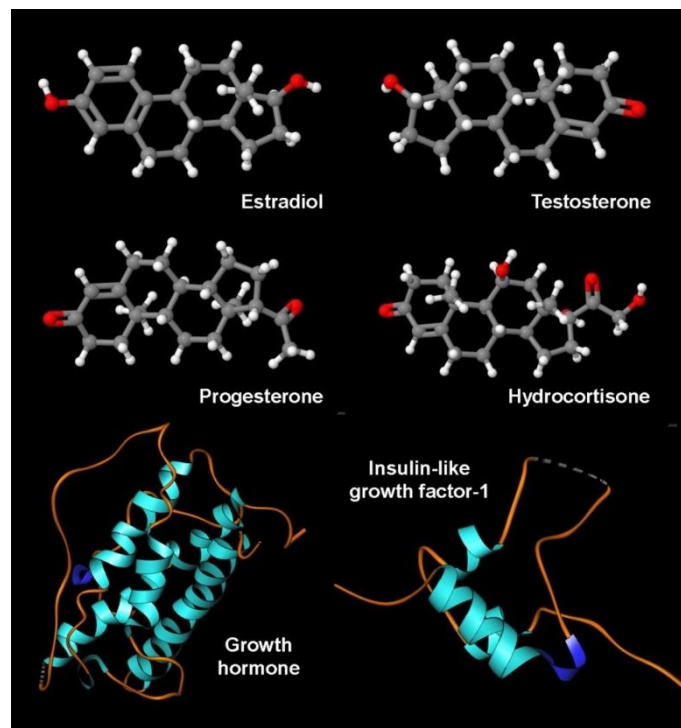
Genomic studies have identified several sex-limited genes that influence liver fibrosis [57]. For example, a male-specific Y chromosome gene sex-determining region Y (SRY) is linked to fibrogenesis and can affect hepatic stellate cell (HSC) activation and fibrosis progression. This was demonstrated in hepatocyte-specific *Sry* knock-in mice that developed exacerbated liver fibrosis, whereas *Sry* knockout mice had alleviated liver fibrosis when subjected to bile duct ligation for 2 weeks or carbon tetrachloride treatment [31]. Mechanistically, it was suggested that the SRY expression in hepatocytes can transcriptionally regulate *Pdgfra* expression and promote high mobility group box 1 release, which are key factors in the activation of HSCs and transdifferentiation into myofibroblasts [32].

Conversely, females benefit from X-linked genes that promote protective pathways. The X-linked inhibitor of apoptosis (XIAP), for instance, plays a key role in liver maintenance, and its loss can trigger liver diseases, underscoring its importance under normal physiological conditions [58]. It is well accepted that XIAP is a potent anti-apoptotic protein that can physically interact and block the enzymatic activities of various caspases, thereby inhibiting both the extrinsic and intrinsic apoptotic pathways [59,60]. In the same line, the absence of XIAP has been shown to sensitize cells and mice to lipopolysaccharide and TNF-mediated cell death. Mice lacking XIAP are more susceptible to liver damage than wildtype mice [61].

## 2.2. Hormonal Influence

Hormones such as estrogens, progesterone, androgens (such as testosterone), cortisol, growth hormone, and insulin-like growth factor (IGF) significantly impact liver metabolism and pathobiology by influencing immune responses, inflammation, and fibrogenesis (Figure 1). Estrogen is known for its anti-fibrogenic properties, occurring via inhibition of HSC activation and extracellular matrix (ECM) deposition. Estrogen receptors (ERs), especially ER $\alpha$ , reduce fibrosis by decreasing collagen synthesis and increasing collagenase activity [32]. On the other hand, androgens may have a pro-fibrogenic effect, potentially worsening liver fibrosis in males. Therefore, hormonal balance is crucial in disease progression [62].

Cortisol, a stress hormone, also impacts liver fibrosis by modulating immune responses and interacting with other sex hormones. Male mice exhibit more severe insulin resistance than female mice when exposed to high cortisol levels, while female mice show more protective metabolic adaptations in adipose tissue [63]. Similarly, growth hormone and IGF have sex-specific effects, influencing fibrosis progression by regulating liver regeneration [64].



**Figure 1.** Hormones contributing to sex differences in the pathogenesis of liver fibrosis. Legend to Figure 1. The sex hormones estradiol, testosterone, and progesterone, along with hydrocortisone (cortisol) and the cytokines growth hormone and insulin-like growth factor-1 (IGF-1), significantly contribute to sex differences in the pathogenesis of liver fibrosis. This figure illustrates that

the molecular drivers contributing to sex differences in the pathogenesis of liver fibrosis can vary from a biochemical standpoint and can include hormones or proteinogenic factors. Structures depicted were generated with Jmol (version 14.2., 2015.07.09), and chemical depiction information sourced from the PubChem Compound Database [65]. The structures for growth hormone and insulin-like growth factor (IGF) were drawn with Ribbons XP software (version 3.0) using the coordinates 1GZZ and 4HGU deposited in the RCSB Protein Data Bank [66].

### 2.3. Immune Response Mechanisms

Research shows that innate and adaptive immune responses differ between men and women, with females typically exhibiting a more robust immune response [67]. This enhanced immune activity can lead to more effective pathogen clearance but also predisposes women to autoimmune hepatic disorders. In the context of liver fibrosis, the imbalance in cytokine production is crucial. Males typically have higher levels of pro-inflammatory cytokines (e.g., IL-1 $\beta$ , IL-6, and TNF- $\alpha$ ) compared to females [33]. These elevated cytokines promote inflammation and, ultimately, fibrosis during liver injury.

### 2.4. Sex Differences in the Activation and Function of HSC and Extracellular Matrix Remodeling

In a CCl<sub>4</sub>-induced liver injury mouse model, testosterone significantly influences liver injury by regulating the NLRP3 inflammasome activation-mediated inflammatory response [68]. In contrast, estrogens reduce HSC activation, mitigating the fibrogenic response in females [69]. Receptor and ligand expression involved in HSC activation also differ by sex. Female and male mice display different estrogen receptor expressions in HSCs, influencing fibrogenic responses [70]. Furthermore, studies identify sex differences in the expression and activation of the transforming growth factor- $\beta$  (TGF- $\beta$ ) pathway, a key mediator in fibrosis. For example, female mice show lower TGF- $\beta$  expression than males in the CCl<sub>4</sub>-induced liver injury model [46].

Fibroblasts and HSCs produce collagens (types I, III, and IV) and glycoproteins that constitute the ECM. Sex-dependent variations in ECM production are evident, with females demonstrating considerably lower levels of collagen deposition in response to liver injury than males [46]. Sex hormones also affect matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), which regulate ECM remodeling. Males tend to have lower MMP levels, leading to excessive fibrosis, while females typically have a higher MMP/TIMP ratio, indicating a more balanced fibrotic response [46].

### 2.5. Microbiota Influences on Liver Fibrosis

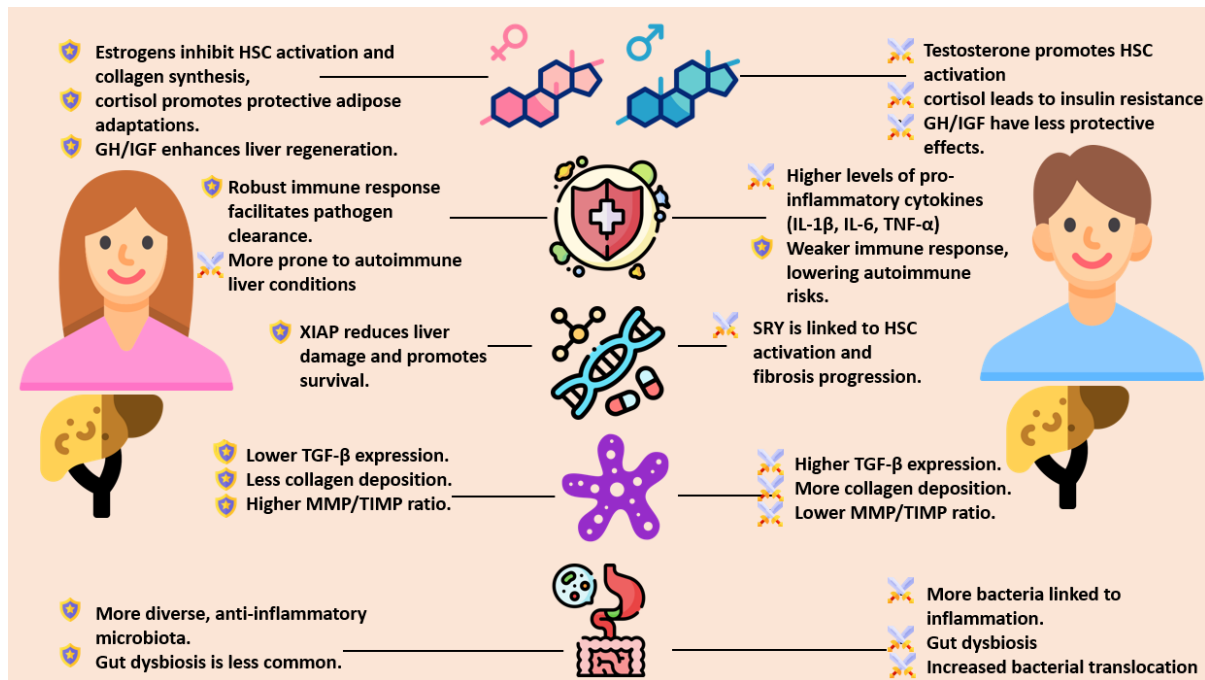
The composition of gut microbiota affects the progression of liver fibrosis, with differences in microbial diversity and abundance based on sex. Emerging evidence links sex-dimorphic gut microbiota and bile acid profiles to different immune responses in the liver [71]. Males tend to have a higher abundance of certain bacteria associated with increased inflammation, thereby contributing to more severe fibrosis [72]. In contrast, females often exhibit more varied gut microbiota associated with anti-inflammatory markers, potentially offering protection against liver damage [72]. Additionally, gut dysbiosis can trigger systemic inflammation, further promoting liver fibrosis via elevated levels of gut-derived bacterial translocation, which fuels inflammation and fibrogenesis [73]. Studies in mice show that modifying gut microbiota through diet, probiotics, or antibiotic therapy can effectively reduce or worsen liver fibrosis. This underscores the importance of the gut-liver axis in understanding and addressing gender-related disparities in fibrosing liver disease [74].

