# Microplastics and Nanoplastics: Emerging Drivers of Hepatic Pathogenesis and Metabolic Dysfunction

**Running head:** microplastics in metabolic dysfunction

**Yusuf Yilmaz[1,2], Cem Simsek[3], Mete Ucdal[4], Eda Kaya[2,5]**

[1] Department of Gastroenterology, School of Medicine, Recep Tayyip Erdoğan University, Rize, Türkiye

[2] The Global NASH Council, Washington, DC, USA

[3] Department of Gastroenterology, Faculty of Medicine, Hacettepe University, Ankara, Türkiye

[4] Department of Internal Medicine, Faculty of Medicine, Hacettepe University, Ankara, Türkiye

[5] Department of Medicine, University Hospital Knappschaft Kliniken Bochum, Ruhr University Bochum, Bochum, Germany

**Corresponding author:**

Prof. Yusuf Yilmaz, M.D.

Recep Tayyip Erdoğan Üniversitesi Rektörlügü, Zihni Derin Yerleşkesi, 53100, Rize, Türkiye.

E-mail: dryusufyilmaz@gmail.com

**Key words:** Micronanoplastics, Hepatotoxicity, Metabolic dysfunction-associated steatotic liver disease, Cirrhosis, Hepatocellular carcinoma



## ABSTRACT

Advanced liver disease, including cirrhosis and hepatocellular carcinoma (HCC), represents a major global health challenge, particularly due to the increasing prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD). Simultaneously, micronanoplastics (MNPs) have emerged as pervasive environmental contaminants with potential hepatotoxic effects. In this review, our aims were to provide an in-depth analysis of the current knowledge on the role of MNPs in the pathogenesis of cirrhosis and HCC, particularly in the context of the increasing prevalence of MASLD, and to identify key areas for future research. The search strategy encompassed original studies and review articles included in PubMed/MEDLINE, Web of Science, Scopus, and Google Scholar databases from January 1, 2014, to November 1, 2024. Growing evidence indicates that MNPs exposure in animal models may induce hepatic changes similar to those observed in human MASLD and metabolic dysfunction-associated steatohepatitis through both direct and indirect mechanisms. Importantly, MNPs may function as a "second hit" in the presence of pre-existing metabolic stress, potentially exacerbating hepatotoxic damage. However, data from human studies remain limited, with only two small-scale investigations examining MNPs in clinical cohorts. Recent advancements in analytical methods for quantifying MNPs in blood present new opportunities to investigate their association with the risk of MASLD, cirrhosis, and HCC in clinical cohorts. In conclusion, while significant progress has been made in elucidating the hepatotoxic effects of MNPs in experimental models, their clinical relevance to human liver disease progression remains largely unexplored. Further multidisciplinary research integrating environmental science, molecular biology, and clinical hepatology is urgently needed.

**Keywords:** Micronanoplastics, Hepatotoxicity, Metabolic dysfunction-associated steatotic liver disease, Cirrhosis, Hepatocellular carcinoma

## 1. INTRODUCTION

Advanced liver disease, encompassing cirrhosis and hepatocellular carcinoma (HCC), constitutes a significant global health burden, accounting for approximately 4% of all deaths worldwide [1], or 1 million fatalities annually [2]. Cirrhosis, characterized by extensive fibrosis and nodule formation, disrupts the normal hepatic lobular architecture and progressively leads to liver decompensation, manifesting as ascites, hepaticencephalopathy, and variceal hemorrhage [3]. This condition is one of the leading causes of mortality worldwide, ranking as the fifth-leading cause of death in the Eastern Mediterranean region, ninth in both Southeast Asia and Europe, and tenth in Africa [1]. Moreover, cirrhosis significantly increases the risk of HCC, the most prevalent form of primary liver cancer and the third leading cause of cancer related mortality worldwide [4, 5]. The annual incidence of this malignancy in patients with cirrhosis is estimated to be between 0.2% and 5%, underscoring the need to implement pathophysiology-informed monitoring and prevention strategies [6]. Notably, the etiology of advanced liver diseases has undergone substantial changes over time, warranting consideration of these evolving trends [7].The increasing coverage of hepatitis B virus vaccination and the advent of highly effective antiviral pharmacotherapies have led to a decline in viral hepatitis-related cases of chronic liver disorders in an advanced stage [8]. Conversely, epidemiological evidence demonstrates a marked surge in metabolic dysfunction-associated steatotic liver disease (MASLD), MASLD-related cirrhosis and HCC [9, 10]. This trend is particularly significant as MASLD has become the predominant cause for liver transplantation in developed countries [10]. Given its global prevalence—reaching up to 50% and increasingly affecting young adults—its burden must be regarded with utmost seriousness [11-14]. Even among liver transplant recipients, MASLD remains a significant concern, with reported prevalence rates exceeding 30%, suggesting a disease burden comparable to that observed prior to transplantation [15]. It is also a notable issue in other transplant populations, including kidney

transplant recipients [16]. Furthermore, MASLD is increasingly becoming one of the leading causes of referral to tertiary care centers for advanced hepatological evaluation [17]. Additionally, MASLD poses a unique risk by promoting hepatocarcinogenesis even in non-cirrhotic livers,warranting further investigation into its underlying mechanisms [18-20].

In the context of the evolving epidemiological landscape of hepatic disorders, micronanoplastics (MNPs) have emerged as a novel environmental risk factor with potential implications for liver health [21-25]. The ubiquitous presence of permanent plastic particles – from air to drinking water and food [26] – coupled with their potential to bioaccumulate in hepatic tissue, necessitates a comprehensive examination of their role in the pathogenesis of advanced liver diseases [27, 28]. In this narrative review, we sought to provide a comprehensive and critical examination of the current understanding regarding the potential role of MNPs in the pathogenesis of cirrhosis and HCC, particularly in the context of the escalating incidence of MASLD [8]. By synthesizing the available evidence and identifying major knowledge gaps, our overarching goal is to identify key areas for future research.

## 2. METHODS

For the purpose of this review, the search strategy (**Table 1**) encompassed original studies and review articles included in PubMed/MEDLINE, Web of Science, Scopus, and Google Scholar databases from January 1, 2014, to November 1, 2024. This timeframe was selected to ensure that the latest relevant research over the past decade was captured. The search terms employed included “microplastics,” “nanoplastics,” “liver,” “hepatic,” “metabolic dysfunction- associated steatotic liver disease,” “non-alcoholic fatty liver disease,” “advanced liver disease,” “cirrhosis,” and “hepatocellular carcinoma.” To maintain the quality and relevance of the included studies, case reports, conference abstracts, and articles not published in the English language were excluded. The literature search consisted of three stages. Initially,

a preliminary screening of the title and abstract of each document was conducted to exclude documents that were not pertinent to the research topic. Subsequently, during the full-text screening phase, the study investigators independently evaluated the full text of each article to determine its eligibility for inclusion in the review. Finally, key data were extracted and subjected to narrative synthesis.

