REVIEW ARTICLE

A Systematic Literature Review on Methotrexate Hepatotoxicity in Psoriasis Management: Preconceived Notion or Real Threat?

Wolf-Henning BOEHNCKE[1, 2], Maria-Magdalena CONSTANTIN[3, 4], José-Manuel CARRASCOSA-CARRILLO[5], Pariyawan RAKVIT[6], Alice-Anaïs VARLET[7], Solenn LE CLANCHE[7], Linda A. W. VERHAGEN[8] and Manuelle VIGUIER[9*]

[1]Division of Dermatology and Venereology, Geneva University Hospitals, Geneva, Switzerland, [2]Department of Pathology and Immunology, University of Geneva, Geneva, Switzerland, [3]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania, [4]IInd Department of Dermatology, Colentina Clinical Hospital, Bucharest, Romania, [5]Dermatology Department, Hospital Universitari Germans Trias i Pujol, IGTP, UAB, Barcelona, Spain, [6]Dermatology Department, East Lanchashire Hospitals Trust, Blackburn, United Kingdom, [7]Medical Affairs Department, Public Health Expertise, Paris, France, [8]Medical Affairs Department, Nordic Pharma, Hoofddorp, Netherlands, and [9]Department of Dermatology, Robert Debré University Hospital, Reims, France

Methotrexate (MTX) is a widely used, cost-effective systemic treatment for moderate-to-severe psoriasis, but concerns about hepatotoxicity often limit its long-term use. Hepatic adverse effects range from transient enzyme elevations to fibrosis and cirrhosis. Despite established guidelines, monitoring practices remain inconsistent, and the mechanisms underlying MTX-induced hepatotoxicity in psoriasis patients are not fully elucidated. This systematic literature review evaluates the association between MTX and hepatotoxicity, identifies key risk factors, assesses monitoring strategies and addresses misconceptions about its hepatic safety. A comprehensive search of MEDLINE/PubMed, EMBASE, Cochrane Library and grey literature (2003–2024) included English and French studies on human subjects, encompassing guidelines, reviews and observational/interventional studies. MTX-related hepatotoxicity is multifactorial, with risk factors including obesity, diabetes, hyperlipidaemia, excessive alcohol consumption and pre-existing liver disease. Psoriasis itself may also contribute to liver dysfunction. There is no consensus on optimal monitoring frequency for liver function tests or the role of noninvasive tools like transient elastography. While folic acid supplementation may mitigate risk, dosing remains inconsistent.Though MTX carries a potential hepatotoxic risk, this is patient-specific rather than inherent to the drug. Standardized monitoring protocols and risk stratification are essential to optimize safety, prevent unnecessary treatment discontinuation and improve long-term psoriasis management.

Key words: psoriasis; hepatotoxicity; methotrexate.

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Corr: Manuelle Viguier, Department of Dermatology, Robert Debré University Hospital, Avenue du Général Koenig, 51092 Reims Cedex, France. *Email: mviguier@chu-reims.fr

SIGNIFICANCE

Our review gathered and analysed existing research to understand the association between methotrexate and hepatotoxicity in psoriasis patients, addressing concerns over its liver-related side-effects and the variability in monitoring practices. Our work identifies key risk factors (e.g. obesity, diabetes, alcohol use) influencing methotrexate hepatotoxicity and highlights the lack of consensus on monitoring strategies. It also emphasizes the need for standardized monitoring protocols for methotrexate hepatotoxicity, taking patient-specific risk factors into account. Altogether, this review suggests that a better understanding of these risks can help optimize treatment plans and improve long-term psoriasis care.

Psoriasis is a chronic immune disorder causing red, scaly patches due to inflammation and skin imbalance (1, 2). It varies in form and severity, affecting 2–3% of the global population (3). Methotrexate (MTX), an immune modulator used for decades in moderate-to-severe psoriasis, reduces T-cell inflammation and modulates key signalling pathways (4). Its efficacy, safety and low cost make it a common treatment. MTX can cause temporary liver enzyme elevation, linked to its conversion into polyglutamates, triggering oxidative stress, hepatocyte apoptosis and inflammation (5). High doses may lead to hepatic fibrosis or cirrhosis (6), though liver injuries are sometimes misattributed to MTX. Recent studies suggest hepatotoxicity in psoriasis patients may result from risk factors like alcohol, obesity, type II diabetes, hyperlipidaemia, inherited liver diseases, female sex or hepatitis (7–12). Psoriasis itself may contribute to liver dysfunction, but its biochemical impact remains unclear (13).

This systematic literature review aimed to investigate the links between MTX and hepatotoxicity in psoriatic patients, raise clinician awareness and dispel misconceptions about MTX use in psoriasis.

MATERIALS AND METHODS

This systematic review (CRD42025634732) evaluates MTX-related hepatotoxicity in psoriasis management.

Literature search

A comprehensive search was conducted in PubMed/MEDLINE, EMBASE, Cochrane Library, Google Scholar and grey literature (health authority websites, patient advocacy materials, learned societies) on September 12, 2023. The search (Appendix S1) included human studies in English or French, published between 1 January 2015 and 1 January 2023, using relevant keywords and MeSH terms to capture literature relevant to current practice.

Study selection

Two reviewers independently assessed eligibility. Title and abstract screening excluded irrelevant studies. Full texts were reviewed, with exclusions documented.

Study designs

- Included: Randomized controlled trials (RCTs), observational studies, systematic reviews, meta-analyses, clinical guidelines and consensus statements.
- Excluded: opinion pieces, narrative reviews, case reports, animal studies and nonprimary data unless directly relevant.

Population

Patients diagnosed with psoriasis based on established criteria. No exclusion criteria applied.

Interventions/Exposures

MTX treatment (oral, subcutaneous, intramuscular) at standard doses. The review examined hepatotoxic effects (enzyme elevation, fibrosis, cirrhosis) and monitoring strategies (liver function tests, advanced diagnostics). Folic acid's role in mitigating toxicity was explored.

Outcomes

Primary outcomes:

- Liver Enzyme Elevation: Defined as the elevation of liver enzymes (aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP))
- Development of Liver Fibrosis or Cirrhosis: Defined as the progression to liver fibrosis or cirrhosis

Secondary outcomes.

- Adverse events and discontinuation rates due to hepatotoxicity.
- Any other hepatotoxicity-related complications such as liver failure.