### 2.6. Future Directions and Conclusion

Future research should focus on elucidating the biological mechanisms behind sex disparities in liver disease. Investigating the roles of sex chromosomes in gene expression patterns related to fibrosis may provide new therapeutic targets [31]. Clinical studies should also incorporate sex stratification to improve understanding of liver disease outcomes. Potential therapies could involve sex hormone modulation, such as exploring estrogen-based treatments to prevent or treat liver fibrosis in at-risk individuals. Furthermore, targeting gut microbiota through dietary interventions or probiotics may offer a novel approach to reducing fibrosis, particularly in male patients.

The complex interaction of genetic, hormonal, immune, and environmental factors drives sex differences in liver fibrosis. Figure 2 summarizes the protective and harmful pathomechanisms underlying these differences between males and females. Understanding these pathomechanisms is essential for developing targeted interventions and improving clinical outcomes in patients with liver disease. Future research must continue to uncover the intricate details of these

mechanisms to create personalized treatments that address the unique needs of male and female patients. This knowledge is crucial for developing sex-specific therapies for liver diseases like cirrhosis and fibrosis, as well as for designing preventive strategies.



**Figure 2.** Comparative summary of protective and harmful pathomechanisms underlying sex differences in liver fibrosis. Legend to Figure 2. Based on references in the text, Figure 2 summarizes the most well-characterized hormonal, immune, genetic, and gut-liver axis-related mechanisms involved in sex and gender-disparities in liver fibrosis. The sword icon represents harmful pathomechanisms, and the shield icon represents protective ones. HSC—Hepatic stellate cell; GH—Growth hormone; IGF—Insulin-like growth factor; XIAP—X-linked inhibitor of apoptosis; TGF- $\beta$ —Transforming growth factor-beta; MMP—Matrix metalloproteinase; TIMP—Tissue inhibitor of metalloproteinase; IL—Interleukin; TNF- $\alpha$ —Tumor necrosis factor-alpha.

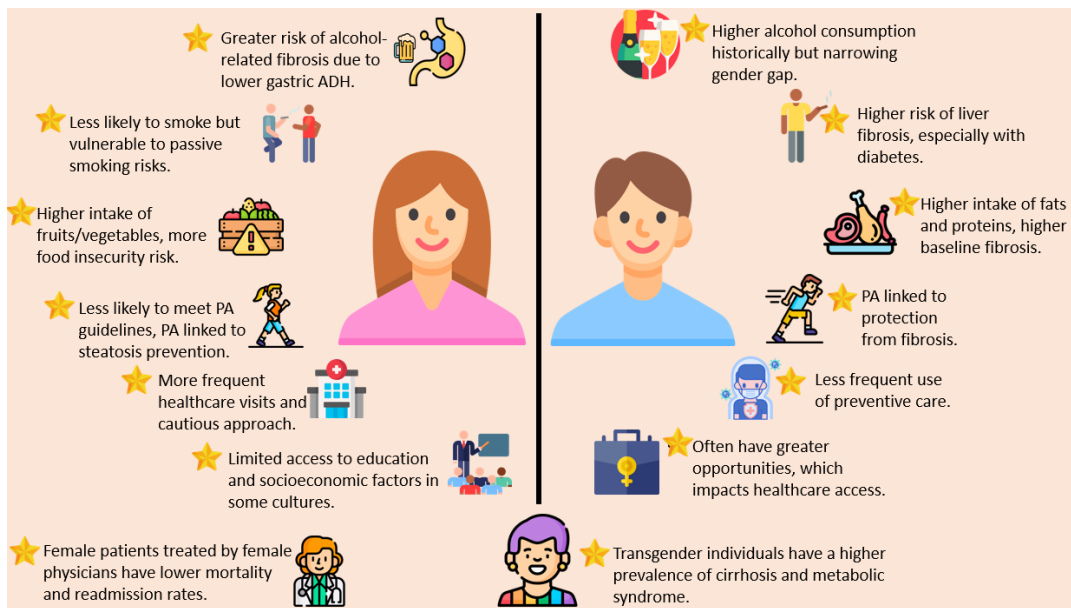
### 3. Role of Gender

While sex is a binary biological variable, gender refers to social norms that shape roles, expectations, opportunities, and the distribution of power for women and men, and it is more fluid throughout a person’s lifetime [75,76]. Importantly, gender identity may differ from biological sex, as seen in transgender individuals, who may have been under-represented in medical studies [77]. Gender is just as important as biological sex in its impact on health, influencing both patients and healthcare providers [78]. For example, gender affects health maintenance and susceptibility to liver disease through behaviors such as diet, smoking, and physical activity (cf. Table 1), which can alter gene expression and clinical phenotype via epigenetic modifications [79,80]. Typically, men are more likely to engage in risky behaviors such as excessive alcohol consumption and smoking, increasing the risk of liver fibrosis [81]. In addition, gender plays a key role in access to preventive healthcare, acceptance of invasive diagnostic and therapeutic strategies, and overall utilization of healthcare services [82,83].

Given the complexity of this topic—intertwined with race, ethnicity, historical determinants, and shifting political attitudes—in this section, we will explore well-characterized examples of how gender may affect liver fibrosis.

Figure 3 summarizes the gender differences in liver fibrosis. However, the full picture is still evolving, and more research is needed to better understand how sex and gender impact liver fibrosis.





**Figure 3.** Comparative summary of gender differences in liver fibrosis. PA—Physical activity; ADH—alcohol dehydrogenase. Legend to Figure 3. Based on the references discussed below, the cartoon illustrates the varying impact that alcohol consumption, physical activity, diet, socio-economic status, and hormonal therapies may have on liver fibrosis.

### 3.1. Alcohol

A robust body of research indicates that women are at a higher risk of alcohol-related liver fibrosis compared to men [84]. This difference is partly due to variations in enzymatic activity. Men have 70–80% higher gastric alcohol dehydrogenase (ADH) activity, which plays a role in initial alcohol metabolism, while women exhibit higher hepatic ADH activity [85]. Alcohol use disorder (AUD) affects approximately one in three individuals in the United States during their lifetime [86]. While men have traditionally been more impacted by AUD, recent data shows that the gender gap has significantly narrowed due to a concerning rise in AUD prevalence among women. This underscores the urgent need for preventive measures to address the long-term impact of alcohol on liver health [87].

### 3.2. Smoking of Tobacco

Men may be at a higher risk of developing liver fibrosis and HCC due to tobacco use [88]. Additionally, tobacco use can worsen the risk of liver fibrosis in individuals with MASLD and diabetes, suggesting that those with diabetes should consider quitting smoking [89]. A recent study found that cotinine, a biomarker of tobacco exposure, is associated with liver fibrosis in adolescents [90]. This highlights the importance of implementing strict laws to prevent both active and passive smoking in order to decrease the risk of liver fibrosis.