## 3. RESULTS

### 3.1. Classification and composition of micronanoplastics

A precise classification of MNPs (Figure 1) provides a crucial foundation for comprehending their biological effects and underlying toxicological mechanisms. Broadly, these synthetic particles can be categorized into primary and secondary types based on their origin [29]. Intentionally manufactured primary MNPs emerge from direct industrial production or as manufacturing byproducts, encompassing abrasive materials, injection molding powders, and resin pellets [29]. The generation of these particles can also occur through mechanical degradation during the production, utilization, or maintenance of plastic products. In contrast, the secondary fraction, which predominantly exists in the environment and poses significant health concerns, originates from the gradual degradation of larger plastic materials,including ubiquitous items such as packaging, containers, and disposable products. The liberation of secondary MNPs occurs through various processes, including mechanical abrasion, ultraviolet (UV) radiation exposure, and chemical decomposition. These factors work synergistically to fragment larger plastic debris into microscopic particles [29]. In addition to their origin, MNPs can be categorized based on their size into three distinct categories:microplastics, which range from 5 mm to 1 μm, submicroplastics, spanning from 1 μm to 100 nm, and nanoplastics, which are less than 100 nm in diameter [30]. Notably, the size of MNPs significantly influences their interactions with biological systems, with smaller particles,particularly those at the nanoscale,

more readily crossing biological barriers and penetrating cells [31]. From a chemical perspective, the most frequently encountered polymers in MNPs found in environmental matrices include polyethylene (PE), polypropylene (PP), polyoxymethylene (POM), polyethylene terephthalate (PET), polystyrene (PS), polyvinyl chloride (PVC), and polymethyl methacrylate (PMMA) [31]. In addition, MNPs commonly contain a range of chemical additives – such as plasticizers, lubricants, fillers, UV stabilizers, pigments, dyes, and flame retardants – which are intentionally incorporated during the manufacturing process to enhance mechanical strength, color, transparency, and overall performance [32]. Importantly, beyond their inherent chemical toxicity, MNPs possess the capacity to adsorb a wide range of microorganisms and potentially hazardous molecules,including persistent organic pollutants, due to their hydrophobic properties and high surface area-to-volume ratio [33]. Consequently, their carrier function enables MNPs to act as "Trojan horses," potentially enhancing the bioaccumulation and bioconcentration of chemical toxicants and amplifying their adverse effects on the liver and other organs [34].

### 3.2. The liver as the target of micronanoplastics: direct and indirect hepatotoxic damage

The most compelling evidence for the potential hepatotoxicity of MNPs and their clinical significance in humans stems from a pilot study by Horvatits et al. The results revealed significantly elevated MNPs concentrations in liver tissue samples from patients with cirrhosis (n = 6) compared to those without liver disease (n = 5) [28]. Notably, the latter group tested negative despite rigorous characterization employing chemical digestion, staining, fluorescence microscopy, and Raman spectroscopy. While the authors did not explicitly differentiate between primary and secondary MNPs, the observed surface degradation of certain particles suggests the presence of secondary MNPs resulting from larger plastic item breakdown [28,

29]. In addition, the detected MPs ranged from 4 to 30 μm, falling within the microplastic size range (5 mm to 1 μm) and capable of traversing biological barriers [30]. Chemical analysis identified six distinct polymer types: PS, PVC, PET, PMMA, POM, and PP. Several recent reviews, which we are not attempting to duplicate, have provided detailed accounts of the potential direct and indirect mechanisms by which MNPs can induce hepatotoxicity [21, 22, 25]. In brief, the effects of these particles, extensively elucidated and characterized in preclinical animal models but not yet thoroughly studied in humans, can be broadly classified as direct or indirect (Figure 2). Direct hepatotoxic mechanisms include the induction of oxidative stress [35], inflammation [36], mitochondrial dysfunction [37], activation of hepatic stellate cells [38], disruption of bile acid metabolism [39], and immunotoxicity [40].

Accordingly, the generation of reactive oxygen species by MNPs leads to protein oxidative carbonylation, membrane structure destruction, DNA strand breaks, and eventually apoptosis, pyroptosis, or other forms of cell death [41]. Furthermore, there is substantial evidence to suggest that plastic particle-induced cytokine and chemokine expression in the liver parenchyma can lead to morphological alterations similar to those observed in human metabolic dysfunction-associated steatohepatitis (MASH) [42]. MNPs may compromise mitochondrial function, which has a significant adverse impact on the hepatocyte energy metabolism due to the mitochondria's critical roles in producing ATP and maintaining ion homeostasis [37, 43]. Furthermore, MNPs have been shown to activate hepatic stellate cells, leading to excessive extracellular matrix deposition, fibroblasts proliferation and increased liver blood flow resistance [27, 38]. Finally, the direct disruption of bile acid metabolism by MNPs can result in cholestatic injury, while their deleterious effects on liver-resident immune cells, such as Kupffer cells, may compromise the liver's defense against lipopolysaccharide (LPS) derived from gut Gram-negative bacteria entering via the portal vein [39]. In contrast, the indirect hepatotoxic effects of MNPs are primarily linked to their accumulation in the gastrointestinal tract and their

impact on gut microbiota composition [21, 44-47].This disruption is generally characterized by an increase in harmful bacteria, a decline in beneficial bacterial species, and a reduced bacterial population diversity [21, 48]. In addition, MNPs have been demonstrated to disrupt critical bacterial metabolic pathways within the gut microbiota, leading to the reduced synthesis and release of beneficial postbiotics, including short-chain fatty acids [49]. There is also evidence that MNPs-induced microbiota disruption can compromise the integrity of the intestinal barrier, leading to gut hyperpermeability and translocation of bacteria and their potentially harmful structural and/or metabolic byproducts to the liver parenchyma [50].

### 3.3. Micronanoplastics and MASLD

MASLD is a multisystemic disease that extends beyond the liver. Its pathogenesis involves multiple factors, consistent with a 'multiple-hit' model. Insulin resistance is considered the first hit in the classical 'two-hit hypothesis', followed by oxidative stress, lipid peroxidation, and mitochondrial dysfunction as subsequent hits [51]. However, it is increasingly evident that many additional contributing factors remain unidentified or not yet fully understood.Considering their increasing environmental burden and the broad direct and indirect hepatotoxic effects that MNPs can exert, it is not surprising that these pollutants have been repeatedly hypothesized to play a role in MASLD [23, 25]. However, the evidence suggesting MNPs' potential role in the pathogenesis of this condition is predominantly derived from preclinical studies involving experimental exposure in rodent, fish, and avian models. In a seminal investigation utilizing a mouse model of MASLD, induced through a high-fat diet (HFD) protocol, the intravenous administration of PS nanoparticles was found to precipitate significant histopathological alterations [52]. These changes were characterized by enhanced Kupffer cell infiltration and marked collagen fiber deposition, suggesting a potential acceleration of liver fibrosis compared to HFD alone. Okamura and colleagues administered