Data extraction

Data were extracted using a standardized grid covering.

- Study details (author, title, DOI, country, year, design, sample size),
- Population (demographics, setting, control group),
- Intervention (MTX dosage, route, monitoring, preventive measures),
- Outcomes (enzyme levels, fibrosis/cirrhosis, hepatotoxicity events, adverse effects, discontinuation).

Risk of bias and quality assessment

Two reviewers assessed bias based on design, sample size and evidence quality, resolving disagreements by consensus. Risk of bias was assessed independently by 2 reviewers. Randomized trials were evaluated using the Cochrane Risk of Bias 2 tool; systematic reviews and meta-analyses were appraised using AMSTAR-2; and observational studies were assessed using the Newcastle–Ottawa Scale. Disagreements were resolved by consensus, and when consensus could not be reached, a third reviewer adjudicated. The certainty of evidence was assessed using the GRADE approach.

Data synthesis

Findings were synthesized narratively and descriptively, with key results summarized in tables.

RESULTS

Study selection

Of the 359 hits, 102 hits were selected for full-text reviewing. Among these, 52 studies met the inclusion criteria and were integrated to the literature review (Appendix S1). Characteristics of the included studies are reported in Appendix S1.

Clinical evidence about the link between methotrexate and a possible hepatotoxicity in psoriasis patients

Since 2015, 31 studies have examined MTX-associated hepatotoxicity in psoriasis patients, focusing on liver enzyme levels and the risk of fibrosis or cirrhosis.

Increase in liver enzyme levels

Association of methotrexate with liver enzyme levels elevation (and comparison with other systemic therapies). Liver test abnormalities, typically defined as values of at least 2 upper normal limit (UNL) of AST, ALT, ALP and/or gamma-glutamyl transferase enzymes have been observed for most conventional therapies (MTX, acitretin, cyclosporine) and, more recently, biologic agents (9).

Data from clinical trials. MTX has been associated with liver enzyme elevations in 3 clinical trials (**Table I**). A controlled open trial comparing subcutaneous MTX (15 mg/week) with secukinumab in psoriatic patients with metabolic syndrome reported significant AST and ALT increases in 64 MTX patients, with 6% experiencing 3-fold elevations at 6 months, leading to withdrawal (14). No secukinumab patients required discontinuation. Another RCT found similar hepatic adverse events between oral MTX and ixekizumab, while fumaric acid esters led to discontinuations due to liver issues (15). In a RCT comparing apremilast and MTX for palmoplantar psoriasis, mild, transient liver enzyme disturbances were observed without discontinuation (16). Collectively, these data support that liver enzyme elevations can occur during MTX therapy, but heterogeneity in populations, dose/formulation and assessment schedules limits any between-study dose–response or timing comparisons.

Data from meta-analyses. For the meta-analyses, regimen–toxicity correlations are likewise limited because dosing, route, folate use, baseline liver risk and laboratory monitoring schedules varied widely across included trials and were not reported in a harmonized way; therefore, we summarize hepatic events at the pooled level rather than attributing differences to a specific MTX regimen or timepoint (Table I). In Conway et al. (32 RCTs; RA/PsA/psoriasis; follow-up >24 weeks), MTX was associated with higher risks of overall liver adverse events and both minor (≤3× ULN) and major (>3× ULN) transaminase abnormalities versus comparators, but timing after MTX initiation and MTX dose were not consistently extractable across studies (12). In West et al. (psoriasis; ≥12 weeks), the weighted incidence of abnormal LFTs was ~10% (range 1–23.9) across included studies, again without a uniform dose- or time-resolved analysis (17).

Data from real-world studies. A cohort study of 3,171 patients from the BIOBADADERM registry found that hepatic adverse events were more common in MTX-treated patients (998 patients), with MTX associated with an increased risk of liver test abnormalities compared to anti-TNF-alpha agents (9). An observational study from the SCREAM project showed that the relative rate of mild liver adverse events was 47% higher for MTX compared to biologics (18). In a retrospective registry study of 649 patients, 35.2% discontinued MTX due to liver-related issues, including a 3-fold or greater increase in transaminase levels in 15.4% of cases (19). Another retrospective study reported hepatic abnormalities in 68% of 218 patients during MTX treatment, with 2.8% discontinuing due to liver issues (20). A Swiss registry study found that 11% of 66 patients starting subcutaneous MTX developed liver transaminase levels above the UNL during a 12-week period (21). Additionally, a retrospective study showed that 24% of 393 patients had liver enzyme abnormalities, with MTX being the most common drug associated with these abnormalities (56%) (22). Overall, across real-world cohorts with variable MTX dosing and monitoring, hepatic laboratory abnormalities were reported from as early as the first 12 weeks after initiation and could occur at any time during treatment. Comparative registries consistently showed higher rates of liver test abnormalities with MTX, while most abnormalities were mild/transient and discontinuation rates varied by study definition. These findings are summarized in Table I.

Influence of the disease on hepatotoxicity

In a population-based cohort study, despite similar weekly MTX doses, patients with psoriasis had the highest incidence of liver disease, followed by those with psoriatic arthritis and rheumatoid arthritis among MTX users (23). Psoriatic patients were 1.6–3.4 times more likely to develop liver disease outcomes compared to rheumatoid arthritis patients, while psoriatic arthritis patients were 1.3–1.6 times more likely to develop mild liver disease or cirrhosis, highlighting the need for more conservative monitoring in psoriasis patients. In a prospective study of 235 psoriatic patients who received a 12-week course of low-dose oral MTX (7.5–15 mg weekly), hepatotoxicity occurred in 61 (26%), with elevated ALT (21.3%), AST (12.3%), direct bilirubin (4.7%) and total bilirubin (3.4%). ALT levels were more than double the upper normal limit in 21 (8.9%) and AST in 3 (1.3%) (24). Patients with psoriatic arthritis had higher ALT levels than those without. Multivariate analysis showed MTX significantly increased bilirubin levels by week 12 in both groups and ALT/AST levels in psoriatic arthritis patients. Elevated ALT was linked to higher BMI and smoking, with more pronounced hepatic dysfunction in patients with both psoriasis and psoriatic arthritis.

Although these studies differed in design, patient populations, MTX dosing and treatment duration both suggested a potentially elevated frequency of liver-related abnormalities, particularly in patients with psoriatic disease—especially those with both psoriasis and psoriatic arthritis.