### 3.3. Diet

Dietary differences, such as the consumption of high-calorie diets, sugar, and fats—factors that contribute to MASLD—often vary by gender [91]. Men typically consume higher amounts of fats and proteins, while women tend to eat more fruits and vegetables [92]. These differences in diet lead to variations in antigen exposure and micronutrient intake, contributing to different immune aging trajectories and longevity-associated outcomes [93]. Poor diet interacts with alcohol consumption, making individuals more susceptible to severe ALD [94]. This is particularly relevant given that food insecurity—an emerging risk factor for developing fibrotic liver disease, irrespective of HIV status [95,96]—is more common among women [97].

Additionally, gender may influence treatment response. For instance, in the case of the very low-calorie ketogenic diet (VLCKD), men tend to have higher baseline levels of steatosis and fibrosis than women, and these differences persist even after following the diet [53].

### 3.4. Physical Activity

Physical activity (PA) plays a key role in determining the risk of developing MASLD and HCC [98,99]. PA levels typically vary between sexes, with men often engaging in different types or intensities of exercise compared to women



[100]. Physical inactivity, a risk factor for obesity, is closely linked to liver fibrosis [101], and women are less likely to meet the PA guidelines [102].

A cross-sectional study of 5,933 US adults reported that leisure-time PA is negatively associated with steatosis in women and individuals below 60 years of age but not in men. However, men are significantly protected from liver fibrosis by leisure-time PA [103]. Therefore, promoting PA is crucial in preventing (and possibly reversing) liver fibrosis, and gender-specific strategies to achieve this goal need further exploration.

### 3.5. Cultural Attainment

In certain societies and cultures, gender can restrict access to education, which is a key indicator of socio-economic status [104]. It is closely associated with the risk of developing psychological depression, MASLD, and metabolic syndrome (MetS) [105–107]. Given these factors, advocating for equal opportunities in educational achievement should be a top priority for policymakers engaged in healthcare programs.

### 3.6. Health-Seeking Behavior

Women in Europe tend to take a more cautious approach to their health [108], which may potentially enhance the protective effects of hormones against liver fibrosis. A study in Canada shows that women visit their primary care providers more frequently than men for both physical and mental health concerns. [109]. Another study from India pinpoints gender differences in healthcare preferences, with women favoring socio-cultural and long-term approaches, while men prefer more technological and rapid therapies. [110]. However, a large study in the USA among 3237 respondents (representing 4.6 million adults with CLDs) reports that cost-related medication nonadherence, along with food insecurity (which may be relevant for liver fibrosis), is more prevalent among younger individuals, women, those with low income, and those with multimorbidity [111].

Collectively, these studies support the notion that gender influences health-seeking behavior in ways that are shaped by societal roles. However, further exploration is needed to understand the specific impact of these gender differences on liver fibrosis.

### 3.7. Liver Fibrosis in Cis vs. Transgender People

A large study involving 64,615,316 adults reported that 42,471 (0.07%) identify as transgender. Compared to cis gender adults, those who identify as transgender exhibit a two-fold increased prevalence of cirrhosis, often associated with anxiety, depression, or both [112]. Gender-affirming hormone therapy (GAHT) is commonly administered to transgender individuals to alleviate dysphoria and improve quality of life. A large cohort including 1290 participants shows that estradiol administration in both cisgender and transgender individuals reduces the odds of MetS, while testosterone administration increases this risk. This is especially relevant for the management of MetS, cardiometabolic risk, and MASLD [113], particularly among transgender individuals assigned male at birth, who seem to remain at higher risk of insulin resistance following GAHT [114]. The risk of hepatobiliary cancers in those exposed to GAHT remains uncertain [115], and GAHT poses challenges in the pre- and postoperative care of liver transplant patients [116]. Therefore, further investigation into these obscure aspects of GAHT is warranted.

### 3.8. Does Physicians' Sex Affect Liver Fibrosis Patients' Outcome?

A groundbreaking study of 458,108 female and 318,819 male patients treated by either male or female physicians revealed that patients treated by female physicians experience lower rates of mortality and hospital readmission. The benefits of being treated by female physicians are even greater for female patients than male patients [116]. This study provides strong evidence of an interaction between physicians' and patients' gender. The specific implications of this interaction in the hepatological arena, particularly for liver fibrosis patients, deserve further investigation.

## 4. Sex Differences in Liver-Related Outcomes

A robust body of published evidence supports the notion that certain liver-related complications show significant sex differences. These differences appear to depend on the etiology of liver disease, age, socio-economic status, and variable response rates to different treatment modalities. To summarize the topic, various etiologies are addressed, from alcohol to drug-induced liver injury (DILI) (Table 2). Studies were retrieved using the following research strategy (PubMed, accessed on 4 July 2024): (sex differences [Title/Abstract]) AND (liver fibrosis [Title/Abstract]).

**Table 2.** Sex differences across various etiologies of liver disease.

Author, Year [Ref.]	Method	Findings	Comment
<b>ALD</b>			
Pemmasani G, 2023 [117]	US nationwide study comprising 112,790 patients with AH.	Women accounting for 33.3% of cases and were significantly younger than men. They also had higher rates of HE (11.5% vs. 10.1%), ascites (27.9% vs. 22.5%), PoHtn (18.5% vs. 16.4%), cirrhosis (37.3% vs. 31.9%), weight loss (19.0% vs. 14.5%), HRS (4.4% vs. 3.8%), SBP (1.9% vs. 1.7%), sepsis (11.1% vs. 9.5%), and blood transfusion (12.9% vs. 8.7%) ( $p < 0.001$ for all comparisons). Moreover, women also had a higher 6-month readmission rate [aOR 1.12 (1.06–1.18)], mortality during readmission [OR 1.23 (1.08–1.40)] and composite score of mortality during index hospitalization or readmission (8.7% vs. 7.2%; OR = 1.15 (1.04–1.27)) ( $p < 0.001$ for all comparisons).	Compared to men, women with alcoholic hepatitis are generally younger and have more comorbidities, complications related to alcoholic hepatitis, rehospitalizations, and associated mortality.
Listabarth S, 2022 [118]	All registrations for OLT due to ALC within the Eurotransplant database from 2010 to 2019 were analyzed.	Women on the OLT list, making 24.8% of the patient population, were younger than men. Their RRs for transplantation, removal from the waiting list, and death on the waiting list were 0.74, 1.44, and 1.10, respectively.	In the OLT setting, women with ALC are at a disadvantage compared to men.
<b>HBV</b>			
Chau A, 2024 [119]	A real-world retrospective cohort study of 3388 treatment-naïve adult HB patients (36.89% were women) from America and Asia.	Women were older than men, less likely to have T2DM, overweight/obesity, or cirrhosis; and had a lower HBV DNA level and ALT levels (all $p < 0.01$ ). PSM balanced relevant background characteristics between the two groups. Compared to men, women had similar 5-year cumulative VR and incidence of HCC, but lower BR (84.0% vs. 90.9%; $p < 0.001$ ) and CR (78.8% vs. 83.4%; $p = 0.016$ ). Men were more likely to achieve BR (SHR, 1.31; 95% CI, 1.17–1.46; $p < 0.001$ ) and CR (SHR, 1.16; 95% CI, 1.03–1.31; $p = 0.016$ ), while VR and the odds of HCC were similar.	Men had a 16% higher odds of clinical remission and a 31% higher likelihood of BR than women.
Duan H, 2023 [120]	This study genotyped 30 loci globally in six genes among 1007 Chinese patients with chronic HBV infection compared to 1040 HC.	Two SNP loci in the <i>SRD5A2</i> gene (rs12470143 and rs7594951) showed significant differences in genotype and allele frequencies between sexes, with the proportion of T alleles significantly higher in men than in women. At LRA, the two genetic variants in the <i>SRD5A2</i> gene (rs12470143 C>T, rs7594951 C>T), along with male sex, age over 50 years old, HBeAg positive status, elevated serum HBsAg load, high serum HBV DNA load, and HBV genotype C, were all independent predictors of HBV-related liver fibrosis.	These genetic variants in the <i>SRD5A2</i> gene (rs12470143 C>T, rs7594951 C>T), which play a role in the metabolism and signaling of sex hormones/sex hormone receptors, are associated with sex differences in the clinical characteristics of patients with chronic HBV infection.
<b>HCV</b>			
Corsi D, 2016 [121]	This study examined data regarding 978 individuals with chronic HCV infection followed at the Ottawa Hospital and Regional Viral Hepatitis Program.	32% of the participants were women. Women under 50 years old tended to have lower fibrosis scores than men, while the mean fibrosis scores were similar after the age of 50. Women were less likely to have started IFN-based HCV antiviral therapy (35.3% vs. 43.3%, $p = 0.01$ ). Women with low SES were more likely to be coinfecting with HIV and had higher rates of fibrosis progression. Women in low-income neighborhoods were also less likely to achieve SVR (OR = 0.50, 95% CI: 0.34–0.75, $p = 0.01$ ) compared to women in higher-income areas.	Sex, age, and SES interact to impact fibrosis progression, the likelihood of starting HCV antiviral therapy, and the outcomes of antiviral treatment.

