Risk of liver disease in patients with psoriasis, psoriatic arthritis, and rheumatoid arthritis receiving methotrexate: A population-based study

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Background: Patients with psoriatic disease may be more susceptible to methotrexate hepatotoxicity than those with rheumatoid arthritis (RA); however, direct evidence supporting this notion is lacking.

Objective: To compare liver disease risk among patients with psoriasis (PsO), psoriatic arthritis (PsA), or RA receiving methotrexate.

Methods: In a population-based cohort study, Danish individuals with PsO, PsA, or RA receiving methotrexate between 1997 and 2015 were compared according to 4 disease outcomes: mild liver disease, moderate-to-severe liver disease, cirrhosis, and cirrhosis-related hospitalization.

Results: Among 5687, 6520, and 28,030 patients with PsO, PsA, and RA, respectively, the incidence rate of any liver disease was greatest for PsO, followed by PsA, and lowest for RA. Compared with patients with RA, patients with PsO were 1.6-3.4 times more likely to develop at least one of the liver disease outcomes, whereas those with PsA were 1.3-1.6 times more likely to develop mild liver disease and cirrhosis after adjusting for demographics, smoking, alcohol use, comorbidities, and methotrexate dose.

Limitations: Confounding due to unmeasured variables, misclassification, and surveillance bias.

Conclusion: PsO, PsA, and RA differentially influence liver disease risk in the setting of methotrexate use independent of other major risk factors. More conservative monitoring should be considered in patients receiving methotrexate for psoriatic disease, particularly in PsO patients. (J Am Acad Dermatol 2021;84:1636-43.)

Key words: cirrhosis; hepatotoxicity; liver disesase; methotrexate; psoriasis; psoriatic arthritis; rheumatoid arthritis.

INTRODUCTION

Psoriasis (PsO), psoriatic arthritis (PsA), and rheumatoid arthritis (RA) are common Th1/Th17-mediated disorders that are associated with a spectrum of skin and/or joint manifestations.[1] Methotrexate has long been considered as first-line therapy for all 3 diseases[2-4]; however, hepatotoxicity is a well-recognized side effect of methotrexate

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therapy.[5] The histopathology of methotrexate-induced hepatotoxicity resembles nonalcoholic steatohepatitis, a form of nonalcoholic fatty liver disease (NAFLD) that can lead to cirrhosis. Serious liver complications are thus a leading concern in patients receiving long-term methotrexate therapy for chronic cutaneous and rheumatologic diseases.

PsO, PsA, and RA have previously been associated with an increased risk of liver disease, particularly NAFLD.[1] Based on clinical experience, it is believed that PsO/PsA patients are more susceptible to liver disease and methotrexate hepatotoxicity than are RA patients.[6,7] For example, the monitoring practices for methotrexate hepatotoxicity are more stringent in the dermatologic guidelines than those in the rheumatologic guidelines.[6,8,9] However, empirical evidence for this differential hepatotoxicity among psoriatic patients is limited. While previous studies have observed a higher risk of abnormal liver function test results in PsO/PsA patients who received methotrexate than in those with RA,[7,10] other studies have not identified any differences even after adjusting for demographics and methotrexate dose.[11] In a more recent population-based study, PsO and PsA patients receiving systemic therapy had a significantly higher risk of incident liver disease, especially NAFLD and cirrhosis, compared with that of matched controls and to a greater degree than RA patients on systemic therapy.[12] While such findings provide indirect evidence that methotrexate-associated liver disease risk may differ by PsO, PsA, and RA diagnoses, direct comparisons are lacking. Thus, our objective was to directly compare the risk of liver disease among methotrexate-treated PsO, PsA, and RA patients using a population-based approach.

CAPSULE SUMMARY

- Patients with psoriasis and psoriatic arthritis who received methotrexate were more likely to develop liver disease than patients with rheumatoid arthritis, independent of other major risk factors.
- Conservative hepatotoxicity monitoring may be warranted in patients receiving methotrexate for psoriatic disease.