Influence of the route of administration

Two RCTs assessed the impact of the route of administration of MTX on liver function in psoriatic patients. While Dogra et al. (25) did not identify a significant difference in liver function test abnormalities between patients receiving oral and subcutaneous MTX at the same dose, Choonhakarn et al. (26) described identified elevated liver enzymes as the most common

Table I. Main findings regarding elevation of liver enzyme levels during MTX treatment

Reference	Indication	Total number of patients	Total number of studies	Treatment (number of patients)	MTX regimen	Timing of assessment	Hepatic abnormalities	MTX discontinuation
Clinical trials								
Gisondi 2020 (14)	Moderate to severe chronic plaque psoriasis	*N*=130	N.A.	MTX (64) Secukinumab (66)	15 mg/week by subcutaneous administration	Clinical and laboratory data were evaluated at the baseline and every 3 months up to month 12.	Serum levels of liver enzymes (either AST or ALT) were significantly increased at month 6 and month 12 compared with baseline in patients treated with MTX ($p<0.01$).	Three times elevations of liver enzymes (AST or ALT) were reported in 4 of 64 patients receiving methotrexate at month 6, causing drug withdrawal.
Reich 2020 (15)	Moderate-to-severe plaque psoriasis for ≥ 6 months before baseline, were naive to systemic treatment (except phototherapy) for psoriasis	*N*=162	N.A.	MTX (54) FAE (54) Ixekizumab (54)	Methotrexate was administered as oral tablets, starting with 7.5 mg per week, with a stepwise increase in dosage of 5–7.5 mg per week until a dose of ≥15 mg per week was reached.	Over 24 months	Incidence of hepatic adverse events was similar in patients treated with fumaric acid esters, ixekizumab and MTX.	No discontinuation was reported among patients treated with MTX.
Kt 2021 (16)	Palmoplantar psoriasis	*N*=84	N.A.	MTX (42) Apremilast (42)	Methotrexate was administered orally at a dose of 0.4 mg/kg body weight once weekly, supplemented with folic acid (2.5 mg twice: the day before and the day after MTX administration). Treatment continued for 16 weeks or until a 75% reduction in m-PPPASI was achieved.	Over 16 months	Transaminitis (4/42, 9.5%) was the most common adverse event diagnosed for patients treated with MTX. Only 1 patient with transaminitis had a more than 2-fold rise from the normal upper limit, the other patients had mild and transient derangements in liver enzymes that did not require treatment discontinuation.	Adverse events leading to treatment discontinuation in the MTX group were seen in 4/42 (9.5%) patients and included transaminitis (1/42, 2.4%).
Meta-analysis								
Conway 2015 (12)	Rheumatoid arthritis, psoriatic arthritis and psoriasis	*N*=13 177	32	MTX (6 877) Comparator treatment (6 300)	N.R.	>24 weeks	MTX was associated with a higher risk of overall adverse liver events compared to comparator treatments (RR 2.19, 95% CI 1.73–2.77, I^2=68%). It also increased the risk of minor liver enzyme abnormalities (transaminases ≤3 UNL, RR 2.16, 95% CI 1.67–2.79, I^2=68%) and major liver enzyme abnormalities (transaminases >3 UNL, RR 2.63, 95% CI 1.90–3.64, I^2=10%).	N.R.
West 2016 (17)	*Psoriasis*	*N*=5 995	11	MTX (5 995)	N.R.	≥ 12 weeks	The weighted incidence of abnormal LFTs was 10% (range 1–23.9) reported in 17 studies	N.R.
Real-world studies								
Munera-Campos 2022 (9)	Plaque psoriasis, guttate psoriasis, erythrodermic psoriasis, generalized pustular psoriasis, palmoplantar pustulosis, annular pustular psoriasis, acrodermatitis continua of Hallopeau, psoriatic arthritis	*N*=998	N.A.	MTX (998)	N.R.	N.R.	In multivariate analyses, MTX (adjusted incidence rate ratio (aIRR): 3.06 [2.31–4.4]) and cyclosporine (aIRR: 2.37 [1.05–5.35], p=0.0378) were both associated with an increased risk of liver test abnormalities when compared to anti-TNF-alpha agents and to an increased risk of hepatic events considered as a whole (MTX: aIRR 2.29 [1.71–3.06]; p<0.001; cyclosporine: aIRR 2.13 [1.15–3.97]; p=0.0166)	N.R.
Mazhar 2023 (18)	Psoriasis, psoriatic arthritis	*N*=6294	N.A.	MTX (5,385) Biologics (909)	N.R.	Median follow-up was 4.3 (2–7) years	The relative rate of mild liver adverse events (defined as an elevation in liver enzymes <2 and >5-fold higher than UNL) was 47% higher for MTX users (HR 1.47 [95% CI 1.14–1.88]) compared with biologics	N.R.
Ozkok Akbulut 2021 (19)	Psoriasis	*N*=649	N.A.	MTX (649)	The median duration of MTX treatment was 10 months (range, 1–96). Patients received a median weekly dose of 15 mg (range, 5–25) and a median cumulative dose of 550 mg (range, 10–6,760). MTX was administered orally in 51.9% (*n*=337) of patients and subcutaneously in the remainder, with folate	N.R.	N.R.	144 (35.2%) discontinued MTX treatment for reasons of liver events: 3-fold or more increase in transaminase levels (100 patients (15.4%)) and an increase in levels of

(*Continued*)

Table I. Main findings regarding elevation of liver enzyme levels during MTX treatment (Continued)