Grattagliano I, 2021 [122]	A cohort of 8299 Italian HCV-positive patients (50.93% men) was retrieved using the Health Search database. Patients were followed up until the occurrence of cirrhosis, EV, HCC, and/or OLT.	HCV-related complications were associated with male sex, age, FIB-4 > 3.25, and T2DM.	Patients with specific demographics and clinical characteristics are more prone to experiencing HCV-related complications, which allows for strategies for targeting specific populations at risk of disease progression.
<b>MASLD</b>			
Lonardo A, 2019 [123]	Narrative review of the published literature.	In the general population, the prevalence of MASLD is 23% among women and 40% among men. However, among those with T2DM, these figures are 68% for women and 71% for men.	The presence of T2DM negates the association of MASLD with the male sex, and MASLD has the same prevalence in both sexes.
Balakrishnan M, 2021 [124]	A meta-analytic review of 54 original studies totaling 62,239 individuals for the MASLD analysis, 5428 for the MASH analysis, and 6444 for the analysis of advanced fibrosis.	In the general population, women had a 19% lower risk of MASLD than men (pooled RR, 0.81; 95% CI, 0.68–0.97; $I^2 = 97.5\%$ ). However, the risk of MASH was similar in both sexes (RR, 1.00; 95% CI, 0.88–1.14; $I^2 = 85.1\%$ ), and women had a 37% higher risk of advanced fibrosis (RR, 1.37; 95% CI, 1.12–1.68; $I^2 = 74.0\%$ ) than men. Among individuals aged $\geq 50$ years, the odds of MASH and advanced fibrosis (RR 1.17; 95% CI, 1.01–1.36; and 1.56; 95% CI, 1.36–1.80; $I^2 = 0$ , respectively) were substantially higher in women than in men.	Although women have lower odds of developing MAFLD than men, they have a higher risk of advanced fibrosis, particularly in the post-menopausal age.
Perez-Montes de Oca A, 2022 [125]	2790 patients were analyzed, and liver fibrosis defined by LSM $\geq 8.0$ kPa with Fibroscan®	An interaction was found between dysglycemia and female sex (OR = 1.6 95%, CI 1.0–2.4, $p = 0.030$ ) and age $\geq 50$ years (OR = 0.6, 95% CI 0.3–1.0, $p = 0.046$ ). The global prevalence of LSM $\geq 8.0$ kPa was higher in men than women (8% vs. 4%; $p < 0.001$ ). The prevalence of liver fibrosis increased with age, mainly in men; however, liver fibrosis was not associated with age and gender.	The global prevalence of MASLD is higher in men than in women across all ages; however, the presence of dysglycemia may erase the protective effect of female sex against MASLD among younger women with dysglycemia.
Ciardullo S, 2022 [126]	Cross-sectional, population-based study cohort of 1115 men and 1113 women based on the NHANES 2017–2018 database.	After adjusting for confounding factors, android deposition of body fat was associated with an increased risk of MASLD in both in men and women (OR = 1.79; 95% CI: 1.07, 2.99; $p = 0.029$ ; OR = 1.95; 95% CI: 1.11, 3.41; $p = 0.023$ , respectively). Conversely, android body fat distribution was significantly associated with liver fibrosis only in women, not in men (OR = 2.09; 95% CI: 1.11, 3.97; $p = 0.026$ ; and OR: 0.56; 95% CI: 0.29, 1.08; $p = 0.078$ , respectively).	An android-type distribution of body fat is linked to a higher risk of MASLD in both sexes. However, in women specifically, android fat deposition is also associated with the likelihood of liver fibrosis.
<b>AIH and PBC</b>			
Yan, L J, 2021 [127]	A meta-analytic review of 39 studies.	The pooled incidence rate for the odds of HCC in male AIH patients compared to female patients was 2.16 (95% CI 1.25–3.75), with mild heterogeneity among studies.	A higher incidence of HCC was observed in AIH patients who were male and in Asian populations.
Wu, Y-H, 2022 [128]	A retrospective study of 75 consecutive adult cases with PBC and 66 controls was conducted at the Tri-Service General Hospital in Taiwan.	Among the PBC cases, men had fewer extrahepatic autoimmune disorders and more severe liver injuries than women, either before or after medical treatment ( $p < 0.05$ ). Additionally, the androgen receptor response was positively correlated with the extent of systemic inflammation ( $p < 0.05$ ).	Liver inflammation in men with PBC tends to be more severe than in women, likely due to the association with androgen receptor responses.

Abdulkarim M, 2019 [129]	49 consecutive men with PBC treated at a tertiary care center in Germany were compared to 98 age-matched PBC women controls.	Compared to women, men with PBC had the following features: they had significantly fewer PBC-associated symptoms (34% vs. 71%, $p < 0.01$ ); the median time from onset of PBC-related symptoms and/or first cholestatic laboratory pattern to PBC diagnosis was significantly increased (36 vs. 12 months, $p = 0.02$ ); underwent liver biopsy to establish PBC diagnosis more frequently, tended to show more advanced fibrosis, and had significantly poorer prognostic PBC scores. Finally, HCC was observed only among men ( $n = 3$ ).	Men with PBC suffer from fewer PBC-related symptoms, receive delayed PBC diagnosis, and have a worse prognosis than women.
<b>DILI</b>			
Xiong Y-T, 2023 [130]	441 consecutive patients with biopsy-proven DILI who presented at the local General Hospital in Beijing, China over 17 years.	Among elderly patients with DILI a prevalence of women (73.5%) and subjects with the cholestatic pattern (47.6%) was observed.	The female sex is prevalent among elderly patients with DILI and the presence of autoimmunity is associated with more severe disease.
Nunes DRCMA, 2021 [131]	The PPS was examined for reports of DILI in Portugal over 10 years.	Neither sex was dominant in any age group. Among women, a prevalence of DILI with hepatotoxicity ( $n = 23$ ; 13.8%) and hepatitis ( $n = 610$ ; 25.9%) was observed while cholelithiasis ( $n = 8$ ; 4.8%) and splenomegaly ( $n = 8$ ; 4.8%) were more common among men.	Although neither sex appears to be more prone to the risks of developing DILI, in women, DILI has predominantly “hepatotoxicity” and “hepatitis” patterns, while in men, cholestasis prevailed.
Wang C-Y, 2022 [132]	Retrospective analysis of 3655 out of 5326 patients (2866 submitted to liver biopsy) with chronic (persisting $\geq 6$ months) DILI enrolled at nine participating hospitals across China.	The majority of patients (60.3%) were women. A non-invasive predictive model constructed using this data indicated that the female sex had an OR of 1.488, with a CI of 1.083 to 2.045 and a $p$ -value of 0.014).	Female sex, along together with older age and a more severe biochemical profile is a strong risk factor for BNR.

**List of abbreviations used**—AH—alcoholic hepatitis; AIH—Autoimmune hepatitis; ALC—alcohol-related cirrhosis; ALD—alcohol-related liver disease; ALT—alanine transaminase; aOR—adjusted Odds Ratio; BNR—biochemical non-resolution; BR—biochemical response ; CI—confidence interval; CR—compete response; DILI—drug-induced liver injury; EV—esophageal varices; HC—healthy controls; HE—hepatic encephalopathy; HBV—Hepatitis B virus; HCC -hepatocellular carcinoma; HCV—Hepatitis C virus; LRA—logistic regression analysis; LSM—liver stiffness measurement; MASLD—metabolic dysfunction-associated steatotic liver disease; NHANES—national health and nutrition examination survey; OLT—orthotopic liver transplantation; OR—odds ratio; PoHtn—portal hypertension; PBC—primary biliary cholangitis; PPS—Portuguese Pharmacovigilance System; PSM—propensity-score matching; RR—risk ratio; SBP—spontaneous bacterial peritonitis; SES—socioeconomic status; SNP—single nucleotide polymorphism; SVR sustained virological response; T2DM—type 2 diabetes mellitus; US—United States; VR—virologic response.

#### 4.1. Alcohol-Associated Liver Disease

Alcohol-associated liver disease (ALD) accounts for nearly 5.1% of diseases and injuries worldwide and is one of the leading causes of death, directly linked to the amount of alcohol consumed [133]. Alcohol use disorder (AUD), associated with heavy drinking, affects men more than women and is the second most disabling condition among men [134]. AUD induces a wide spectrum of histological liver lesions, spanning from steatosis, hepatitis, fibrosis/cirrhosis, and HCC. Steatosis, the earliest form of liver injury, occurs in over 90% of heavy drinkers due to enhanced lipogenesis, increased fatty acid influx from adipose tissue, impaired LDL secretion, altered production of adipokines, reduced lipophagy, and diminished fatty acid oxidation [135]. In some cases, steatosis progresses to steatohepatitis, which can lead to pericellular fibrosis and, eventually cirrhosis.