polystyrene microplastics to C57BL6/J mice under two dietary conditions: normal diet and HFD over a four-week period [53]. The authors demonstrated that mice receiving HFD plus microplastics exhibited significantly elevated blood glucose levels, increased serum lipid profiles, and higher MASLD activity scores compared to HFD-only controls. Notably, the metabolic and hepatic perturbations were exclusively observed in the HFD cohort, while mice on normal diet (ND) remained unaffected by microplastic exposure [53]. In a separate study, Wang et al. reported that, while high doses of PS nanoparticles during gestation induced hepatic steatosis specifically in adult female offspring, male offspring remained unaffected [54]. The liver alterations were accompanied by significant upregulation of genes involved in fatty acid uptake and triglyceride synthesis, indicating enhanced lipogenic pathways [54]. Liu et al. conducted experiments using mice, which were given a ND or a HFD plus free drinking of sterile water with or without MNPs, respectively. Expectedly, mice fed a HFD had remarkably greater NAFLD activity scores than those receiving a ND. Interestingly, administration of MNPs plus HFD further worsened the histopathological changes observed in the mice's liver, leading to inflammatory cell infiltration and ballooning degeneration [55]. In a study by Wei et al., C57BL/6 J mice were fed with a ND or a HFD containing 70 nm PS microspheres. The authors found that dietary-derived MNPs adsorbed proteins and agglomerated during the in vivo transportation, enabling HFD-induced hepatic steatosis to progress to MASH. Mechanistically, PS microspheres were found to induce redox imbalance and mitochondrial calcium overload [56]. The study appears to be particularly significant as it demonstrates a direct mechanistic link between nanoplastic exposure and the acceleration of liver disease progression. Another investigation by Zhao et al. examined the metabolic impact of MNPs through the gut-liver-adipose tissue axis [57]. The experiment involved administering C57BL/6J mice with either standard water or water containing PS beads of two different sizes (0.5 and 5 μm) at two distinct concentrations (0.1 μg/mL and 1 μg/mL). Notably, mice that

consumed the smaller PS beads (0.5 μm) at the higher concentration (1 μg/mL) exhibited elevated fasting plasma insulin levels and higher insulin resistance as early as three weeks post-administration. These metabolic alterations were concurrent with shifts in the gut microbiota composition that are characteristic of an obese phenotype and gene expression changes in perivascular adipose tissue that were indicative of increased adipogenesis [57]. Considering their role as emerging pollutants in aquatic environments, Zhou et al. aimed to evaluate the toxicity of MPs in relation to hepatotoxicity using the zebrafish model [58]. Compared to controls, zebrafish exposed to MNPs exhibited significantly higher levels of lipid accumulation, triglycerides, and cholesterol contents, as well as inflammation, in conjunction with oxidative stress in their livers. These alterations were accompanied by a disrupted gut microbiota composition, characterized a markedly lower abundance of Proteobacteria and a higher Firmicutes/Bacteroidetes ratio. Markedly higher levels of the intestinal bacteria-derived LPS were also detected in serum [58]. In a separate study, Boopathi et al. found that zebrafish exposed to the combined effects of a high-fat diet (HFD) and PE. MNPs exhibited increased lipid accumulation, total cholesterol, triglycerides, and severe hepatic necroinflammation resembling MASH, compared to fish fed only the HFD [59]. Chen et al. examined the hepatotoxic effects of nanopolystyrene at environmentally relevant concentrations, as well as the underlying molecular mechanisms, in juvenile Siniperca chuatsi(mandarin fish) [60]. After a 21-day exposure period, the livers of exposed fish exhibited macrostructural and microstructural damage accompanied by oxidative stress. Another recent investigation examined the effects of subchronic exposure to PS microplastics on the liver of gilthead seabreams (Sparus aurata Linnaeus, 1758) [61]. The study involved exposing the fish to PS microplastics of various sizes (1-20 μm) at different concentrations (0, 25, or 250 mg/kg body weight/day) for a period of 21 days through contaminated food. PS microplastics induced an upregulation of mRNA levels of crucial genes associated with lipid synthesis and storage

without modifications of genes involved in lipid catabolism or transport and metabolism in the liver. The increase of pro-inflammatory cytokines gene expression was also observed in exposed gilthead seabreams in a dose-dependent manner. These findings were confirmed by hepatic histological evaluations reporting evidence of lipid accumulation, inflammation, and necrosis [61]. In a study utilizing a female Muscovy duck model, Chen et al. investigated the effects of a two-month co-exposure to cadmium (Cd) and PVC MNPs compared to a control group exposed to pure water. The results demonstrated that both PVC MNPs [62] and Cd accumulation in liver tissues had detrimental effects on hepatocyte morphology and functional activity. Notably, Schwenger et al. recently conducted the first-in-human study investigating MNPs in the context of MASH. Specifically, the authors compared fecal MNP levels among six lean healthy controls, six obese individuals with normal liver function, and eleven patients with MASH [63]. While no significant differences in fecal MNP levels were observed between the three study groups prior to bariatric surgery, fecal MNPs were positively associated with both portal and total macrophages, as well as natural killer cells. In addition, fecal microplastic fibers were positively correlated with the abundance of Bifidobacteria and negatively with Lachnospiraceae, suggesting a potential influence of MNPs on gut microbiota composition. In a follow-up of patients with MASH over 12 months post-bariatric surgery, patients with persistent liver involvement exhibited higher levels of fecal MNP fragments compared to those whose liver histology had normalized [63].

### 3.4. Micronanoplastics and hepatic cirrhosis

Given the substantial preclinical evidence linking MNPs to the pathogenesis of MASLD, it is plausible that these contaminants may also play a role in the progression to cirrhosis. Notably, the incidence of cirrhosis cases attributed to MASLD has risen significantly [64]. Experimental evidence supports this hypothesis, as PS nanoparticles have been

demonstrated to exacerbate liver fibrosis in mice with HFD-induced steatosis [52]. Moreover, 0.1 μm microplastics can directly enter hepatocytes from circulation, where they activate nuclear factor-κB translocation and fibronectin expression19 – both of which have been implicated in the development of cirrhosis [65, 66]. Co-exposure to Cd and MNPs has been demonstrated to synergistically induce liver inflammation and fibrosis [38], while continuous inhalation of PS nanoplastics can cause liver fibrosis and promote hepatocyte ferroptosis [67] – a novel form of iron-dependent cell death implicated in cirrhosis pathogenesis [68].As previously noted, the only direct evidence of MNPs accumulation in human liver tissue has been observed in cirrhotic specimens [28]. Furthermore, a recent study utilizing a functionally active 3D liver microtissue model composed of primary human hepatocytes, Kupffer cells, sinusoidal endothelial cells, and hepatic stellate cells demonstrated that long-term exposure to MNPs resulted in significant pathological changes, including disrupted tissue architecture [42].