Reference	Indication	Total number of patients	Total number of studies	Treatment (number of patients)	MTX regimen	Timing of assessment	Hepatic abnormalities	MTX discontinuation
					supplementation provided to all.			PN3P (35 patients (5.3%))
Tula 201,722(22)	Mild-to-severe psoriasis	*N*=393	N.A.	MTX (N.R.) Acitretin (N.R.)	The mean weekly dose of MTX was 15±4 mg (range: 2.5–25 mg) and mean cumulative dose was 717±803 mg (range: 20–5400 mg).	The average follow-up was 20.3±23.3 (1–120) months	24% of patients presented abnormalities in liver enzymes during follow-up, with the most common drugs associated with high liver function test abnormalities being MTX (56%) and acitretin (13%)	Liver function test abnormalities developed at any time during MTX treatment and in all cases normalized following dose decrease or treatment discontinuation
Cabello Zurita 2017 (20)	Chronic, moderate-to-severe psoriasis	*N*=218	N.A.	MTX (218)	Average treatment duration of 17±13.6 months overall with an average dose per week of 12 mg	48 weeks	Hepatic laboratory abnormalities occurred in 68% of patients during treatment, with the vast majority being mild, transient and asymptomatic	Hepatic abnormalities led to treatment discontinuation in 2.8% of patients. After MTX cessation, hepatic dysfunctions were not progressive and did not significantly impair patients' quality of life
Drach 2019 (21)	Psoriasis	*N*=66	N.A.	MTX (66)	In most cases, patients received 7.5 mg in week 0. In week 1 10 mg and from then on 15 mg weekly. The route of administration was subcutaneous in all patients. 24 h after the injection, oral folic acid 5 mg was routinely given.	Laboratory control was performed before start of therapy and for the first 3 months every 4 weeks.	11% of patients newly developed liver transaminase levels above the UNL during the 12-week study period	N.R.

aIRR: Adjusted Incidence Rate Ratio; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CI: Confidence interval; FAE: Fumaric acid esters; LFTs: Liver function tests; MTX: Methotrexate; N.A.: not applicable; N.R.: not reported; PN3P: Procollagen 3 Peptide; RR: relative risk; UNL: upper normal limit.

adverse event in the subcutaneous MTX group (**Table II**). While these findings hint at a possible differential hepatotoxic risk by administration route, the limited and heterogeneous data underscore the need for further research. This aligns with our prior review on the safety and efficacy of subcutaneous use of MTX in psoriasis (27).

Specific populations: elderly and children. Several studies assessed liver function in pediatric psoriatic patients treated with MTX, with varying dosages and follow-up durations (**Table III**). A subset analysis from the Child-CAPTURE registry, patients received MTX at 0.03 to 0.5 mg/week and were followed for 2 to 267 weeks; 1 patient discontinued MTX due to elevated liver enzymes, which normalized after treatment interruption (28). In a retrospective study of 195 pediatric patients, 3 out of 52 MTX-treated patients discontinued due to elevated liver enzymes (29). Another study of 289 pediatric patients found 1.1% of MTX-treated patients had abnormal liver function tests (30). In a study of 42 patients treated with oral MTX, 28.6% had elevated liver enzymes, but no patients discontinued MTX (31). Finally, in a study of 51 pediatric patients, 1 MTX-treated patient (7.1%) had elevated liver enzymes, though it was deemed unrelated to MTX (32).

A systematic review evaluating the safety of several systemic therapies in elderly patients with psoriasis reported that elevated liver enzyme levels were the second most common adverse effect (after nausea), with 18.2% to 56% of patients treated with MTX reporting such an adverse effect (33).

Overall, these findings support a cautious, individualized approach to hepatic monitoring in specific populations (e.g. elderly and paediatric patients), while acknowledging that the evidence base remains limited by small sample sizes, heterogeneous study designs and variability in MTX dosing and follow-up duration.

MTX in combination with other treatments and hepatotoxicity

In studies evaluating MTX combinations with other treatments generally report low rates of liver-related adverse effects, though findings vary by regimen and follow-up (**Table IV**). In a RCT where patients received MTX (15 mg/week) alone or combined with pioglitazone; only 1 patient (4.5%) in the combination group experienced elevated liver enzymes, leading to treatment discontinuation (34). Another RCT compared standard MTX monotherapy (0.3 mg/kg/week) to a reduced MTX dose combined with cyclosporine (2.5 mg/kg/day) over

Table II. Main findings from RCTs regarding the influence of the route of administration

Study	Population	Route of administration	MTX regimen	Timing of assessment	Liver enzyme abnormalities	Key findings
Dogra 2022 (25)	*N*=100	Oral (*N*=50) SC (*N*=50)	Oral MTX: treatment was initiated at a full dose of 0.3 mg/kg/week (maximum 25 mg/week) for 12 weeks or until PASI90 was achieved. SC MTX: patients received subcutaneous MTX at the same dose and duration. Following treatment, MTX was gradually tapered by 5 mg every 2 weeks before discontinuation.	All patients were followed-up for 24 weeks post-treatment with monthly assessment	**Liver function derangement:** <2-fold ULN: - Oral 18% - SC 20% (*p*=0.80) >2-fold but <3-fold ULN: - Oral 4% - SC 2% (*p*=0.55) >3-fold ULN: - None in both groups	No significant difference in liver function tests between oral and SC MTX
Choonhakarn 2022 (26)	*N*=77	Oral (*N*=39) SC (*N*=38)	Prior to being enrolled into the study, all patients had a 12-week washout period to clear any previous treatment. MTX was started at 10 mg/week in 2 divided doses taken orally (12 h interval between doses; doses taken twice weekly) or in a single dose by weekly SC injection. The dose increased to 15, 20 and 25 mg every 4 week if 100% improvement (PASI100) was not achieved at each follow-up.	Every 4 weeks until Week 32.	**Elevated liver enzymes:** - Oral 7.7% (3/39) - SC 13.2% (5/38)	Elevated liver enzymes (mild, <2 times UNL) more common in SC group; improved with dosage reduction. The second most common adverse event in oral group after anorexia/nausea.

MTX:Methotrexate; SC:Subcutaneous; UNL:Upper normal Limit.

12 weeks (35). While elevated AST levels were more common in the MTX monotherapy group (13.6% vs 10.4%), the difference was not statistically significant. A retrospective study of patients treated with fumaric acid esters (120 mg/day) and MTX (5–20 mg/week) reported slight, nondiscontinuation-warranting increases in liver enzymes in 2 of 7 patients, though follow-up duration was not specified (36). Tula et al. (22) observed a high incidence of liver enzyme abnormalities (42%) in patients using MTX (mean 15±4 mg/week) combined with acitretin, with an average follow-up of 20.3 months, but the abnormalities were reversible with dose adjustments. Conversely, Abidi et al. (37) found no liver-related adverse effects in any group – MTX alone (7.5 mg/week), pioglitazone alone, or their combination – over 12 weeks of follow-up. Overall hepatotoxic risk with MTX combination therapy appears low, but varies by regimen, dose and follow-up duration. Most studies report mild, reversible enzyme elevations, although higher rates with MTX–acitretin warrant closer monitoring. However, heterogeneous designs, sample sizes and follow-up limit possible conclusions.