About one-third of heavy drinkers develop advanced liver disease, influenced by factors that may prevent, slow, or worsen disease progression [135]. Men are more prone to alcohol consumption (68% vs. 64%) and AUD (7% vs. 4%) [81]. However, women face a higher risk of ALD for the same alcohol intake levels [136]. Several pathomechanisms may contribute to the increased prevalence and severity of ALD in women, including differences in hormone regulation of liver metabolism, estrogen-induced liver cell damage, inflammation, activation of Kupffer cells, and sustained liver injury progression. Other factors include variable estrogen receptor expression, differences in liver cell regeneration, alcohol-induced endotoxemia, and the differentially modulated activation of hepatoprotective genes in females. Women also experience more significant alcohol-induced changes in gut permeability [137].

A recent experimental study using wild-type and protein arginine methyltransferase 6 (*Prmt6*) knockout female mice subjected to either ovariectomy (OVX) or sham surgery and then fed a Western diet and alcohol shows that estrogen signaling suppresses the integrin pathway. This leads to a reduction in the expression of proinflammatory genes (*Tnf*, *Il6*) and profibrotic genes (*Tgfb1*, *Col1a1*), independent of PRMT6 levels [39].

Women develop alcoholic hepatitis (AH) and alcohol-related cirrhosis (ALC) at a younger age than men. They also experience more complications, higher rehospitalization rates, and higher mortality [117]. Additionally, women have less favorable outcomes in liver transplantation (LT) [118]. Sex differences in the pathobiology of HCC have been extensively addressed elsewhere [138]. Future studies should explore the pathogenic role of lipidomics, multi-omics, and other cutting-edge approaches in the development of progressive ALD [139,140].

#### 4.2. Hepatitis B Virus

Although a vaccine against the Hepatitis B Virus (HBV) has been available for a long time, one-third of the world's population has been infected with HBV. Nearly 1.5 million new individuals are infected yearly, and nearly 300 million people globally have chronic HBV infection [141]. Sex disparity in HBV infection is well documented in both clinical setting and experimental studies [142]. The men-to-women ratio increases with disease severity, ranging from 1.2 in asymptomatic carriers to 6.3 in chronic hepatitis B and 9.8 in hepatocellular carcinoma (HCC) [143]. Among those vaccinated at birth and followed for over 18 years, 10.7% of men vs 4.4% of women are chronic carriers of HBV [144]. Men with chronic hepatitis B tend to have higher HBV titer than women, even after adjusting for confounders [145]. These findings suggest that sex disparities in HBV-induced HCC begin as early as the chronic hepatitis B stage, influenced by differences in HBV titers, immune response, or viral gene expression [142].

Androgen and estrogen regulate the HBV life cycle differently by affecting viral transcription, HBV replication, and protein expression [142]. Sex hormones also impact disease progression through HBV-specific immune responses [142]. A recent study shows that men are 16% more likely than women to achieve clinical remission and 31% more likely to have a biochemical response [119]. Two variants in the steroid 5- $\alpha$ -reductase type 2 (*SRD5A2*) gene, involved in sex hormone metabolism and signaling, are associated with liver fibrosis in chronic hepatitis B [120].

#### 4.3. Hepatitis C Virus

Regardless of demographics and risk behaviors, women who inject drugs appear to be at a higher risk than men for acquiring HCV due to hormonal factors, social networks, and unequal access to healthcare [146]. However, the female sex positively influences the progression and outcomes of chronic HCV infection. A study from 1978 on individuals with chronic hepatitis C shows that, compared to men, women have lower liver enzymes, lower HCV viral loads, lower weight, and are more likely to be infected with non-genotype-1 HCV. They are also more likely to be Black, Asian, or immigrants from Africa and Asia [121]. Interestingly, pre-menopausal women have lower fibrosis scores than men. However, after the age of 50, the mean fibrosis scores become similar, suggesting a 'catch-up' phase [121]. Moreover, low socioeconomic status (SES) is linked to a higher risk of HIV coinfection and faster fibrosis

progression in women. Women from low-income areas are also less likely to achieve sustained virological response compared to those in higher-income regions [121]. Collectively, these findings support the notion that sex and social factors influence fibrosis progression, likelihood of initiating HCV antiviral therapy, and treatment outcomes.

A recent study has identified significant sex differences and adverse events among individuals undergoing treatment for chronic hepatitis C or HIV/HCV co-infection with direct-acting antivirals (DAAs) [147]. The data indicates that women with HCV genotype (GT) 1 or GT 3 infection have a significantly higher chance of achieving sustained virologic response (SVR) at 12-week post-treatment (SVR12) compared to men. These improved treatment outcomes in women compared to men are particularly noticeable among Whites, individuals aged 40 or older with GT1 or GT3 infections, and those aged 50 years and older, non-cirrhotic, and individuals with HCV GT3 infection who were treatment-experienced. However, these differences are not clinically relevant due to the high SVR12 rate achieved by both sexes. Women also experience milder side effects, but discontinuation rates are similar between men and women [147]. Furthermore, a large study conducted on 15,295 subjects (40% women) found that SVR reduces the risk of extrahepatic complications such as acute coronary syndrome, end-stage renal disease, and ischemic stroke. This reduction is particularly significant in women, who should, therefore, be prioritized for DAAs treatment [148]. Additionally, the male sex interacts with FIB-4 and diabetes in contributing to severe outcomes of fibrosis, such as cirrhosis, EV, HCC and/or OLT [122]. Similar to HBV infection, in the case of HCV infection, sex hormones likely work together with the immune response to influence sex-dependent clinical outcomes [149].

#### 4.4. MASLD

The epidemiological features of sex differences in the MASLD arena have been extensively addressed elsewhere [150,151] and will not be reiterated here. In short, younger women are at a lower risk of MASLD than men, and this protection decreases after menopause [57,123]. However, this protection is rescinded by diabetes and dysglycemia [125,152]. Additionally, once MASLD is established, women are at a higher risk of advanced fibrosis than men, especially after the age of 50 [124]. An android-type body fat deposition is associated with an increased risk of fibrosis in women regardless of body mass index (BMI) [126]. Recent studies illustrate the synergistic interaction between genetics, sex hormones, and sex hormone receptors in the development of MASLD [153,154]. Sexual dimorphism of the innate immune system plays a significant (though under-appreciated) role in the pathogenesis of MASLD [155]. Finally, sex hormones affect the severity of MASH via the pro-inflammatory TLR-MyD88-IL-6 signaling pathway [156].

#### 4.5. Autoimmune Hepatitis

Autoimmune hepatitis (AIH) is a chronic form of hepatitis strongly linked to genes that encode the HLA class II DRB1 alleles. It often develops after exposure to external triggers that cause molecular mimicry, leading to autoimmune responses that are worsened by impaired T-cell regulation [157]. Women generally have a higher risk of developing AIH compared to men [75,158]. However, men face an increased risk of developing HCC in cases of AIH [127]. This risk is connected to the progression of hepatic fibrosis, which involves various factors contributing to fibrosis, such as inflammation, cell apoptosis, and oxidative stress [157]. The chronic inflammation in the liver is mainly driven by autoimmune processes that attract monocytes and macrophages, activating Toll-like receptors (TLRs) in HSCs and Kupffer cells. Cytokines and chemokines then enhance the response of HSCs through factors like transforming growth factor- $\beta$  (TGF- $\beta$ ), the proinflammatory tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 $\beta$  (IL-1 $\beta$ ), and chemokine ligands [157].

The generation of apoptotic bodies is the second main mechanism involved in fibrotic progression in AIH [157]. Finally, increased oxidative stress, facilitated by impaired antioxidant status in these individuals, also contributes to the fibrogenic process in AIH [159]. Sex hormones, which regulate each of the above pathogenic steps [62,160], position themselves as the ideal target for innovative treatment.

#### 4.6. Primary Biliary Cholangitis

Primary biliary cholangitis (PBC) is a chronic cholestatic disease characterized by the non-suppurative destruction of small and medium bile ducts, ultimately leading to fibrosis and cirrhosis in some individuals. PBC is more commonly diagnosed in women, especially during and after menopause, with a female-to-male ratio of approximately 4:1 [161]. However, in men, PBC is often diagnosed later, progresses more rapidly, and is linked to a poorer prognosis and higher all-cause mortality [128,129]. Nevertheless, experts believe sex differences in PBC are gradually becoming less pronounced [162,163]. The interaction between cholangiocytes and sex hormones in the cholestasis associated with PBC has been extensively reviewed in other studies [161].