### 3.5. Micronanoplastics and hepatocellular carcinoma

Recent research has highlighted the potential mechanistic role of MNPs in hepatocarcinogenesis, particularly in the context of chronic inflammation-driven malignant transformation [69]. This pathway bears striking parallels to the potential progression from MASLD to HCC, which may occur even in pre-cirrhotic stages [70]. In a comprehensive investigation employing a multi-model approach, Kim et al. utilized the Comparative Toxicogenomics Database to identify potential human health implications of high-density PE microplastics [71]. Notably, their analysis revealed a relevant adverse outcome pathway involving aflatoxin B1-mediated HCC development. In a recent study, Huang et al. demonstrated that MNPs significantly worsens liver injury under infectious conditions and established a correlation between MNPs pollution levels and human HCC through big data analysis [69]. Interestingly, the authors demonstrated that Spalt-like transcription factor 2

(SALL2), an evolutionarily conserved molecule that is frequently deregulated in various malignancies [72], can act as an oncogenic promoter in the development of MNPs-driven HCC. In addition, liver transcriptome analysis revealed the activation of carcinogenesis pathways in MNPs-exposed samples compared to pre-infection conditions [69]. In the clinical context, compelling evidence linking specific MNPs to HCC has emerged from occupational medicine studies. For instance, exposure to PVC MNPs has been consistently associated with liver toxicity and an elevated risk of both HCC and liver angiosarcoma, as reviewed by Zarus et al. Accordingly, a seminal epidemiological investigation reported 71 cases of primary liver cancer among 12,700 PVC and vinyl chloride workers, with a standardized mortality ratio of 2.40 (95% confidence interval: 1.80–3.14) [73, 74]. Other authors reported a significant excess of non-secondary liver tumors among PVC workers [75]. In contrast, the liver carcinogenic effects of occupational and environmental exposure to other MNPs in humans remain poorly understood.

## 4. DISCUSSION

### 4.1. The converging crises: plastic pollution and liver diseases

The epidemiological burden of advanced liver disease [1, 2, 8] and plastic pollution [29-31] are increasing concurrently, leading to the hypothesis that these phenomena may be interconnected [20-22], potentially mediated by MASLD [23, 25] – a known and increasingly prevalent precursor of both cirrhosis and HCC [8, 19, 20]. Recent years have seen a surge in experimental research elucidating the hepatotoxic effects of MNPs in animal models [52-54, 57].These studies consistently demonstrate that short- and medium-term exposure to these pollutants is associated with the development of hepatic alterations that closely resemble those observed in human MASLD and MASH. Furthermore, the potential direct and indirect

mechanisms by which MNPs may exert their hepatotoxicity have been extensively explored using advanced techniques and have been the subject of several recent reviews [21-25] .

### 4.2. MNPs as a "second hit" in MASLD and potential sex-related effects

Our analysis of the preclinical literature has highlighted two noteworthy observations. First, the available evidence suggests that MNPs require a pre-existing metabolic derangement –typically elicited in rodent models by a HFD [52, 53] – to induce MASLD-like histological alterations. Considering that mice fed a ND and exposed to MNPs do not exhibit steatotic liver changes [52-54], it is likely that MNPs may act as a "second hit" when a metabolic stress is already present. Second, an intriguing sex-specific effect of exposure to MNPs has been reported in mice, suggesting that sex hormones and/or sex-specific epigenetic mechanisms may play a role in modulating the liver toxicological profile of these contaminants [54].

### 4.3. Gaps in current research: the need for systematic approaches and quantification of MNPs in human blood

Although experimental findings have been congruent and promising, it is notable that animal studies have not yet employed a systematic approach to investigate the effects of MNPs. In this regard, the effects of primary versus secondary MNPs, specific size ranges (microplastics, submicroplastics, and nanoplastics), and different chemical compositions should be analyzed and compared more thoroughly. Another significant gap in current research is the involvement of MNPs in the pathogenesis of human MASLD, a topic that remains largely unexplored, with only a single pilot study providing initial insights [63]. This point is particularly relevant as animal MASLD models do not fully recapitulate the human disease clinically, biochemically, and histologically [76]. To achieve this objective, two methodological approaches can be pursued. First, following the methodology outlined by

Horvatits et al., the presence and characteristics of MNPs should be investigated in biopsy liver tissue samples obtained from patients within MASLD/MASH [28]. However, while the authors' approach was methodologically robust, the analysis of hepatic tissue using this techinque is time- consuming and challenging to standardize across different centers [28]. An appealing alternative is to quantify MNPs in human blood and analyze them cross-sectionally and longitudinally in relation to the presence and severity of MASLD, its histological characterization, and the risk of developing cirrhosis and HCC over time. In this regard, recent studies have successfully detected and quantified MNPs in human blood. In a seminal study, pyrolysis-gas chromatography/mass spectrometry (Py-GC-MS) was used to analyze blood samples from 22 healthy volunteers, identifying four high-production volume polymers: PET, PE, PS, and PMMA [77]. A more recent investigation optimized Py-GC-MS conditions to enhance method sensitivity and selectivity, detecting six high-production volume polymers in 68 individuals, with PE being the predominant polymer detected [78]. Another study applied micro-Fourier Transform Interferometer microscopy to identify and characterize microplastic polymers in blood samples from 20 healthy individuals, detecting 24 different polymer types in 90% of participants [79]. These findings collectively substantiate the ubiquitous presence and quantifiability of MNPs in human blood. Although the advanced analytical techniques employed in these studies are not yet suitable for routine clinical laboratory applications, a work of Cao et al. has demonstrated the feasibility of generating PS-specific antibodies [80]. This breakthrough represents a promising avenue for the development of research-grade, user friendly immunoassays capable of detecting these plastic particles in standard biological specimens. Such advancements have the potential to bridge the gap between cutting-edge research methodologies and routine clinical research, thereby paving the way for a more comprehensive and accessible assessment of MNPs exposure.

### 4.4. MNPs as potential biomarkers in advanced fibrosis, cirrhosis progression and fibrosis reversibility

The investigation of MNPs in blood is poised to be particularly significant in the context of advanced liver disease, offering potential insights into disease progression and prognosis. This emerging field of study may provide valuable biomarkers for predicting clinical outcomes in cirrhosis. In the natural history of this condition, patients may remain in a compensated state for extended periods, with disease progression varying considerably among individuals [81]. This heterogeneity is primarily influenced by the persistence of underlying liver damage and the presence of multiple pathogenic factors [82]. Given the substantial interindividual differences in the risk of decompensation, investigating whether persistently elevated levels or specific types of MNPs could serve as reliable biomarkers for predicting decompensation is a promising avenue of research [83]. Moreover, the potential role of MNPs in cirrhosis reversibility warrants exploration. Although traditionally considered irreversible, mounting evidence suggests that cirrhosis reversal – characterized by a reduction in fibrosis score on biopsy samples – can occur under certain conditions [84]. However, the precise triggers and thresholds that determine when cirrhosis becomes irreversible remain poorly understood [85]. Assessing the role of MNPs in this process is crucial, as it may provide novel insights into the key factors influencing the progression and potential regression of cirrhosiss over time.