Fibrosis and cirrhosis development

Eleven studies have investigated the possible links between MTX and development of fibrosis or cirrhosis (**Table V**). Almost all concluded that there is no association, and report that comorbidities associated with psoriasis rather than MTX are more likely to cause serious liver problems.

A meta-analysis of RCTs including 32 studies with 13,177 participants reported no increased risk of liver failure, cirrhosis, or death in MTX-treated patients compared to comparator agents (12). Similarly, a prospective study found no association between MTX and NAFLD over a mean follow-up of 1.9 years (9). Retrospective studies showed mixed results. One study found that 18% of MTX-treated patients discontinued due to liver dysfunction, but cirrhosis cases were primarily linked to NAFLD, NASH or other factors (38). Another reported cirrhosis in only 0.8% of psoriatic patients, attributed to alcohol, HCV, or NASH rather than MTX (22). In Rongngernn et al. (39), 10 out of 41 MTX patients had liver injury, with no correlation to MTX dose or comorbidities. Ozkok Akbulut et al. (19) found

Table III. Main findings from studies on pediatric psoriasis patients regarding elevation of liver enzyme levels during MTX treatment

Reference	Population	MTX dosage (mg/week)	Follow-up	Hepatic abnormalities	MTX discontinuation
Van Geel 2015 (28)	*N*=25	0.03 to 0.5	2 to 267 weeks	N.R.	Discontinuation of MTX was reported in 1 patient because of increased liver enzymes. Normalization of these enzymes was observed after treatment interruption, and MTX was re-introduced
Sahin 2021 (29)	*N*=.52	Up to 15	N.R.	N.R.	3 patients out of 52 (6%) discontinued treatment due to elevated liver enzymes
Ergun 2017 (30)	*N*=88	0.3 to 0.7	Follow-up visits and laboratory monitoring were performed at least every 3 months (range, 2–12 weeks). Median follow-up period was 12 months (range, 5–24).	Abnormal liver function tests were reported in 1.1% of MTX-treated patients	N.R.
Wang 2022 (31)	*N*=42	0.1 to 10	N.R.	Elevated liver enzymes were reported in 12 (28.6%) patients and resolved after hepatoprotective treatment such as glucurolactone and bicyclol	No patient discontinued MTX due to elevated liver enzymes
Klufas 2016 (32)	*N*=14	3.8 to 21.4	At baseline, 5 to 7 months and 1 year of treatment duration.	Elevated liver enzymes were reported in 1 patient (7.1%) but this was deemed to be unrelated to MTX	N.R.

MTX:methotrexate; N.R.:Not reported.

Table IV. Key findings on MTX-related hepatotoxicity in combination with other treatments

Study	Population	Treatment groups	MTX dosage	Follow-up	Findings on liver-related adverse effects
Lajevardi 2015 (34)	*N*=44	MTX alone (*n*=22) MTX + pioglitazone (*n*=22)	MTX: 15 mg/week Pioglitazone: 15 mg/day, 16 weeks	Subjects were followed at weeks 1, 2, 4, 6, 10 and 16 after the start of the study.	Elevated liver enzymes in 1 (4.5%) patient in the combination group, leading to treatment discontinuation
Wilsmann-Theis 2015 (36)	*N*=17	FAEs alone (*n*=9) FAEs + MTX (*n*=5) FAEs + leflunomide (*n*=3)	FAEs: 120 mg daily MTX: 5 and 20 mg orally Leflunomide: 20 mg	N.R.	Slight increases in liver enzymes in 2 of 7 patients treated with FAEs combined with MTX, but none discontinued treatment due to hepatic dysfunction
Tula 2017 (22)	*N*=393	MTX alone Acitretin alone INH Acitretin + MTX Acitretin + INH MTX + statins Acitretin + statins MTX + INH Acitretin + MTX + INH	MTX : mean 15±4 mg/week (range: 2.5–25 mg) Others are not reported	The average follow-up was 20.3±23.3 (1–120) months	Elevation of liver enzymes: - MTX alone (*n*=30, 56%) - Acitretin alone (*n*=7, 13%) - INH (*n*= 2, 4%) - Acitretin + MTX (*n*=4, 7%) - Acitretin + INH (*n*= 1, 2%) - MTX + statins (*n*= 2, 4%) - Acitretin + statins (*n*=1, 2%) - MTX + INH (*n*=3, 6%) - Acitretin + MTX + INH (*n*=1, 2%)
Abidi 2020 (37)	*N*=90	MTX alone (*n*=29) Pioglitazone alone (*n*=30) MTX + pioglitazone (*n*=30)	MTX: 7.5 mg/week Pioglitazone: 15 mg/day, 12 weeks	At baseline and every 4 weeks for 12 weeks.	No liver-related adverse effects in any group
Singh 2021 (35)	*N*=133	MTX alone (*n*=66) MTX + Cyclosporine A (*n*=67)	MTX: 0.3 mg/kg/week Cyclosporine A: 2.5 mg/kg/day, 12 weeks	Patients were followed-up at every 2 weeks for 12 weeks.	AST >2x UNL, <3 UNL : *p*= 0.605 - MTX: 9 (13.6%) - MTX + Cyclosporine A: 7 (10.4%) ALT >2 UNL, <3 UNL: *p*=0.236 - MTX: 5 (7.6%) - MTX + Cyclosporine A: 2 (3.0%) AST ≥3 UNL: *p*=0.988 - MTX: 2 (3.0%) - MTX + Cyclosporine A: 2 (3.0%) ALT >2x UNL, <3 UNL: *p*=1.000 - MTX: 0 (0.0%) - MTX + Cyclosporine A: 1 (1.5%)

FAE:Fumaric Acid Esters; INH:Isoniazid; MTX:Methotrexate; UNL:Upper Normal Limit.

that 2.3% of patients discontinued MTX due to liver dysfunction, often with comorbidities. Among psoriatic patients with chronic hepatitis, MTX was not associated with fibrosis or cirrhosis after 9 years (11). Another study reported a higher incidence of liver disease in psoriasis patients but could not determine whether MTX, the disease itself, or other factors were responsible (23). Mahajan et al. (10) found no association between MTX and liver fibrosis. However, Mazhar et al. (18) reported a higher incidence of severe liver pathologies with MTX compared to biologics. Talme et al. (40) found that MTX treatment >24 months increased the risk of severe fibrosis and cirrhosis, while shorter durations did not.