METHODS

Data sources

The Danish health care system enables free, equal, and universal medical access for all citizens.[13] At birth or immigration, citizens are assigned a registration number, which enables individual-level linkage across multiple registries that can be used for research.[14] The National Patient Register contains information on medical diagnoses according to the International Classification of Diseases Tenth Revision (ICD-10).[15] Since 1994, all pharmacy-claimed prescriptions have been recorded in the Registry of Medicinal Products Statistics.[16] Most patients claim medications at the pharmacy, but medications may sometimes be given directly from hospital clinics, in which case they are recorded in the National Patient Register.

Study design, population, and variables

We performed a cohort study of PsO, PsA, or RA patients who received ≥1 prescription for methotrexate through either a pharmacy-claimed prescription or its dispensation from a hospital clinic between January 1, 1997, and December 31, 2015.

The exposure was the underlying disease, that is, PsO, PsA, or RA, which was defined by the presence of ≥1 ICD-10 diagnostic code. PsO patients were diagnosed by dermatologists while those with PsA or RA were diagnosed by rheumatologists. If a patient had more than 1 diagnosis (eg, both PsO and PsA), the diagnosis closest to and preceding methotrexate initiation was used.

The outcomes were mild liver disease (defined as chronic hepatitis or cirrhosis without portal hypertension), moderate-to-severe liver disease (defined as liver failure, hepatic encephalopathy, portal hypertension, or esophageal varices), liver cirrhosis, and hospitalization due to cirrhosis. Liver disease severity categories are consistent with those used in the Charlson Comorbidity Index (CCI).[14] These outcomes were derived from ICD-10 codes.[15]

The start date was defined as the latter of the earliest diagnosis date or earliest methotrexate prescription date. It was possible for the methotrexate prescription to precede the generation of diagnostic codes for patients who were initially treated in a private clinic (where their diagnoses may not be captured in our data source) but were later referred to the hospital setting for further treatment. The end date was determined from the earliest date of liver outcome, death, migration, or until December 31, 2015. Potential confounders were measured at cohort entry and included age, sex, calendar year, smoking, alcohol abuse, diabetes, and hyperlipidemia (including statin use). CCI (excluding liver disease and RA) and average weekly methotrexate dose were regarded as continuous variables. Smoking, alcohol abuse, and comorbidities were

Abbreviations used:

BMI:	body mass index
CCI:	Charlson Comorbidity Index
CI:	confidence interval
HR:	hazard ratio
ICD-10:	International Classification of Diseases Tenth Revision
NAFLD:	nonalcoholic fatty liver disease
PsO:	psoriasis
PsA:	psoriatic arthritis
RA:	rheumatoid arthritis

identified from the ICD-10 codes in the patient register data.

Statistical analysis

The only variable with missing data was methotrexate dose (43,616 [7.5%] of 580,821 observations); thus, 5 datasets were imputed using monotone regression methods based on age, sex, smoking, alcohol abuse, diabetes, statin use, year of cohort entry, CCI, and methotrexate dosage when available. The average weekly dose for each patient was calculated. If there was only one record on dosage (11.2% of patients), 15 mg was considered to be the average weekly dosage according to routine methotrexate prescription patterns in Denmark.[17,18]

We calculated the risk of each disease outcome among the 3 disease cohorts using Cox regression analysis. The proportional hazards assumption for continuous variables was examined using an empirical exploration process, and when violated, a quadratic form was considered. In this case, the quadratic forms for average weekly methotrexate dose and age were included. The proportional hazards assumption for categorical variables was examined using Kaplan-Meier plots; however, the survival curves between different groups changed very slowly over time, thus, nonproportionality was ignored. The duration of methotrexate use was compared across the 3 cohorts through Kaplan-Meier plots. The study was approved by the Danish Data Protection Agency and conducted and reported in accordance with Strengthening the Reporting of Observational Studies in Epidemiology recommendations.[19]

RESULTS

A total of 5687, 6520, and 28,030 PsO, PsA, and RA patients received methotrexate (Table I), respectively. RA patients were older and more likely to be female than PsA patients, and PsA patients were slightly older and more likely to be female than PsO patients. The average weekly dose of methotrexate was similar among the 3 groups, but cumulative methotrexate dose and duration of use were greatest in RA, followed by PsA, then PsO (Table I). Similarly, drug survival (ie, time to discontinuation of therapy) was longest for patients with RA (50% discontinuation after 80 months), followed by patients with PsA (50% discontinuation after 54 months), and shortest for PsO patients (50% discontinuation after 26 months) (Fig 1).