### 4.5. MNPs and hepatocellular carcinoma: a new frontier

In light of previous evidence, we believe that investigating MNPs in blood could be valuable in HCC research, with potential applications across the spectrum of disease management, from prevention to treatment. Given the preclinical evidence demonstrating that MNPs can exacerbate liver injury under infectious conditions [69] and complicate underlying metabolic stress [52-54], a primary research focus could be quantifying blood MNPs levels in

vulnerable populations such as patients with chronic viral hepatitis and MASLD to assess their relationship with HCC incidence in the future. While data on the association between MNPs and HCC incidence are currently very limited, investigations into MNP concentrations and their relationship with metastasis-free and overall survival in HCC cases may reveal novel biomarkers and open new research directions. The currently established markers, such as α-fetoprotein used in HCC surveillance, also have significant limitations; therefore, further investigations to establish other biomarkers could be highly beneficial [86]. A better understanding of the complex interactions between MNPs and HCC may contribute to the development of innovative therapeutic strategies. If certain types or patterns of MNPs are found to be associated with adverse outcomes, it is possible that interventions targeting their accumulation or effects could be explored. Notably, incorporating MNP analysis into HCC management would be consistent with the ongoing shift toward precision medicine in hepatology [87, 88]. By integrating data on MNPs with other biomarkers and clinical parameters, clinicians may enhance risk stratification, optimize treatment selection, and improve monitoring of disease progression, thereby advancing our capacity to combat this aggressive malignancy. It should be acknowledged that this is a nascent research area, and substantial work remains before MNPs can be regarded as a prognostic biomarker in this context.

## 5. LIMITATIONS

In this review, we provided a comprehensive overview of the literature on MNPs and their role in liver damage, with a focus on MASLD and advanced liver injury. The strength of this narrative review lies in its broad search strategy, covering multiple databases—including PubMed/MEDLINE, Web of Science, Scopus, and Google Scholar—and focusing on studies from the past decade, representing the most recent period in the field. On the other hand, most

of our current knowledge is derived from animal studies, with only a small proportion coming from human studies, which themselves have included very limited numbers of patients. Therefore, our interpretation of the data should be viewed with caution.

## 6. CONCLUSION

In conclusion, although substantial progress has been made in elucidating the hepatotoxic effects of micro- and nanoplastics in experimental models, their role in human MASLD and advanced liver conditions such as cirrhosis and HCC remains largely unexplored. Bridging these knowledge gaps will necessitate a multidisciplinary approach, integrating environmental science, epidemiology, toxicology, molecular biology, and hepatology. Considering the global rise in both plastic pollution and advanced liver diseases, this area of research offers significant potential for advancing public health outcomes.

## DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

## REFERENCES


1. Devarbhavi, H., S.K. Asrani, J.P. Arab, Y.A. Nartey, E. Pose, and P.S. Kamath, *Global burden of liver disease: 2023 update.* J Hepatol, 2023. **79**(2): 516-537.
2. Younossi, Z.M., G. Wong, Q.M. Anstee, and L. Henry, *The Global Burden of Liver Disease.* Clin Gastroenterol Hepatol, 2023. **21**(8): 1978-1991.
3. Ginès, P., A. Krag, J.G. Abraldes, E. Solà, N. Fabrellas, and P.S. Kamath, *Liver cirrhosis.* Lancet, 2021. **398**(10308): 1359-1376.
4. Tarao, K., A. Nozaki, T. Ikeda, A. Sato, H. Komatsu, T. Komatsu, et al., *Real impact of liver cirrhosis on the development of hepatocellular carcinoma in various liver diseases-meta-analytic assessment.* Cancer Med, 2019. **8**(3): 1054-1065.
5. Kaya, E., G. Daniel Mazzolini, Y. Yilmaz, and A. Canbay, *Prevention of hepatocellular carcinoma and monitoring of high-risk patients.* Hepatol Forum, 2022. **3**(1): 33-38.
6. Ioannou, G.N., P. Green, K.F. Kerr, and K. Berry, *Models estimating risk of hepatocellular carcinoma in patients with alcohol or NAFLD-related cirrhosis for risk stratification.* J Hepatol, 2019. **71**(3): 523-533.
7. Dai, J.J., Y.Y. Liu, and Z.H. Zhang, *Changes in the etiology of liver cirrhosis and the corresponding management strategies.* World J Hepatol, 2024. **16**(2): 146-151.
8. Manikat, R., A. Ahmed, and D. Kim, *Current epidemiology of chronic liver disease.* Gastroenterol Rep (Oxf), 2024. **12**: goae069.
9. Vaz, J., P. Jepsen, U. Strömberg, P. Midlöv, B. Eriksson, D. Buchebner, et al., *Metabolic dysfunction-associated steatotic liver disease has become the most common cause of hepatocellular carcinoma in Sweden: A nationwide cohort study.* Int J Cancer, 2025. **156**(1): 40-51.
10. Paklar, N., M. Mijic, and T. Filipec-Kanizaj, *The Outcomes of Liver Transplantation in Severe Metabolic Dysfunction-Associated Steatotic Liver Disease Patients.* Biomedicines, 2023. **11**(11).

11. Yilmaz, Y., N. Yilmaz, F. Ates, F. Karakaya, H. Gokcan, E. Kaya, et al., *The prevalence of metabolic-associated fatty liver disease in the Turkish population: A multicenter study.* Hepatol Forum, 2021. **2**(2): 37-42.

12. Kaya, E. and Y. Yilmaz, *Insidious danger for young adults: Metabolic (dysfunction)-associated fatty liver disease.* Hepatol Forum, 2022. **3**(2): 39-40.

13. Younossi, Z.M., P. Golabi, J. Paik, S. Owrangi, Y. Yilmaz, M. El-Kassas, et al., *Prevalence of metabolic dysfunction-associated steatotic liver disease in the Middle East and North Africa.* Liver Int, 2024. **44**(4): 1061-1070.

14. Kaya, E., D. Demir, Y.O. Alahdab, and Y. Yilmaz, *Prevalence of hepatic steatosis in apparently healthy medical students: a transient elastography study on the basis of a controlled attenuation parameter.* Eur J Gastroenterol Hepatol, 2016. **28**(11): 1264-7.

15. Adali, G., N.M. Bilgic, A.E. Kalaman, O. Ozturk, and K. Ozdil, *Prevalence and predictors of metabolic-associated fatty liver disease in liver transplant recipients: A cross-sectional prospective study.* Hepatol Forum, 2023. **4**(3): 129-134.

16. Yesil, E.E., Y. Yilmaz, A. Yesil, M. Mese, E. Kaya, and E.A. Bakir, *Prevalence of metabolic dysfunction-associated fatty liver disease in kidney transplant recipients: A cross-sectional study using FibroScan.* Hepatol Forum, 2023. **4**(1): 14-18.