Thus, the weight of evidence suggests that MTX is not a primary cause of fibrosis or cirrhosis in psoriatic patients. Most studies attribute severe liver outcomes to underlying comorbidities such as NAFLD, NASH, alcohol use, or viral hepatitis rather than MTX itself. However, the findings of Mazhar et al. (18) and Talme et al. (40) highlight the potential for increased risk with prolonged MTX use, underscoring the importance of vigilant monitoring, especially in patients with pre-existing liver conditions or long-term MTX exposure.

Current guidelines about MTX, hepatotoxicity and recommended monitoring

Monitoring hepatotoxicity. Recent guidelines and expert recommendations stress the risk of MTX-associated hepatotoxicity in psoriasis treatment. They emphasize liver assessments before starting MTX and regular monitoring throughout treatment (1, 6–8, 18, 41–55). These recommendations align with recent expert guidance (1, 7, 46) (**Table VI**).

Risk factors for increased hepatotoxicity. According to current guidelines, some patients are at higher risk to develop hepatic issues. Monitoring must thus be even closer for these patients. Identified risk factors for increased liver abnormalities are the following:

–Previous/current excessive alcohol consumption (1, 6, 43, 46, 47),
–Persistent abnormal liver functions (6, 46),
–Co-existing liver disease (1, 6, 46, 47) or history of one (6),
–Diabetes (6, 8, 41, 43),
–Obesity (6, 41, 43, 46),
–Hyperlipidaemia (6, 46),
–Exposure to other hepatotoxic agents (46) or history of exposure (6),
–Hepatitis (43),
–Lack of folate supplementation (46),
–Renal insufficiency (1),
–Increased age (1),
–Hypoalbuminaemia (1)
–MTX dosing errors (1),
–Metabolic syndrome (defined as obesity, hyperlipidaemia, hypertension, type 2 diabetes mellitus) (47),

Table V. Main findings from studies regarding severe liver issues during MTX treatment

Reference	Population	MTX dosage	Follow-up	Severe liver issues
Munera-Campos 2022 (9)	*N*=998 (Psoriasis)	N.R.	Average follow-up time (Mean (SD)): 1.9 (2.1) years	MTX (aIRR: 1.06 [0.48-2.34], *p*=0.888) was not associated with an increased risk of NAFLD compared to anti-TNF.
Koch 2021 (38)	*N*=66 (Psoriasis)	Cumulative MTX dose, mean (SD) 5.7 g (7.1)	Duration of therapy, mean (SD): 72.5 (60.8) months	9.1% of patients had mild fibrosis, 12.1% had moderate fibrosis and 22.7% had severe fibrosis or cirrhosis A review of the medical cases of these patients by gastroenterology revealed that no case of cirrhosis was primarily due to MTX.
Tula 2017 (22)	*N*=393 (Psoriasis)	The mean weekly dose of MTX was 15 ± 4 mg (range: 2.5–25 mg) and mean cumulative dose was 717± 803 mg (range : 20–5400 mg).	The average follow-up was 20.3 ± 23.3 (1–120) months	0.8% of patients had cirrhosis, that was associated with alcohol, HCV, herbal medicine use and NASH.
Rongngernn 2017 (39)	*N*=41 (Psoriasis)	N.R.	N.R.	10 patients had liver injury (Roenigk≥3a), among whom 2 developed significant liver fibrosis (Metavir≥F2) The total cumulative dosage of MTX (≤ 1.5g or > 1.5g), comorbidities and body mass index were not associated with transient elastography values or Roenigk grades.
Ozkok Akbulut 2021 (19)	*N*=649 (Psoriasis)	The median duration of MTX treatment was 10 months (range, 1–96). Patients received a median weekly dose of 15 mg (range, 5–25) and a median cumulative dose of 550 mg (range, 10–6,760). MTX was administered orally in 51.9% (*n*=337) of patients and subcutaneously in the remainder, with folate supplementation provided to all.	N.R.	15 patients (2.3%) had liver fibrosis. They all suffered from at least 2 comorbidities among hyperlipidaemia, obesity, hypertension, hepatosteatosis, diabetes, depression/anxiety and metabolic syndrome.
Tang 2018 (11)	*N*=370 (Psoriasis and chronic hepatitis B) *N*=174 (Psoriasis and chronic hepatitis C)	For CHB (Chronic hepatitis B) patients: Average cumulative MTX dose: 3.9±5.8 grams Mean duration of treatment: 123 months (~10.25 years) For CHC (Chronic hepatitis C) patients: Average cumulative MTX dose: 4.4±7.9 grams Mean duration of treatment: 122 months (~10.2 years)	Mean follow-up: 10 years	MTX use was not associated with fibrosis development (HR 0.72 [95% CI 0.42–1.25] for patients with CHB; HR 0.96 [95% CI 0.58–1.57] for patients with CHC), even at high cumulative doses (1.5–3g: HR 0.43 [95% CI 0.06–3.08] for patients with CHB; HR 1.04 [95% CI 0.25–4.25] for patients with CHC; ≥ 3g: HR 0.56 [95% CI 0.08–4.07] for patients with CHB; HR 0.53 [95% CI 0.07–3.89] for patients with CHC). There was no difference in terms of survival between MTX users and nonusers in cirrhosis-free patients.
Gelfand 2021 (23)	*N*=5,687 (Psoriasis) *N*=6,520 (Psoriatic arthritis) *N*=28,030 (Rheumatoid arthritis)	Average weekly methotrexate dose,* mg Mean (SD): Psoriasis: 19.2 (2.8) psoriatic arthritis: 19.8 (2.3) rheumatoid arthritis: 19.9 (2.2)	N.R.	The incidence rates per 1,000 persons-year of mild-liver disease, moderate-to-severe disease, cirrhosis and hospitalisation due to cirrhosis were respectively of 4.22 [95% (CI) 3.61–4.91], 0.98 [95%CI 0.7–1.33], 1.89 [95%CI 1.49–2.37] and 0.73 [95% CI 0.49–1.05] in psoriasis patients (5,687 patients). As confounding variables such as obesity were not considered, the study did not have the ability to distinguish if liver disease was associated with MTX use, an underlying disease or a combination of both.
Mahajan 2020 (10)	*N*=77 (Psoriasis)	Total cumulative dose: 0–5.2 g	Patients with 10 validated measurements	The proportion of fibrosis was the same among MTX-treated patients (25%) and MTX-untreated patients (23%, *p*=1.0), regardless of the cumulative dose MTX was not associated with the development of fibrosis.
Mazhar 2023 (18)	*N*=6,294 (Psoriasis)	N.R.	Median follow-up was 4.3 (2–7) years	The incidence of a composite outcome of serious liver adverse event was higher for MTX, with an absolute risk difference of 5.6% (95% CI 1.6–9.6) at 10 years. Compared to biologics, the relative rates of severe liver adverse events for MTX were 115% higher (HR 2.15 [1.16–4.0]).
Talme 2017 (40)	*N*=201 (Psoriasis)	10 to 20 mg/week - Group 1: *N*=47 (MTX for ≤ 24 months) - Group 2: *N*=122 (MTX for >24 months) - Group 3: *N*=32 (biologicals = controls; they had received MTX for a maximum of 6 months >4 years ago, group 3)	N.R.	Multivariate analyses showed that MTX treatment was not associated with mild fibrosis, regardless of therapy duration (≤ 24 months: OR 0.94 [95% CI 0.37–2.42], p = 0.9; >24 months: OR 0.12 [95% CI 0.63–2.02], *p*=0.71). MTX therapy during > 24 months was associated with the development of severe fibrosis and/or cirrhosis (OR 3.04 [95% CI 1.07–10.87], *p*=0.05) whereas MTX therapy during ≤ 24 months was not (OR 2.11 [95% CI 0.26–43.82], *p*=0.52).