#### 4.7. Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) is a chronic cholestatic autoimmune condition characterized by inflammation, fibrosis, and stricturing of intrahepatic and/or extrahepatic biliary ducts [164]. PSC tends to affect men more often (up to 60%) than women, with the average age at diagnosis being around 40 years [161]. The prevalence rate of PSC is reportedly increasing globally due to the widespread use of magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography. Although PBC and PSC are cholestatic disorders, the reasons for their markedly contrasting sex distribution are not fully understood. One possible explanation involves the enzyme cytochrome P450 3A4, which is up-regulated by the farnesoid X receptor (FXR) to protect against cholestasis. This enzyme is more elevated in premenopausal women than men, but its effectiveness decreases in the presence of high bile acid levels and significantly decreases after menopause [161]. The association of PSC with ulcerative colitis may offer further insights into the role of the gut microbiome in the pathogenesis of cholestasis [164].

#### 4.8. Drug-Induced Liver Injury

The prevalence of drug-induced liver injury (DILI) is higher among elderly women [130], and women also exhibit more severe inflammatory liver histology [131]. Being female is a significant risk factor for the failure of chronic DILI to resolve biochemically [132].

Next, we will discuss specific liver-related complications ranging from portal hypertension to HCC (Table 3). The studies were identified using the same research methodology outlined previously.



**Table 3.** Relation of sex with individual complications of liver fibrosis.

Author, Year [Ref.]	Method	Findings	Comment
<b>PoHTN compared to NVB</b>			
Erasmus, H-P, 2021 [165]	A total of 271 patients with suspected upper GIB who underwent endoscopy were included. Patients were followed up at 1 week, 6 months, and 1 year after admission.	After the excluding 42 individuals, the remaining patients were classified into those with VB ( $n = 115$ ) or NVB ( $n = 156$ ). Men ( $n = 155$ ) had a higher mortality rate in VB than in NVB, while in women ( $n = 116$ ), the mortality rate was similar regardless of the type of bleeding, as confirmed after matching in both sexes. Additional strong predictors of mortality were MELD in both sexes and in men: BUN, and ALT; in women: age, leukocytes, history of ascites and HE.	VB, compared to NVB, has higher mortality in men, while in women, the type of GIB does not impact the outcome. Additional independent predictors of mortality after GIB are sex-specific. Collectively, these findings highlight that sex-specific clinical management should be based on bleeding type after endoscopy.
<b>HE</b>			
Lee DU, 2024 [166]	After PSM, 3972 women/men postmatch homeless patients with ALD were identified in the National Inpatient Sample database (2012 to 2017).	Women had higher odds of HE (aOR) 1.02, 95% CI: 1.01–1.04, $p < 0.001$ ).	Homeless women with ALD are at a greater risk of HE than men.
Saboo K, 2021 [48]	761 subjects were included globally, 619 with cirrhosis (466 men, 153 women) and 142 controls (92 men, 50 women).	The levels of no-HE were higher in women than in men, but the adjusted AUC for No-HE vs. HE-Rif was higher in men. Degradation of androstenedione, an estrogenic precursor, was lower in men than in women in HE-Rif, likely enhancing feminization.	Sex differences in gut microbial function and composition between individuals with cirrhosis could be involved in differential responses to HE therapies.
<b>HCC</b>			
Degasperi E, 2019 [167]	A retrospective study of 565 patients with cirrhosis treated with DAAs at a single center in Italy (2014–2016) was submitted to HCC surveillance during a median 25-month follow-up.	Male sex (HR = 6.17; 95% CI 1.44–26.47; $p = 0.01$ ), diabetes (HR = 2.52; 95% CI, 1.08–5.87; $p = 0.03$ ), LSM (HR = 1.03; 95% CI, 1.01–1.06; $p = 0.01$ ), and FIB-4 score (HR = 1.08; 95% CI, 1.01–1.14; $p = 0.01$ ) were independently associated with de novo HCC.	Male sex, diabetes, and liver fibrosis identify patients at increased risk for HCC after DAAs therapy.
Ladenheim MR, 2016 [168]	A retrospective cohort study of 1,886 HCC patients seen in a US medical center in 1998–2015.	At LRA, significant predictors of improved survival included younger age, surgical or non-surgical treatment (vs. supportive care), diagnosis by screening, tumor within Milan criteria, and lower MELD. However, female sex was not found to be as significant predictor of survival (aHR = 1.01, CI 0.82 to 1.24, $p = 0.94$ ).	Men are at a much higher risk for HCC development, but there were no significant sex differences in disease presentation or survival except for older age and lower tumor burden at diagnosis in women. Female sex was not an independent predictor for survival.
Huang J, 2023 [169]	The long-term prognostic outcomes of 642 HCC patients undergoing hepatectomy were analyzed retrospectively.	At LRA MAFLD was identified as a significant risk factor for mortality in women (HR = 5.177, 95%CI: 1.475–18.193).	MAFLD was found to be associated with a significantly higher mortality rate in women with HCC. However, MAFLD did not have a significant effect on RFS and mortality among men.

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De la Cruz Ku G, 2022 [170]	A total of 13,401 patients underwent elective hepatic resection between 2014–2017.	PHLF was highest among men with HCC (OR = 2.81, 95% CI: 1.40–5.62). Male sex was independently associated with increased PHLF (OR = 1.47, 95% CI: 1.15–1.88), major complications (OR = 1.25, 95% CI: 1.08–1.45), and mortality (OR = 1.61, 95% CI: 1.03–2.50).	Women undergoing liver resection are exposed to a significantly lower risk of PHLF compared to men.
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**List of abbreviations used** ALD— alcohol-related liver disease; ALT—alanine transaminase; aOR—adjusted Odds Ratio; AUC—area under the curve; BUN—blood urea nitrogen; DAAs—direct-acting antivirals; FIB-4—fibrosis 4; GIB—gastrointestinal bleeding; HE -hepatic encephalopathy; HE-Rif—subjects with HE treated with rifaximin + lactulose; HR—hazard ratio; LSM—liver stiffness measurement; MELD—model for end-stage liver disease; No-HE—those with cirrhosis without HE; NVB—nonvariceal bleeding; PHLF—post-hepatectomy liver failure; PSM—propensity score matching; RFS—recurrence-free survival; VB—variceal bleeding; MAFLD- metabolic dysfunction-associated fatty liver disease.

#### 4.9. Portal Hypertension

Variceal bleeding, as opposed to non-variceal bleeding, is linked to higher mortality rates in men but not in women [165]. If these results are confirmed by larger studies, they could potentially support sex-specific clinical management approaches depending on the type of bleeding identified through endoscopy.

#### 4.10. Hepatic Encephalopathy

Compared to men, women are at a significantly higher risk of hepatic encephalopathy (HE) [166]. The different compositions of intestinal microbiota may account for this disparity and the sex differences in responses to HE therapies [48].

#### 4.11. Hepatocellular Carcinoma

Sex hormones can have either a protective or harmful effect on both sexes, influenced by factors such as BMI, alcohol consumption, active smoking, and social determinants [138]. Sexual dimorphism is a common feature of HCC, with men at the highest risk, especially in virus-related chronic liver disease (CLD) [171,172]. Male sex, diabetes, and liver fibrosis predict the risk of HCC after DAAs therapy [167]. However, female sex is not an independent predictor of survival [168], while MAFLD is a significant risk factor for mortality in women [169]. Women who undergo liver resection have a lower risk of post-hepatectomy liver failure [170], likely due to sex hormone-related differences in hepatic regeneration [173].