17. Eris, T., M. Hassan, Y. Hikal, E. Sawah, F. Daneshgar, A.G. Teker, et al., *Changes in the etiology of chronic liver disease by referral to a FibroScan center: Increasing prevalence of the nonalcoholic fatty liver disease.* Hepatol Forum, 2023. **4**(1): 7-13.

18. Phoolchund, A.G.S. and S.I. Khakoo, *MASLD and the Development of HCC: Pathogenesis and Therapeutic Challenges.* Cancers (Basel), 2024. **16**(2).

19. Leyh, C., J.D. Coombes, H.H. Schmidt, A. Canbay, P.P. Manka, and J. Best, *MASLD-Related HCC-Update on Pathogenesis and Current Treatment Options.* J Pers Med, 2024. **14**(4).

20. Shi, Y., E. Taherifard, A. Saeed, and A. Saeed, *MASLD-Related HCC: A Comprehensive Review of the Trends, Pathophysiology, Tumor Microenvironment, Surveillance, and Treatment Options.* Curr Issues Mol Biol, 2024. **46**(6): 5965-5983.

21. Wang, X., K. Deng, P. Zhang, Q. Chen, J.T. Magnuson, W. Qiu, et al., *Microplastic-mediated new mechanism of liver damage: From the perspective of the gut-liver axis.* Sci Total Environ, 2024. **919**: 170962.

22. Chiang, C.C., H. Yeh, R.F. Shiu, W.C. Chin, and T.H. Yen, *Impact of microplastics and nanoplastics on liver health: Current understanding and future research directions.* World J Gastroenterol, 2024. **30**(9): 1011-1017.

23. Shen, Q., Y.J. Liu, T.T. Qiu, K.S. Loon, and D. Zhou, *Microplastic-induced NAFLD: Hepatoprotective effects of nanosized selenium.* Ecotoxicol Environ Saf, 2024. **272**: p. 115850.

24. Yin, J., Y. Ju, H. Qian, J. Wang, X. Miao, Y. Zhu, et al., *Nanoplastics and Microplastics May Be Damaging Our Livers.* Toxics, 2022. **10**(10): 586.

25. Auguet, T., L. Bertran, A. Barrientos-Riosalido, B. Fabregat, B. Villar, C. Aguilar, et al., *Are Ingested or Inhaled Microplastics Involved in Nonalcoholic Fatty Liver Disease?* Int J Environ Res Public Health, 2022. **19**(20).

26. Li, Y., L. Tao, Q. Wang, F. Wang, G. Li, and M. Song, *Potential Health Impact of Microplastics: A Review of Environmental Distribution, Human Exposure, and Toxic Effects.* Environ Health (Wash), 2023. **1**(4): 249-257.

27. Shen, R., K. Yang, X. Cheng, C. Guo, X. Xing, H. Sun, et al., *Accumulation of polystyrene microplastics induces liver fibrosis by activating cGAS/STING pathway.* Environ Pollut, 2022. **300**: 118986.

28. Horvatits, T., M. Tamminga, B. Liu, M. Sebode, A. Carambia, L. Fischer, et al., *Microplastics detected in cirrhotic liver tissue.* EBioMedicine, 2022. **82**: 104147.

29. Ziani, K., C.B. Ioniță-Mîndrican, M. Mititelu, S.M. Neacșu, C. Negrei, E. Moroșan, et al., *Microplastics: A Real Global Threat for Environment and Food Safety: A State of the Art Review.* Nutrients, 2023. **15**(3).

30. Bermúdez, J.R. and P.W. Swarzenski, *A microplastic size classification scheme aligned with universal plankton survey methods.* MethodsX, 2021. **8**: 101516.

31. Khan, A. and Z. Jia, *Recent insights into uptake, toxicity, and molecular targets of microplastics and nanoplastics relevant to human health impacts.* iScience, 2023. **26**(2): 106061.

32. Campanale, C., C. Massarelli, I. Savino, V. Locaputo, and V.F. Uricchio, *A Detailed Review Study on Potential Effects of Microplastics and Additives of Concern on Human Health.* Int J Environ Res Public Health, 2020. **17**(4).

33. Hu, L., Y. Zhao, and H. Xu, *Trojan horse in the intestine: A review on the biotoxicity of microplastics combined environmental contaminants.* J Hazard Mater, 2022. **439**: 129652.

34. Fabra, M., L. Williams, J.E.M. Watts, M.S. Hale, F. Couceiro, and J. Preston, *The plastic Trojan horse: Biofilms increase microplastic uptake in marine filter feeders impacting microbial transfer and organism health.* Sci Total Environ, 2021. **797**: 149217.

35. Zou, H., H. Qu, Y. Bian, J. Sun, T. Wang, Y. Ma, et al., *Polystyrene Microplastics Induce Oxidative Stress in Mouse Hepatocytes in Relation to Their Size.* Int J Mol Sci, 2023. **24**(8).

36. Yin, K., D. Wang, Y. Zhang, H. Lu, L. Hou, T. Guo, et al., *Polystyrene microplastics promote liver inflammation by inducing the formation of macrophages extracellular traps.* J Hazard Mater, 2023. **452**: 131236.

37. Lin, S., H. Zhang, C. Wang, X.L. Su, Y. Song, P. Wu, et al., *Metabolomics Reveal Nanoplastic-Induced Mitochondrial Damage in Human Liver and Lung Cells.* Environ Sci Technol, 2022. **56**(17): 12483-12493.

38. Huang, H., G. Li, S. Guo, K. Li, W. Li, Q. Zhou, et al., *RNA Methylation and Transcriptome Analysis Reveal Key Regulatory Pathways Related to Cadmium-Induced Liver Damage.* Chemical Research in Toxicology, 2025. **38**(4): 717-732.

39. Yang, M., R. Wang, L. Wei, H. Liu, Y. Wang, H. Tang, et al., *PLA plastic particles disrupt bile acid metabolism leading to hepatic inflammatory injury in male mice.* Biochem Biophys Res Commun, 2024. **732**: 150410.

40. Cheng, H., Z. Duan, Y. Wu, Y. Wang, H. Zhang, Y. Shi, et al., *Immunotoxicity responses to polystyrene nanoplastics and their related mechanisms in the liver of zebrafish (Danio rerio) larvae.* Environ Int, 2022. **161**: 107128.

41. Kadac-Czapska, K., J. Ośko, E. Knez, and M. Grembecka, *Microplastics and Oxidative Stress-Current Problems and Prospects.* Antioxidants (Basel), 2024. **13**(5).

42. Guraka, A., G. Souch, R. Duff, D. Brown, W. Moritz, and A. Kermanizadeh, *Microplastic-induced hepatic adverse effects evaluated in advanced quadruple cell human primary models following three weeks of repeated exposure.* Chemosphere, 2024. **364**: 143032.

43. Haldar, S., N. Yhome, Y. Muralidaran, S. Rajagopal, and P. Mishra, *Nanoplastics Toxicity Specific to Liver in Inducing Metabolic Dysfunction-A Comprehensive Review.* Genes (Basel), 2023. **14**(3).