The incidence of all liver disease outcomes was greatest for PsO, followed by PsA, and lowest for RA (Table II). The most common outcome, which was mild liver disease, had an incidence rate per 1000 person-years of 4.22 (95% confidence interval [CI] 3.61-4.91) for PsO, 2.39 (95% CI 1.95-2.91) for PsA, and 1.39 (95% CI 1.25-1.55) for RA. For the least common but most serious outcome of cirrhosis-related hospitalization, the incidence rate per 1000 person-years was 0.73 (95% CI 0.49-1.05) for PsO, 0.32 (95% CI 0.18-0.54) for PsA, and 0.22 (95% CI 0.17-0.29) for RA.

Cox regression analysis revealed that PsO patients had significantly increased risks of mild liver disease (hazard ratio [HR] 2.22, 95% CI 1.81-2.72), moderate-to-severe liver disease (HR 1.56, 95% CI 1.05-2.31), cirrhosis (HR 3.38, 95% CI 2.44-4.68), and hospitalization due to cirrhosis (HR 2.25, 95% CI 1.37-3.69) compared with those of RA patients (Table III). Similarly, PsA patients also had significantly greater risk of mild liver disease (HR 1.27, 95% CI 1.01-1.60) and cirrhosis (HR 1.63, 95% CI 1.10-2.42) compared with that of patients with RA. However, there were no differences in their risks of moderate-to-severe liver disease or cirrhosis-related hospitalization. Additional sensitivity analyses yielded similar findings (Table IV). External adjustment for body mass index (BMI) using UK population-based data and assuming a two-fold risk of cirrhosis due to obesity indicated potential biases of 8.2% and 9.7% away from the null for PsO and PsA, respectively. Thus, the incomplete measurement of obesity in the dataset is unlikely to significantly impact the results.[12,20-22]

DISCUSSION

In this study of methotrexate users, psoriatic disease patients were more likely to develop liver disease than RA patients, with the greatest effects observed among those with PsO. While such differences in hepatotoxicity risk were previously attributed to differences in rates of alcoholism, obesity, diabetes, and other comorbidities between the disease populations,[6] our study found that the underlying disease influences liver disease risk independent of age, sex, smoking, alcohol use, diabetes, hyperlipidemia, overall comorbidities, and average weekly methotrexate dose.

Table I. Characteristics of the study population

Characteristic, No. (%)	PsO N = 5687	PsA N = 6520	RA N = 28,030
Age at cohort entry, mean (SD), y	47.7 (17.2)	50.7 (13.7)	59.7 (14.6)
Female sex	2577 (45.3)	3737 (57.3)	20,066 (71.6)
History of smoking	1211 (21.3)	1169 (17.9)	6577 (23.5)
History of alcohol abuse	418 (7.4)	294 (4.5)	775 (2.8)
Diabetes	471 (8.3)	486 (7.5)	1953 (7.0)
Hyperlipidemia or statin use	774 (13.6)	1067 (16.4)	4560 (16.3)
Charlson Comorbidity Index, mean (SD)			
Overall	0.24 (0.78)	0.17 (0.62)	0.51 (0.88)
Excluding liver disease	0.22 (0.75)	0.17 (0.61)	0.50 (0.87)
Excluding liver disease and RA	0.22 (0.74)	0.14 (0.59)	0.22 (0.68)
Duration of methotrexate use, mon			
Mean (SD)	43.0 (52.8)	56.3 (59.7)	72.1 (65.6)
Median (IQR)	20 (3-67)	35 (7-91)	14 (54-119)
Range	0-227	0-227	0-227
Cumulative methotrexate dose,* g			
Mean (SD)	2.1 (2.5)	3.0 (3.1)	4.0 (3.8)
Median (IQR)	1.2 (0.5-2.8)	1.8 (0.8-4.3)	2.8 (1.0-5.8)
Range	0.03-37.30	0.08-23.75	0.08-59.64
Average weekly methotrexate dose,* mg			
Mean (SD)	19.2 (2.8)	19.8 (2.3)	19.9 (2.2)
Median (IQR)	20.8 (17.9-20.8)	20.8 (20.5-20.8)	20.8 (20.5-20.8)
Range	1.0-23.6	3.1-24.3	3.3-24.6

IQR, Interquartile range; *PsA*, psoriatic arthritis; *PsO*, psoriasis; *RA*, rheumatoid arthritis; *SD*, standard deviation.
*Cumulative and weekly methotrexate dose data were averaged across all 5 imputed datasets.