aIRR:Adjusted Incidence Rate Ratio; CHB:Chronic Hepatitis B; CHC:Chronic Hepatitis C; CI:Confidence Interval; HCV:Hepatitis C Virus; HR:Hazard Ratio; MTX:Methotrexate; NASH:Non-Alcoholic Steatohepatitis; N.R.:Not Reported; OR:Odds Ratio.

–Chronic viral hepatitis B and C[47],
–Haemochromatosis (47),
–Other co-medications susceptible to induce hepatotoxicity (antibiotics, nonsteroidal anti-inflammatory drugs, others (6).

MTX treatment regimen and discontinuation. Recent European and American guidelines recommend weekly rather than daily MTX dosing for greater benefits and reduced risk of elevated liver enzymes (6, 43). The initial dose is typically 15 mg/

Table VI. Comparison of guidelines on monitoring hepatic function in adult patients with psoriasis treated with MTX

Reference	Country	Before MTX treatment initiation			During follow-up		
		Liver enzymes, albumin and bilirubin	PIIINP	Liver ultrasound	Liver enzymes, albumin and bilirubin	PIIINP	Liver ultrasound
Nast 2018 (41) *	Germany	ALT, AST and GGT	May be considered	Yes	ALT, AST and GGT after 1 week, 6 weeks and then every 6–12 weeks	May be considered during follow-up in case of long-term treatment In case of abnormal results, perform Fibroscan	Annually if MTX weekly dose ≥ 15 mg
Raaby 2017 (47) *	Denmark	ALT Consider another treatment in case of abnormal results	In case of abnormal results, perform Fibroscan	In case of abnormal results at fibroscan, consider liver biopsy	ALT Every 2nd week for 2 months followed by every 3 months <3-fold elevated: repeat in 2–4 weeks time >3-fold elevated: stop treatment and repeat in 2–6 weeks time	Every 6 months In case of elevated levels, repeat within weeks In case of elevated levels in 3 successive samples, perform Fibroscan	Yes If fibroscan is abnormal, consider biopsy
Amatore 2019 (48) *	France	ALT, AST, GGT, albumin and bilirubin	N.R.	Yes Fibroscan before treatment should be performed in obese patients	ALT, AST, GGT, bilirubin At week 2, week 4, then every 2–3 months	Every 6–12 months	Yes Every 1–2 years for fibroscan
Nast 2020 (43)	Europe	Liver enzymes Albumin in selected cases (patients with suspected hypoalbuminaemia or using other drugs with high binding affinity for serum)	If available	N.R.	Liver enzymes Albumin in selected cases Once every 4 weeks during first 2 months Thereafter, every 3 months	Every 3 months In case of abnormal PIIINP during MTX treatment, a hepatologist should be consulted	N.R.
Warren 2016 (53) Nice 2017 (49)	United Kingdom	Standard LFTs LFTs	N.R.	N.R.	LFTs, every 1–2 weeks for the first months and until a steady dosing regimen; every 2–3 months thereafter Patients with risk factors such as renal insufficiency or advanced age may need closer monitoring, both at the onset of treatment and after dosage increases In case of AST and ALT <2-fold elevated, repeat LFTs in 2–4 weeks In case of AST and ALT ≥2/3-fold elevated, withhold/decrease dose of MTX; consider other risk factors and consider discussing with gastroenterologist	Four times a year if available	N.R.
Menter 2020 (6)	USA	LFT one of the following: - FIB-4 - Fibrosure - Fibrometer - Hepascore	Possible, but test not widely used in the USA	Depending on the results of the other tests	Every 3–6 months assuming abnormal results Every 2–4 weeks in case of abnormal results	N.R.	Depending on the results of the other tests
Arnone 2019 (55)	Brazil	Mention of the risk of elevated transaminase levels without mentioning monitoring					
Hsu 2012 (8)	Canada	Mention of the risk of hepatotoxicity without mentioning monitoring					

AST:aspartate transaminase; GGT:gamma-glutamyl transferase; LFTs:liver function tests; LT:alkaline phosphatase; MTX:Methotrexate; N.R.:Not Reported; PIIINP:peptide of procollagen III.

week, adjustable to 20 mg for a better response. Long-term therapy requires personalized dosage adjustments. National guidelines in Germany and France align with these recommendations (41, 48). Elevated transaminase levels above 3 times the UNL indicate treatment interruption in German guidelines and expert recommendations (43, 45, 56). American guidelines recommend discontinuing MTX for patients with stage 3 liver fibrosis (1, 6).

Use of folic acid. MTX inhibits the enzyme dihydrofolate reductase, which can lead to depletion of folate levels in the body. Folic acid supplementation is suggested to help replenish folate levels, which is essential for normal cell function and growth (4). European, French and German guidelines recommend a 5 mg dose of folic acid 24 hours after each MTX administration, although there is conflicting evidence regarding the benefit of this intervention (41, 43, 48).