44. Xu, R., J.W. Cao, H.L. Lv, Y. Geng, and M.Y. Guo, *Polyethylene microplastics induced gut microbiota dysbiosis leading to liver injury via the TLR2/NF-κB/NLRP3 pathway in mice.* Sci Total Environ, 2024. **917**: 170518.

45. Zhang, K., J. Yang, L. Chen, J. He, D. Qu, Z. Zhang, et al., *Gut Microbiota Participates in Polystyrene Microplastics-Induced Hepatic Injuries by Modulating the Gut-Liver Axis.* ACS Nano, 2023. **17**(15): 15125-15145.

46. Chen, X., J. Zhuang, Q. Chen, L. Xu, X. Yue, and D. Qiao, *Chronic exposure to polyvinyl chloride microplastics induces liver injury and gut microbiota dysbiosis based on the integration of liver transcriptome profiles and full-length 16S rRNA sequencing data.* Sci Total Environ, 2022. **839**: p. 155984.

47. Lu, L., Z. Wan, T. Luo, Z. Fu, and Y. Jin, *Polystyrene microplastics induce gut microbiota dysbiosis and hepatic lipid metabolism disorder in mice.* Sci Total Environ, 2018. **631-632**: 449-458.

48. Sofield, C.E., R.S. Anderton, and A.M. Gorecki, *Mind over Microplastics: Exploring Microplastic-Induced Gut Disruption and Gut-Brain-Axis Consequences.* Curr Issues Mol Biol, 2024. **46**(5): 4186-4202.

49. Tilves, C., H.J. Zhao, M.K. Differding, M. Zhang, T. Liu, C. Hoyo, et al., *Associations of Plastic Bottle Exposure with Infant Growth, Fecal Microbiota, and Short-Chain Fatty Acids.* Microorganisms, 2023. **11**(12).

50. Wen, S., Y. Zhao, S. Liu, Y. Chen, H. Yuan, and H. Xu, *Polystyrene microplastics exacerbated liver injury from cyclophosphamide in mice: Insight into gut microbiota.* Sci Total Environ, 2022. **840**: 156668.

51. Kaya, E. and Y. Yilmaz, *Metabolic-associated Fatty Liver Disease (MAFLD): A Multi-systemic Disease Beyond the Liver.* J Clin Transl Hepatol, 2022. **10**(2): 329-338.

52. Li, L., M. Xu, C. He, H. Wang, and Q. Hu, *Polystyrene nanoplastics potentiate the development of hepatic fibrosis in high fat diet fed mice.* Environ Toxicol, 2022. **37**(2): 362-372.

53. Okamura, T., M. Hamaguchi, Y. Hasegawa, Y. Hashimoto, S. Majima, T. Senmaru, et al., *Oral Exposure to Polystyrene Microplastics of Mice on a Normal or High-Fat Diet and Intestinal and Metabolic Outcomes.* Environ Health Perspect, 2023. **131**(2): 27006.

54. Wang, X., Z. Zhao, X. Wang, W. Hu, L. Chao, X. Chu, et al., *Effects of polystyrene nanoplastic gestational exposure on mice.* Chemosphere, 2023. **324**: 138255.

55. Liu, W., M. Li, H. Guo, S. Wei, W. Xu, Y. Yan, et al., *Single-cell transcriptome analysis of liver immune microenvironment changes induced by microplastics in mice with non-alcoholic fatty liver.* Sci Total Environ, 2024. **912**: 168308.

56. Wei, J., J. Liu, H. Wang, K. Wen, X. Ni, Y. Lin, et al., *Nanoplastic propels diet-induced NAFL to NASH via ER-mitochondrial tether-controlled redox switch.* J Hazard Mater, 2024. **465**: 133142.

57. Zhao, J., D. Gomes, L. Jin, S.P. Mathis, X. Li, E.C. Rouchka, et al., *Polystyrene bead ingestion promotes adiposity and cardiometabolic disease in mice.* Ecotoxicol Environ Saf, 2022. **232**: 113239.

58. Zhou, W., W. Shi, X. Du, Y. Han, Y. Tang, S. Ri, et al., *Assessment of Nonalcoholic Fatty Liver Disease Symptoms and Gut-Liver Axis Status in Zebrafish after Exposure to Polystyrene Microplastics and Oxytetracycline, Alone and in Combination.* Environ Health Perspect, 2023. **131**(4): 47006.

59. Boopathi, S., B. Haridevamuthu, E. Mendonca, A. Gandhi, P.S. Priya, S. Alkahtani, et al., *Combined effects of a high-fat diet and polyethylene microplastic exposure induce impaired lipid metabolism and locomotor behavior in larvae and adult zebrafish.* Sci Total Environ, 2023. **902**: 165988.

60. Chen, T., H. Jiang, Y. He, Y. Shen, Z. Huang, Y. Gu, et al., *Nanoplastics and chrysene pollution: Potential new triggers for nonalcoholic fatty liver disease and hepatitis, insights from juvenile Siniperca chuatsi.* Sci Total Environ, 2024. **922**: 171125.

61. Del Piano, F., B.C. Almroth, A. Lama, G. Piccolo, N.F. Addeo, O. Paciello, et al., *Subchronic oral exposure to polystyrene microplastics affects hepatic lipid metabolism, inflammation, and oxidative balance in gilthead seabream (Sparus aurata).* Ecotoxicol Environ Saf, 2024. **279**: 116455.

62. Chen, Y., H. Jin, W. Ali, T. Zhuang, J. Sun, T. Wang, et al., *Co-exposure of polyvinyl chloride microplastics with cadmium promotes nonalcoholic fatty liver disease in female ducks through oxidative stress and glycolipid accumulation.* Poult Sci, 2024. **103**(11): 104152.

63. Schwenger, K.J.P., Y. Ghorbani, S. Bharatselvam, L. Chen, K.M. Chomiak, A.C. Tyler, et al., *Links between fecal microplastics and parameters related to metabolic dysfunction-associated steatotic liver disease (MASLD) in humans: An exploratory study.* Sci Total Environ, 2024. **953**: 176153.

64. Sultanik, P., G. Lherault, C. Bouzbib, V. Ratziu, R. Pais, S. Mouri, et al., *Prevalence and prognosis of patients with MASLD-related cirrhosis after an ICU hospitalization in France: A single-centre prospective study.* Aliment Pharmacol Ther, 2024. **60**(6): 796-810.

65. Elsharkawy, A.M. and D.A. Mann, *Nuclear factor-kappaB and the hepatic inflammation-fibrosis-cancer axis.* Hepatology, 2007. **46**(2): 590-7.

66. Liu, X.Y., R.X. Liu, F. Hou, L.J. Cui, C.Y. Li, C. Chi, et al., *Fibronectin expression is critical for liver fibrogenesis in vivo and in vitro.* Mol Med Rep, 2016. **14**(4): 3669-75.