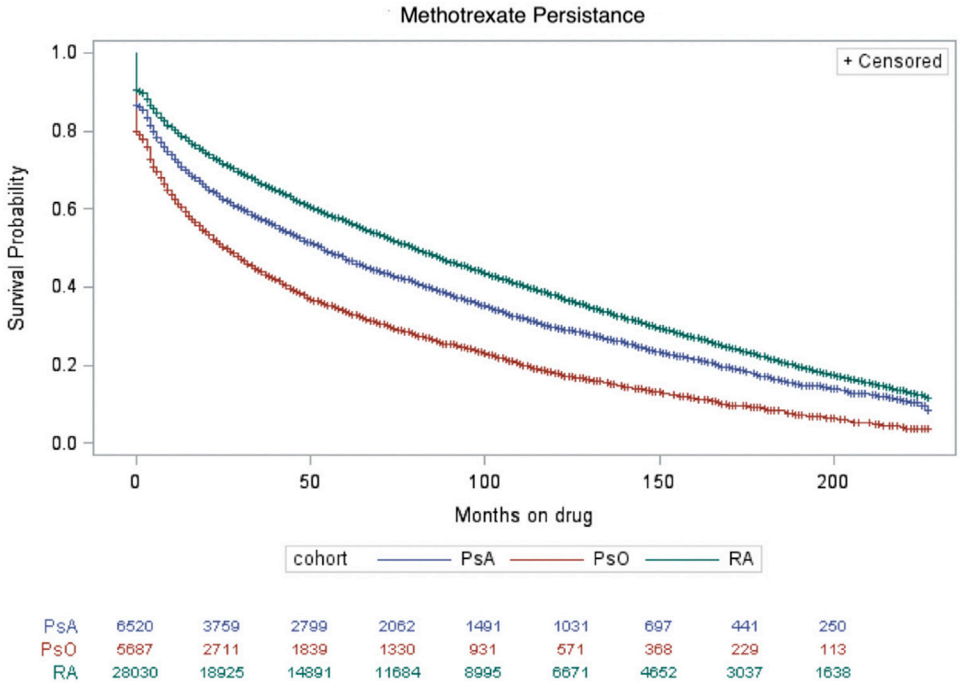

Fig 1. Duration of methotrexate use in the psoriasis, psoriatic arthritis, and rheumatoid arthritis cohorts. *PsA*, Psoriatic arthritis; *PsO*, psoriasis; *RA*, rheumatoid arthritis.

To our knowledge, this study is one of the first and largest population-based studies to directly compare PsO, PsA, and RA patients with respect to liver disease in the setting of methotrexate use. Previous studies were relatively small and often used indirect measures of hepatic injury, such as laboratory tests,

Table II. Incidence rates of liver disease outcomes, per 1000 person-years, by underlying disease

	PsO	PsA	RA
Mild liver disease			
No. of events	169	102	329
Follow-up time, mean (SD), y	7.0 (5.1)	6.5 (4.9)	8.4 (5.4)
IR per 1000 PY (95% CI)	4.22 (3.61-4.91)	2.39 (1.95-2.91)	1.39 (1.25-1.55)
Moderate-to-severe liver disease			
No. of events	40	22	108
Follow-up time, mean (SD), y	7.2 (5.2)	6.6 (4.9)	8.5 (5.4)
IR per 1000 PY (95% CI)	0.98 (0.70-1.33)	0.51 (0.32-0.77)	0.46 (0.37-0.55)
Cirrhosis			
No. of events	77	36	100
Follow-up time, mean (SD), y	7.2 (5.2)	6.6 (4.9)	8.5 (5.4)
IR per 1000 PY (95% CI)	1.89 (1.49-2.37)	0.84 (0.59-1.16)	0.42 (0.34-0.51)
Hospitalization due to cirrhosis			
No. of events	30	14	53
Follow-up time, mean (SD), y	7.2 (5.2)	6.6 (4.9)	8.5 (5.4)
IR per 1000 PY (95% CI)	0.73 (0.49-1.05)	0.32 (0.18-0.54)	0.22 (0.17-0.29)

CI, Confidence interval; *IR*, incidence rate; *PsA*, psoriatic arthritis; *PsO*, psoriasis; *PY*, person-years; *RA*, rheumatoid arthritis; *SD*, standard deviation.