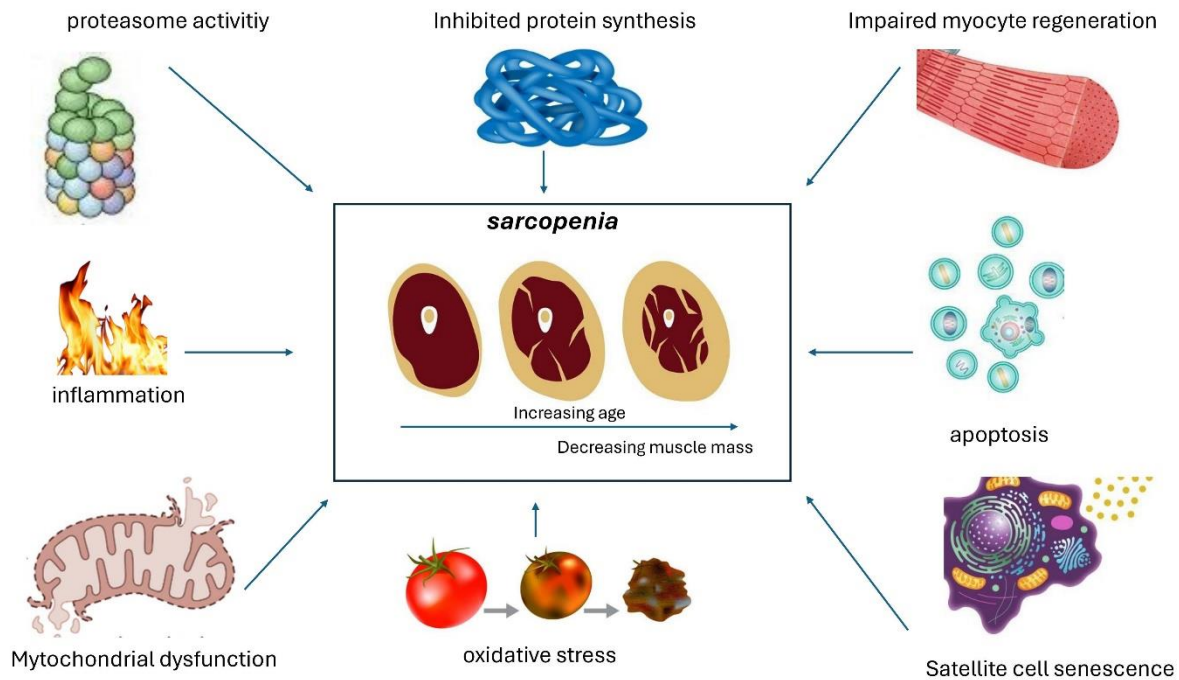
In conclusion, significant sex differences characterize the epidemiological and clinical features of various types of CLD and the specific complications of liver fibrosis. Collectively, these sex differences may potentially influence clinical outcomes and provide a basis for sex-specific precision medicine approaches.

### 5. Sex Differences in Extra-Hepatic Outcomes

The spectrum of health issues associated with liver fibrosis in the context of MASLD is broad. It has recently expanded to include extra-hepatic cancers such as gynecological cancers and malignant neoplasms of the gastro-intestinal tract. These have been extensively discussed in recent literature [174,175] and will not be reiterated here. Therefore, among the various extra-hepatic outcomes associated with advanced liver fibrosis, we will focus on sarcopenia, CVD, diabetes, CKD, and dementia. These conditions have the potential to impact quality of life and life expectancy.

#### 5.1. Sarcopenia

Defined as the “*progressive and generalized loss of muscle mass and strength*”, sarcopenia is a common feature of liver cirrhosis that negatively affects patient outcomes while on a liver transplantation (LT) waiting list, as well as after LT and during HCC treatment [176]. Various pathomechanisms may be responsible for the development of sarcopenia in patients with cirrhosis (Figure 4).



**Figure 4.** Pathogenesis of sarcopenia associated with advanced liver fibrosis. Schematic illustration of the multiple cellular and molecular mechanisms involved in the development of sarcopenia [177].

Furthermore, a proof-of-concept cross-sectional study demonstrates that individuals with liver cirrhosis and muscle wasting have an altered gut microbiome composition [178]. A recent meta-analytic review of 63,330 patients and 29 studies finds a strong association of sarcopenia with MASLD (aOR 2.08, 95% CI 1.58–2.74,  $I^2 = 93.6\%$ ) irrespective of stratification by confounding factors [179]. Moreover, this study also shows an association of sarcopenia with poor prognosis in MASLD (aHR 1.59, 95% CI 1.33–1.91,  $I^2 = 0\%$ ) [179]. Most published investigations concur that men exhibit a higher prevalence of sarcopenia, possibly owing to anatomy-related causes [176,180]. However, the retrospective study design and different diagnostic criteria for sarcopenia hinder our understanding of sex differences in this area [176,180].

## 5.2. Cardiovascular Disease

The stage of liver fibrosis is a principal risk modifier of CVD among individuals with fibrosing MASLD. Vilar-Gomez, Calzadilla Bertot and their colleagues conducted a collaborative study involving 458 patients with biopsy-proven MASLD. Among these patients, 159 had bridging fibrosis (F3) and 222 had class A Child-Turcotte-Pugh compensated cirrhosis. The study took place from 1995 to 2013 and follow-up continued until December 2016 [8]. The authors found that individuals with MASLD-cirrhosis primarily experienced liver-related events, while those with bridging fibrosis were more prone to extra-hepatic cancers and vascular events [8].

Recent evidence suggests that regardless of the diagnostic terminology used (NAFLD or MAFLD), the risk of developing CVD events is not significantly different between the two definitions. However, MAFLD is associated with a higher number of CVD events compared to NAFLD [181]. It is important to note that MASLD is strongly linked to an increased risk of CVD events, with this risk further escalating in the presence of advanced stages of liver fibrosis [182]. In the realm of gender-specific medicine, alcohol consumption, which is more commonly associated with males, particularly in the context of MetALD, a subtype of SLD, is linked to the highest odds of CVD [81]. This was revealed in a Korean Genome and Epidemiology study involving 9497 participants followed for 17.5 years [183]. On the other hand, cryptogenic SLD, representing 3.5% of SLD patients, carries the lowest risk of CVD [184].

Sex also plays a key role in CVD risk in the MASLD arena, as reported by Ren et al. [185]. These authors analyzed data from adults in the National Health and Nutrition Examination Surveys from 2000–2014 and found that men have a significantly higher all-cause mortality rate compared to women (12.4% vs. 7.7%;  $p = 0.005$ ). The risk of CVD death is higher in women aged 60 or younger with NAFLD (adjusted hazard ratio [aHR]: 0.214, 95% CI: 0.053–0.869,  $p = 0.031$ ). Men with a BMI > 30 kg/m<sup>2</sup> and diabetes show a higher risk of all-cause mortality. However, sex differences in CVD events are not as apparent in patients aged over 60 years. Despite some methodological limitations, the study

by Ren et al. suggests that MASLD eliminates the natural protection women have from CVD, which is in line with previous studies [186].

Another example of sexual dimorphism in the association between liver fibrosis and major events of CVD comes from the study by Parikh et al. [187]. These authors studied 572 participants with incident ischemic stroke and 1104 participants in a stratified cohort random sample, following them for ischemic stroke. They found that advanced liver fibrosis, as assessed by FIB-4 and NFS, is linked to a higher risk of ischemic stroke in women but not in men.

### 5.3. Diabetes and Impaired Glucose Tolerance

Sex-specific differences exist in the categories of prediabetes. Impaired glucose tolerance, which reflects postprandial insulin resistance, is more prevalent in women than in men. On the other hand, impaired fasting blood glucose, which reflects fasting insulin resistance, is more prevalent in men than in women [75]. Additionally, the risk of developing impaired glucose tolerance (IGT) is influenced by pregnancy and menopause [188]. A strong, likely bidirectional relationship exists between liver fibrosis and type 2 diabetes mellitus (T2DM) across various forms of CLD, with the most well-characterized being SLD resulting from chronic HCV infection and NAFLD/MASLD [189,190]. Mantovani et al., in a meta-analysis of 33 studies including 501,022 individuals, show that over a median follow-up of 5 years, NAFLD is associated with a higher risk of developing diabetes compared to NAFLD-free controls ( $n = 26$  studies; random-effects HR 2.19, 95% CI 1.93–2.48;  $I^2 = 91.2\%$ ). Interestingly, subjects with more ‘severe’ NAFLD face higher odds of incident diabetes ( $n = 9$  studies; random-effects HR 2.69, 95% CI 2.08 to 3.49;  $I^2 = 69\%$ ), and this risk markedly increases with the severity of liver fibrosis ( $n = 5$  studies; random-effects HR 3.42, 95% CI 2.29 to 5.11;  $I^2 = 44.6\%$ ), regardless of common metabolic confounding risk factors [191]. Additional investigation is warranted to address the various genetic, hormonal, and lifestyle factors that differently modulate the odds of IGT and T2DM among men and women with fibrosing CLD.

### 5.4. Chronic Kidney Disease

A robust body of published literature supports that MASLD is a risk factor for incident and prevalent CKD assessed with either estimated glomerular filtration rate (eGFR)  $< 60$  mL/h or proteinuria [192–195]. While some studies show no association [196], other researchers suggest that steatosis, rather than liver fibrosis, maybe the key driver of CKD risk in MASLD [197]. This could be due to the fact that steatosis, in turn, is the precursor of fibrosis in MASLD via steatohepatitis [198]. Sexual medicine approaches in the realm of CKD associated with MASLD are not yet fully developed, and information seems scarce and preliminary. A meta-analysis published in 2017 [199] found no significant difference between the sexes in diabetes-related CKD, with a pooled adjusted women-to-men relative risk ratio of 1.14 (95% CI 0.97, 1.34). However, among individuals with diabetes, women have a higher risk of end-stage renal disease (ESRD) than men, indicating a greater risk of CKD progression among women. This could be linked to autoimmune mechanisms to which women are more susceptible than men [200]. Conversely, men seem to have a higher risk of CKD and ESRD compared to women, primarily driven by arterial hypertension, as supported by strong meta-analytic evidence [201]. This difference may be influenced by sex hormones affecting vascular tone, oxidative stress, inflammation, and apoptosis [202], as well as variations in the function of endothelin receptors (ET-B vs. ET-A) between the sexes [203].