American guidelines and research also support folic acid to potentially mitigate liver toxicity risk (6, 13, 57) although there is no consensus on the optimal dosing regimen to administer (57). In rheumatoid arthritis, meta-analysis shows folic acid can reduce gastrointestinal issues, liver enzyme elevations and MTX withdrawal without affecting its efficacy (57). Such data are lacking in the psoriasis field.

Methods for hepatotoxicity assessment

Several methods are used to assess liver structural or functional issues during MTX treatment in psoriasis patients. Noninvasive methods include

–Transient elastography: Measures liver stiffness to evaluate fibrosis or cirrhosis using ultrasonography (38).
–Magnetic resonance elastography (MRE): Uses imaging to assess liver stiffness, particularly useful when transient elastography is technically challenging or in high-risk patients like those with obesity (39).
–Liver function tests (LFTs): Includes measurements of liver enzymes (ALT, AST, ALP, GGT), bilirubin and albumin in serum (51).
–FIB-4 index: A screening test for hepatic fibrosis based on platelet count, age and transaminases (58).
–Serum aminoterminal peptide of procollagen (P3NP): An indirect marker of liver fibrosis, although its availability and cost-effectiveness vary (6, 38).
–Enhanced Liver Fibrosis test: Combines serum markers (P3NP, hyaluronic acid, TIMP-1) to assess fibrosis risk (47).
–Liver biopsy remains the gold standard but is invasive with significant risks, suitable mainly for severe hepatic pathologies (39).

DISCUSSION

This systematic review investigated MTX-related hepatotoxicity in psoriasis. Data on the MTX-hepatotoxicity link remain limited, with studies lacking adequate confounding control and small sample sizes, restricting generalizability.

Clinical trials (14–16), meta-analyses (12, 17) and real-world (9, 18–22) studies consistently show that MTX treatment causes transient liver enzyme elevations, reversible with dose reduction or discontinuation. However, the association with severe hepatic dysfunction (fibrosis, cirrhosis) is inconsistent. Some studies reported no significant association (9, 10, 12, 22, 39), while others suggest that prolonged MTX therapy may increase the risk of severe liver outcomes (18, 38, 40). Comorbid factors like obesity and type II diabetes appear to play a more significant role in acute liver dysfunction than MTX itself (11, 19, 23, 45, 59). Studies in paediatric patients show varying rates of elevated liver enzymes (28–32), while research in elderly patients indicates that elevated liver enzyme levels are a common adverse effect (33). These differences could be related to age-related variations in drug metabolism and organ function. Altogether, this suggests that severe hepatotoxicity may be more driven by underlying conditions than by MTX.

The data suggest differences in liver function and hepatotoxicity risks between oral and subcutaneous MTX administration, with hepatotoxicity being expected with the subcutaneous route due to higher effective dose delivery compared to oral administration. While one RCT found no significant difference between the 2 routes (25), another suggested that subcutaneous MTX may cause higher liver enzyme elevations (26). Although both routes carry similar hepatotoxicity risks, subcutaneous MTX may offer advantages like improved distribution, bioavailability and overall safety (27). However, the limited data make it difficult to draw definitive conclusions regarding the hepatotoxicity risks of subcutaneous versus oral MTX.

Psoriasis patients have a higher incidence of liver disease compared to individuals with other inflammatory conditions. Specifically, psoriasis patients are 1.6–3.4 times more likely to develop liver disease outcomes than those with rheumatoid arthritis (23). Patients with psoriatic arthritis are also more likely to develop mild liver disease or cirrhosis. These findings suggest a potentially higher risk of MTX-related hepatotoxicity in psoriasis patients. However, psoriasis patients without psoriatic arthritis seem to tolerate MTX better and experience fewer adverse effects, including hepatotoxicity (24). These data remain limited, and further research is needed to explore the specific impact of psoriasis on MTX-related hepatotoxicity and refine monitoring strategies.

European guidelines warn against combining MTX with certain drugs, such as antifungal imidazoles and retinoids, due to the risk of liver toxicity (41, 43, 48–50, 53). Despite these warnings, studies evaluating MTX combination therapies report minimal liver-related adverse effects, typically reversible with dose adjustments. RCTs have shown no liver-related adverse effects with MTX alone or in combination with pioglitazone, although one study reported a single case of elevated liver enzymes leading to discontinuation (25, 37). Other studies have observed mild liver enzyme increases in patients using MTX in combination with fumaric acid esters or acitretin, but these effects were also reversible with dose modifications (22, 36). These findings suggest that MTX combinations may pose a low risk for liver toxicity, with manageable adverse effects.

The literature emphasizes the importance of monitoring MTX-associated hepatotoxicity, as recommended by dermatology guidelines (1, 6–8, 18,

41–54). However, compliance with these guidelines appears to be low. A Swedish study found many patients missed required pretreatment tests, with liver function monitoring declining over time (50). Another study showed dermatologists performed more tests and detected more enzyme abnormalities, while rheumatologists had higher drug survival rates (60). Psoriasis patients discontinued MTX more often due to liver enzyme issues, while remission was the main reason in psoriatic arthritis. Despite rheumatologists' less intensive monitoring, serious adverse events were not higher. Authors concluded extensive monitoring increases abnormal results and early withdrawals without clear clinical benefit. Barriers to optimal monitoring may include limited patient awareness, variability in physician adherence to guidelines and systemic constraints such as time and resource availability. Further research is needed to establish an evidence-based, risk-adapted approach to MTX monitoring those balances early detection of hepatotoxicity with treatment continuity.

Strengths and limitations

This systematic review provides a comprehensive view of associated risks with MTX-related hepatotoxicity in psoriasis. Its strength lies in the inclusion of diverse study designs. It is limited by the scarcity of large RCTs in psoriasis, small sample sizes, heterogeneous study populations (including differences in age and baseline risk), variable comparator regimens and treatment durations, inconsistent MTX dosing/route and folate supplementation, nonuniform timing and definitions of liver outcomes and inadequate adjustment for key confounders. Adherence to liver monitoring guidelines is poorly documented, limiting insights into real-world practice.

Conclusion

MTX can increase liver enzyme levels in psoriasis, reversible with dose reduction or discontinuation. However, it does not appear to cause serious liver disease and remains crucial for psoriasis treatment. Future research should control confounders and use appropriate tools to detect clinically relevant liver disease.

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