Table III. Adjusted hazard ratios of liver outcomes using Cox regression analysis*

	Outcome, HR (95% CI)			
Variable	Mild liver disease	Moderate-to-severe liver disease	Cirrhosis	Hospitalization due to cirrhosis
Disease				
RA	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
PsO	2.22 (1.81-2.72)	1.56 (1.05-2.31)	3.38 (2.44-4.68)	2.25 (1.37-3.69)
PsA	1.27 (1.01-1.60)	0.93 (0.58-1.50)	1.63 (1.10-2.42)	1.17 (0.64-2.16)
Male sex	1.05 (0.88-1.24)	1.37 (1.00-1.88)	0.93 (0.70-1.24)	1.36 (0.89-2.06)
Smoking	0.90 (0.68-1.20)	0.72 (0.42-1.24)	0.80 (0.51-1.25)	0.58 (0.26-1.28)
Alcohol abuse	3.62 (2.86-4.59)	5.49 (3.68-8.19)	5.94 (4.24-8.31)	6.50 (3.95-10.72)
Diabetes	1.89 (1.43-2.50)	2.24 (1.40-3.57)	2.50 (1.67-3.72)	1.56 (0.77-3.14)
Hyperlipidemia	1.01 (0.78-1.31)	1.01 (0.65-1.58)	0.92 (0.62-1.38)	0.97 (0.51-1.82)
Year of cohort entry	1.02 (1.00-1.04)	1.06 (1.02-1.11)	1.04 (1.00-1.08)	1.03 (0.98-1.09)
CCI excluding liver disease and RA	1.12 (1.01-1.24)	1.13 (0.97-1.32)	1.24 (1.09-1.40)	1.10 (0.87-1.40)

CCI, Charlson Comorbidity Index; *CI*, confidence interval; *HR*, hazard ratio; *PsA*, psoriatic arthritis; *PsO*, psoriasis; *RA*, rheumatoid arthritis.
*Adjusted also for age, age^2, average weekly methotrexate dose, and dose^2 (estimates not shown owing to limited interpretability of quadratic terms).

which may incur detection bias, rendering their clinical outcomes less meaningful than the confirmed diagnoses utilized in our study. In one previous study, methotrexate-treated PsA patients had a higher incidence of transaminitis than RA patients.[10] Similarly, a meta-analysis that evaluated biopsy-proven liver fibrosis in methotrexate-treated RA or PsA/PsO patients found greater rates of advanced hepatic fibrosis in those with psoriatic disease after controlling for cumulative methotrexate dose.[7] In contrast, another study identified no differences in abnormal liver function tests among patients with PsO, PsA, and RA after adjusting for age, sex, and cumulative methotrexate dose.[11] However, these studies were limited by their small sample size and lack of full adjustment for confounding variables. In a more recent UK population-based cohort study using disease diagnoses as outcomes, PsO and PsA were associated with higher risk of incident liver disease relative to unaffected controls in both the absence and presence of systemic therapy use. The study adjusted for age, sex, smoking, alcohol use, BMI, and oral steroid and nonsteroidal anti-inflammatory drug use found that RA patients had an elevated risk of liver disease only in the absence of systemic therapy compared with that of non-RA controls.[12] While these findings indirectly suggested that liver disease risk differed among PsO, PsA, and RA patients receiving systemic therapy, our results now provide direct comparative evidence of