67. Ge, Y., S. Yang, T. Zhang, S. Gong, X. Wan, Y. Zhu, et al., *Ferroptosis participated in inhaled polystyrene nanoplastics-induced liver injury and fibrosis.* Sci Total Environ, 2024. **916**: 170342.

68. Zhu, L., S. Luo, Y. Zhu, S. Tang, C. Li, X. Jin, et al., *The Emerging Role of Ferroptosis in Various Chronic Liver Diseases: Opportunity or Challenge.* J Inflamm Res, 2023. **16**: 381-389.

69. Huang, H., J. Hou, C. Yu, F. Wei, and B. Xi, *Microplastics exacerbate tissue damage and promote carcinogenesis following liver infection in mice.* Ecotoxicol Environ Saf, 2024. **286**: 117217.

70. Ma, Y., J. Wang, W. Xiao, and X. Fan, *A review of MASLD-related hepatocellular carcinoma: progress in pathogenesis, early detection, and therapeutic interventions.* Front Med (Lausanne), 2024. **11**: 1410668.

71. Kim, Y., J. Jeong, S. Lee, I. Choi, and J. Choi, *Identification of adverse outcome pathway related to high-density polyethylene microplastics exposure: Caenorhabditis elegans transcription factor RNAi screening and zebrafish study.* J Hazard Mater, 2020. **388**: 121725.

72. Hermosilla, V.E., M.I. Hepp, D. Escobar, C. Farkas, E.N. Riffo, A.F. Castro, et al., *Developmental SALL2 transcription factor: a new player in cancer.* Carcinogenesis, 2017. **38**(7): 680-690.

73. Zarus, G.M., C. Muianga, S. Brenner, K. Stallings, G. Casillas, H.R. Pohl, et al., *Worker studies suggest unique liver carcinogenicity potential of polyvinyl chloride microplastics.* Am J Ind Med, 2023. **66**(12): 1033-1047.

74. Ward, E., P. Boffetta, A. Andersen, D. Colin, P. Comba, J.A. Deddens, et al., *Update of the follow-up of mortality and cancer incidence among European workers employed in the vinyl chloride industry.* Epidemiology, 2001. **12**(6): 710-8.

75. Fedeli, U., P. Girardi, and G. Mastrangelo, *Occupational exposure to vinyl chloride and liver diseases.* World J Gastroenterol, 2019. **25**(33): 4885-4891.

76. Vacca, M., I. Kamzolas, L.M. Harder, F. Oakley, C. Trautwein, M. Hatting, et al., *An unbiased ranking of murine dietary models based on their proximity to human metabolic dysfunction-associated steatotic liver disease (MASLD).* Nat Metab, 2024. **6**(6): 1178-1196.

77. Leslie, H.A., M.J.M. van Velzen, S.H. Brandsma, A.D. Vethaak, J.J. Garcia-Vallejo, and M.H. Lamoree, *Discovery and quantification of plastic particle pollution in human blood.* Environ Int, 2022. **163**: 107199.

78. Brits, M., M.J.M. van Velzen, F.Ö. Sefiloglu, L. Scibetta, Q. Groenewoud, J.J. Garcia-Vallejo, et al., *Quantitation of micro and nanoplastics in human blood by pyrolysis-gas chromatography–mass spectrometry.* Microplastics and Nanoplastics, 2024. **4**(1): 12.

79. S, V.L.L., C.R. Liddle, C.A. Atherall, E. Chapman, M. Watkins, D.J.C. S, et al., *Microplastics in human blood: Polymer types, concentrations and characterisation using μFTIR.* Environ Int, 2024. **188**: 108751.

80. Cao, L., X. Zeng, and J. Lin, *Generation of polystyrene-specific antibodies for developing immunoassays to analyze microplastics and nanoplastics.* Chemical Engineering Journal, 2023. **465**: 142843.

81. Lee, S. and S. Saffo, *Evolution of care in cirrhosis: Preventing hepatic decompensation through pharmacotherapy.* World J Gastroenterol, 2023. **29**(1): 61-74.

82. Kumar, R., S. Kumar, and S.S. Prakash, *Compensated liver cirrhosis: Natural course and disease-modifying strategies.* World J Methodol, 2023. **13**(4): 179-193.

83. Balcar, L., M. Tonon, G. Semmler, V. Calvino, L. Hartl, S. Incicco, et al., *Risk of further decompensation/mortality in patients with cirrhosis and ascites as the first single decompensation event.* JHEP Rep, 2022. **4**(8): 100513.

84. Jung, Y.K. and H.J. Yim, *Reversal of liver cirrhosis: current evidence and expectations.* Korean J Intern Med, 2017. **32**(2): 213-228.

85. Lee, M.J., *A review of liver fibrosis and cirrhosis regression.* J Pathol Transl Med, 2023. **57**(4): 189-195.

86. Hanif, H., M.J. Ali, A.T. Susheela, I.W. Khan, M.A. Luna-Cuadros, M.M. Khan, et al., *Update on the applications and limitations of alpha-fetoprotein for hepatocellular carcinoma.* World J Gastroenterol, 2022. **28**(2): 216-229.

87. Panduro, A., S. Roman, I.M. Mariscal-Martinez, A. Jose-Abrego, K. Gonzalez-Aldaco, C. Ojeda-Granados, et al., *Personalized medicine and nutrition in hepatology for preventing chronic liver disease in Mexico.* Front Nutr, 2024. **11**: 1379364.

88. Sookoian, S. and C.J. Pirola, *Precision medicine in nonalcoholic fatty liver disease: New therapeutic insights from genetics and systems biology.* Clin Mol Hepatol, 2020. **26**(4): 461-475.

**TABLE 1.** Search strategy

| Variable | Specification |
|---|---|
| Search date | November 1, 2024 |
| Databases | PubMed/MEDLINE, Web of Science, Scopus, Google Scholar |
| Search terms | "microplastics," "nanoplastics," "liver," "hepatic," "metabolic dysfunction-associated steatotic liver disease," "non-alcoholic fatty liver disease," "advanced liver disease," "cirrhosis," and "hepatocellular carcinoma" |
| Timeframe | January 1, 2014, to November 1, 2024 |
| Inclusion and exclusion criteria | Inclusion: original studies, review articles; Exclusion: case reports, conference abstracts, articles not published in the English language |
| Selection process | Preliminary screening of titles and abstracts, followed by full-text screening and narrative synthesis of key data extracted from eligible studies. |

## Figure legends

**FIGURE 1.** Classification of micronanoplastics. *Created with Biorender.com*

**FIGURE 2.** Schematic representation of the direct and indirect mechanisms of hepatotoxicity induced by micronanoplastics. The indirect effect occurs through gut dysbiosis, characterized by an imbalance in gut microbiota. This leads to the translocation of endotoxins via the portal vein to the liver, resulting in hepatic inflammation. Direct effects include oxidative stress, inflammation, mitochondrial dysfunction, activation of hepatic stellate cells, bile acid disruption, and immunotoxicity. *Created with Biorender.com*