Hyperuricemia is also identified as a potential risk factor for liver fibrosis in MASLD [204–206], although findings are conflicting [207]. Interestingly, the female sex may be protected from some of the harmful outcomes of hyperuricemia, including renal disease, CVD, and metabolic syndrome [208]. Finally, a study conducted in a cohort of 432 patients with CLD of varying etiologies found that the female sex, together with CKD, was associated with muscle cramps in CLD [209], supporting further investigation into this association.

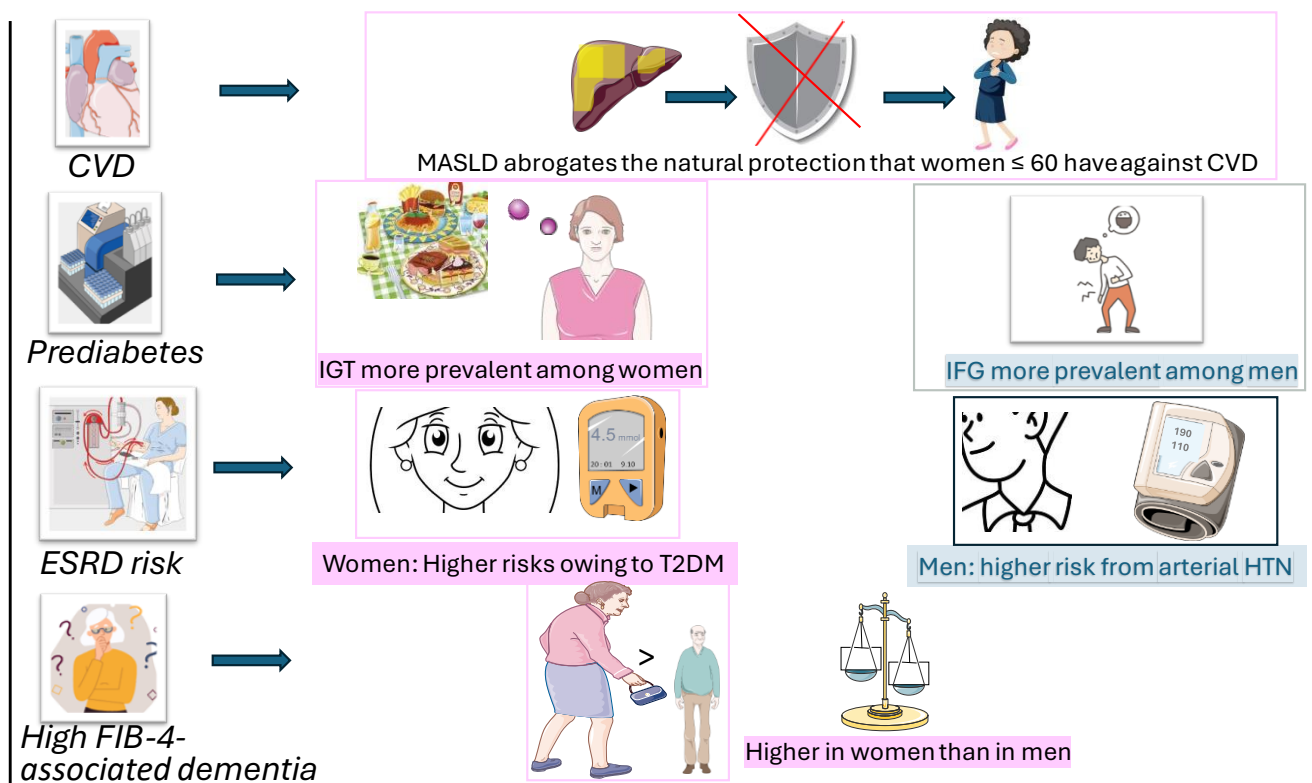
### 5.5. Dementia

Research on the impact of MASLD on cognitive function, particularly dementia, yields conflicting results [210–215]. A meta-analysis of seven prospective cohorts reports that MASLD does not significantly increase the risk of dementia (HR: 1.01). However, other studies demonstrate that the presence of liver fibrosis in MASLD patients markedly elevates this risk [19,211,216,217]. For instance, a nationwide retrospective cohort study by Weinstein et al. [218] finds that over a median follow-up of 17 years, individuals with a FIB-4  $> 2.67$  have an 18% increased risk of developing dementia. Similarly, a study by Parikh et al. [219], using data from the UK Biobank, reports a 52% increased risk of dementia associated with FIB-4  $> 2.67$  over a median follow-up of 9 years. However, these studies differ in both

the magnitude of dementia risk associated with liver fibrosis and the role of sex differences in this relationship. These discrepancies are likely due to variations in methods and sample selection, including differences in follow-up duration and the prevalence of fibrosis in the study populations. While Parikh et al. [219] found no significant modification of dementia risk by sex, Weinstein et al. [218] demonstrated that the risk of dementia associated with advanced fibrosis (FIB-4 > 2.67) was higher in females than in males (22% vs. 17%). The more pronounced sex differences observed with longer follow-up (17 years vs. 9 years) suggest that the moderating role of liver fibrosis in the relationship between sex and dementia may increase with age, becoming more prominent in later life.

Several factors could explain this modifying effect. The progression to advanced fibrosis accelerates in females during later life [124], particularly after menopause [25]—a period when the majority of dementia cases occur. This accelerated fibrosis may exacerbate underlying pathophysiological processes that lead to cognitive decline, such as impaired clearance of peripheral amyloid-beta (Aβ) [220], inflammation [221,222], gut dysbiosis [223–226], and vascular damage [227–230].

In summary, although data on the relationship between sex, liver fibrosis, and dementia are limited, preliminary studies suggest that sex differences may influence the impact of liver fibrosis on the risk of dementia. Figure 5 summarizes the principal notions discussed in Section 5.



**Figure 5.** Overview of extrahepatic outcomes in MASLD. Legend to Figure 5. This cartoon, based on the bibliographic references discussed in the text, specifically focuses on sex differences in cardio-nephro-metabolic risk. Moreover, sex differences in dementia associated with liver fibrosis are highlighted. CVD—cardiovascular disease; ESRD—end-stage renal disease; FIB-4—fibrosis 4; HTN—hypertension; IFG—impaired fasting glucose; IGT—impaired glucose tolerance; MASLD—metabolic dysfunction-associated steatotic liver disease; T2DM—type 2 diabetes mellitus.

## 6. Conclusions

Sex and gender differences play a significant role in the profibrogenic pathomechanisms that impact the prevalence, severity, and outcomes of liver fibrosis. Genetic factors, hormonal influences, immune responses, and lifestyle choices contribute to these disparities between men and women. Generally, females have a lower risk of fibrosis due to protective genetic and hormonal factors, such as estrogen’s anti-fibrogenic properties and a more balanced immune response. Conversely, males are more prone to fibrosis due to factors like testosterone’s fibrogenic effects, higher levels of pro-inflammatory cytokines, and riskier lifestyle behaviors. Additionally, sex differences in the gut microbiota further modulate the progression of liver fibrosis, with males showing a tendency for more severe fibrosis linked to inflammation-inducing gut bacteria. The exploration of sex differences in liver-related outcomes also reveals substantial

disparities that vary depending on the etiology of liver disease, age, and other factors such as socio-economic status and treatment responses. Women have distinct vulnerabilities and outcomes compared to men across various liver diseases, from alcohol-related liver disease to MASLD, AIH, and DILI. Similarly, sex differences significantly impact the risk and progression of extra-hepatic outcomes, including sarcopenia, CVD, diabetes, CKD, and dementia.

Collectively, the evidence underscores the necessity of a sex-specific approach in the management of CLD and its complications. Such an approach could potentially optimize outcomes by addressing the unique risk profiles and therapeutic needs of men and women, while also revealing novel therapeutic targets. Further research is warranted to deepen our understanding of these sex-specific mechanisms and to translate this knowledge into precision medicine strategies that improve patient care and prognosis for both genders.

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All authors contributed equally to Conceptualization, Methodology, Data Curation, Writing, Review & Editing of this manuscript.

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