Table IV. Sensitivity analyses

Variable	Outcome, HR (95% CI) [Reference group: RA]			
	Mild liver disease	Moderate-to-severe liver disease	Cirrhosis	Hospitalization due to cirrhosis
Primary analysis				
PsO (vs RA)	2.22 (1.81-2.72)	1.56 (1.05-2.31)	3.38 (2.44-4.68)	2.25 (1.37-3.69)
PsA (vs RA)	1.27 (1.01-1.60)	0.93 (0.58-1.50)	1.63 (1.10-2.42)	1.17 (0.64-2.16)
Excluding viral, alcoholic, and autoimmune etiologies of liver disease				
PsO (vs RA)	2.46 (1.94-3.13)	1.48 (0.96-2.27)	3.09 (2.11-4.52)	1.89 (1.03-3.48)
PsA (vs RA)	1.59 (1.22-2.06)	0.94 (0.57-1.57)	1.61 (1.03-2.52)	1.02 (0.48-2.16)
Among patients without overlapping diagnoses				
PsO (vs RA)	1.17 (1.81-2.79)	1.62 (1.07-2.45)	3.56 (2.53-5.00)	2.70 (1.62-4.48)
PsA (vs RA)	2.25 (0.84-1.41)	0.72 (0.41-1.26)	1.48 (0.96-2.29)	0.90 (0.44-1.86)

CCI, Charlson Comorbidity Index; *CI*, confidence interval; *HR*, hazard ratio; *PsA*, psoriatic arthritis; *PsO*, psoriasis; *RA*, rheumatoid arthritis.

these findings in the setting of methotrexate use. Finally, our study covers a period of nearly 2 decades, longer than many previous studies. Although biologics have become available for PsO, PsA, and RA during this period, nationwide guidelines in Denmark require patients to fail conventional systemics, with nearly universal use of methotrexate, before starting biologics.[23] Additionally, national requirements for methotrexate monitoring include checking liver enzymes every 3 months, thus reducing the risk of changing surveillance practices over the study period.

We can only speculate on the reason behind the relative differences in liver disease risk among methotrexate-treated PsO, PsA, and RA patients. One possibility is that, although systemic inflammation in all 3 diseases induces metabolic changes that predispose the patient toward developing liver disease, additional exposure to hepatotoxic therapies differentially impacts psoriatic disease versus RA (ie, PsO interacts with methotrexate in a way that increases liver disease risk to a greater extent than RA does). Alternatively, it is possible that inflammation in PsO inherently induces greater liver injury than inflammation in RA, reducing the threshold for hepatotoxicity in methotrexate users. The concept of a "psoriatic liver," referring to an increased propensity for liver disease in PsO, has previously been recognized.[24] The mechanistic connections between PsO and liver disease, described as the "hepato-dermal axis," postulate that pro-inflammatory cytokines, such as IL-6, IL-17, and tumor necrosis factor-α, are produced by lymphocytes and keratinocytes derived from psoriatic skin and circulate to the liver to induce metabolic derangements such as insulin resistance that promote the development of NAFLD.[25,26] An inversion of this axis, whereby hepatic inflammation promotes keratinocyte proliferation and cutaneous inflammation in PsO, may also hold.[25] Finally, another possibility is that PsO, PsA, and RA have no inherent differences in terms of their effects on the liver, but methotrexate is more effective in reducing systemic inflammation in RA than in PsO, thereby leading to relatively greater reduction of liver disease risk in the former.

Our study additionally shows that the duration of methotrexate use was shortest for PsO patients, followed by PsA patients, and longest in RA patients. Although shorter treatment duration in psoriatic disease may be due to early development of liver disease, RA patients were still relatively less likely to develop liver toxicity despite receiving methotrexate for longer periods of time and reaching higher cumulative doses. Similar to our results, a clinic-based study in the Netherlands previously found that the first methotrexate treatment course was twice as short in PsO patients than in PsA patients.[8] A US claims database study also reported earlier discontinuation of methotrexate in new users with PsA compared with those with RA.[27] Given the greater risk of diagnosed liver disease in the PsO group, it is possible that drug discontinuations occurred earlier in this population owing to clinically significant liver disease and/or hepatoxicity identified on laboratory testing. However, since dermatology and rheumatology guidelines for methotrexate monitoring differ, dermatologists may perform more frequent laboratory monitoring, leading to the earlier identification of liver abnormalities, both genuine and spurious. It is also possible that drug discontinuation was more frequent in PsO owing to lack of treatment efficacy. Practice differences between dermatologists and rheumatologists can lead to lower methotrexate

dosing for PsO patients than for PsA and RA patients, resulting in decreased response to therapy in PsO patients.[28]

There are limitations to note. First, not all exposure and outcome definitions have been formally validated in the Danish national registries. However, similar approaches were utilized in other population-based studies, and a recent validation study of PsO using the Danish National Patient Register found >90% positive predictive value for the presence of 1 ICD-10 code.[29] Validation of CCI diagnoses in the Danish register shows >95% positive predictive value for ICD-10 codes for liver disease and connective tissue disease, including RA.[14] Although disease misclassification in patients with multiple underlying diseases (eg, PsO and PsA) is possible, sensitivity analyses including only patients with purely PsO, PsA, or RA led to similar findings. As disease severity data were unavailable, we could not examine the impact of PsO, PsA, or RA severity on liver disease risk. Although we did not directly account for folic acid use or potential variations in methotrexate administration (eg, daily, alternate day, or once-weekly dosing),[5,30] these concerns are mitigated by the uniform prescribing practices in Denmark, whereby methotrexate is always administered once weekly and folic acid is given 2 days postmethotrexate administration. While we adjusted for many confounders, confounding by unmeasured variables, such as BMI, remains a potential limitation as obesity is associated with psoriatic disease and liver disease. Although BMI is generally higher in PsO/PsA than RA, absolute differences are small.[12] External adjustment also suggests that BMI is unlikely to meaningfully impact our estimates. Surveillance bias is possible, as dermatologists may check liver function tests more frequently than rheumatologists.[6,8] However, rates of cirrhosis and cirrhosis-related hospitalization were also significantly higher in the PsO group; as these outcomes are less susceptible to detection bias alone, differential surveillance is unlikely to fully explain our findings. Finally, this study does not have the ability to distinguish if, and to what extent, liver disease is attributed to methotrexate use, the underlying disease, or a combination of both.

In summary, patients with psoriatic disease are more prone to liver complications than patients with RA in the setting of methotrexate use. These findings suggest that conservative liver monitoring is warranted in patients receiving methotrexate for psoriatic disease, particularly PsO. Future studies are needed to determine the mechanisms driving differences in liver disease risk among PsO, PsA, and RA patients.

Conflict of interest

Dr Gelfand has served as a consultant for Abcentra, BMS, Boehringer Ingelheim, Cara (DSMB), GSK, Lilly (DMC), Janssen Biologics, Novartis Corp, UCB (DSMB), Neuroderm (DSMB), Dr. Reddy's Labs, Pfizer Inc., and Sun Pharma, receiving honoraria; received research grants (to the Trustees of the University of Pennsylvania) from AbbVie, Boehringer Ingelheim, Janssen, Novartis Corp, Celgene, Ortho Dermatologics, and Pfizer Inc.; received payment for continuing medical education work related to psoriasis that was supported indirectly by Lilly, Ortho Dermatologics, and Novartis; is co-patent holder of resiquimod for treatment of cutaneous T cell lymphoma; serves as a deputy editor for the *Journal of Investigative Dermatology*, receiving honoraria from the Society for Investigative Dermatology; and is a member of the Board of Directors of the International Psoriasis Council, receiving no honoraria. Dr Wan has received a research grant and fellowship support (to the Trustees of the University of Pennsylvania) from Pfizer Inc. Dr Ogdie has served as a consultant for AbbVie, Amgen, BMS, Celgene, Corrona, Global Health Living Foundation, Janssen, Lilly, Novartis, Pfizer, and Takeda; received grants to the University of Pennsylvania from Pfizer and Novartis and to Forward from Amgen. Dr Syed has received fellowship support (to the Trustees of the University of Pennsylvania) from Pfizer Inc. Dr Egeberg has received research funding from Pfizer, Eli Lilly, Novartis, AbbVie, Janssen Pharmaceuticals, the Danish National Psoriasis Foundation, the Simon Spies Foundation, and the Kgl Hofbundtmager Aage Bang Foundation, and honoraria as consultant and/or speaker from AbbVie, Almirall, Leo Pharma, Samsung Bioepis Co., Ltd., Pfizer, Eli Lilly and Company, Novartis, Galderma, Dermavant, UCB, Mylan, Bristol-Myers Squibb, and Janssen Pharmaceuticals. Drs Zhang and Shin declare no conflicts of interest.

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