LIVER ABNORMALITIES IN PATIENTS WITH PSORIATIC ARTHRITIS

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ABSTRACT

Objective: We aimed to determine the prevalence and incidence, and identify the factors associated with liver abnormalities in patients with psoriatic arthritis (PsA).

Methods: From a longitudinal cohort study we identified PsA patients with either elevated serum transaminase or alkaline phosphatase levels or liver disease after the first visit to the PsA clinic (cases). Controls were subjects from the same cohort who never had such abnormalities or liver disease. Cases and controls were matched 1:1 by sex, age at the first clinic visit, and follow-up duration, variables at the onset of the first appearance of liver test abnormality associated with liver abnormalities were identified using univariate logistic and multivariate logistic regression analyses.

Results: Among 1061 patients followed in the PsA clinic, 343 had liver abnormalities. 256 patients who developed liver abnormalities after the first visit were identified as cases, 718 patients were identified as controls. The prevalence of liver abnormalities was 32% and the incidence was 39/1000 patient-years where there were 256 cases over 6533 total person years in the PsA cohort. Liver abnormalities were detected after a mean (s.d.) follow up duration of 8.3 ±7.8 years. The common causes of liver abnormalities were drug- induced hepatitis and fatty liver. Higher BMI, daily alcohol intake, higher damaged joint count, elevated CRP, use of methotrexate (MTX), leflunomide (LFN) or TNF inhibitors were independent factors associated with liver abnormalities.

Conclusion: Liver abnormalities are common among patients with PsA and are associated with higher BMI, more severe disease and certain therapies.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory disease which affects the skin and musculoskeletal system. PsA patients frequently suffer from comorbidities including premature cardiovascular disease (CVD), metabolic syndrome, inflammatory bowel disease (IBD), liver disease, osteoporosis, malignancy, and ophthalmic disease. Among psoriasis patients, the prevalence of biochemical liver abnormalities has been reported as 24-36%[1-3]. The commonest factor associated with liver abnormalities in psoriatic disease is non-alcoholic fatty liver disease (NAFLD)[2]. The prevalence of NAFLD in psoriasis patients (17.4-59%) is two folds higher compared to the general population (7.9-28%)[4-7] The reported risk factors associated NAFLD in psoriasis patients include obesity, metabolic syndrome, duration of psoriasis, PsA, severity of psoriasis or PsA, and level of high-sensitivity C-reactive protein (hs-CRP)[4-7]. Furthermore, psoriasis patients had more severe NAFLD than non-psoriasis NAFLD patients[4,7].

Liver abnormalities can result from the medications used to treat PsA (e.g. methotrexate (MTX) and leflunomide (LEF)). Fifteen to thirty-five percent of PsA patients initiating disease-modifying anti-rheumatic drugs (DMARDs) developed biochemical liver abnormalities which was 2.76-4 fold more likely in PsA patients compared to rheumatoid arthritis (RA) patients[8,9]. In addition, the hepatotoxicity of tumor necrosis factor (TNF) inhibitors is still debated. However, a recent study showed TNF inhibitors had a protective effect against the development of liver fibrosis in PsA patients[10]. Among the liver comorbidities in psoriasis patients, viral hepatitis is of particular interest as it is a relative contraindication for biologic therapies[11].

Our aims were to determine the prevalence and incidence of liver abnormalities among patients with PsA, and identify the factors associated with liver abnormalities in these patients.

MATERIALS AND METHODS

Study design

We used a cohort study to define the prevalence of liver abnormalities followed by a nested case control study.

Study Population

Setting

The study was conducted at the University of Toronto Psoriatic Arthritis Clinic where patients have been followed prospectively since 1978. Other forms of inflammatory arthritis are ruled out at the initial evaluation to the PsA clinic[12]. The majority (98%) of the patients fulfill the classification of Psoriatic Arthritis (CASPAR) criteria for PsA[13,14]. Patients are assessed at 6-12 month intervals according to the standard protocol that consists of a detailed history, physical examination, and laboratory evaluation. Liver enzymes are measured and recorded at every protocol visit. All data are entered into a database.

Patient Selection

Cases were selected from the PsA program database and included patients who had either liver biochemical abnormalities or liver disease documented after the first evaluation at the clinic. Control subjects were selected from the same database and included patients who never had any liver test abnormality or any liver disease during the follow-up. For the matched case-control study, each case were matched to each control by sex, age at the first evaluation in the clinic (± 5 years), and follow-up duration (time from the first evaluation to the first appearance of liver abnormalities for the cases and the duration from the first evaluation to an evaluation date of equivalent duration (± 2 years) for controls), to identify factors at the onset of the first appearance of liver test abnormality which were associated with liver abnormalities.

Liver Abnormalities

Liver biochemical abnormalities were defined by elevated transaminases ≥ 1.5 times the upper limit of normal (ULN) (aspartate transaminase (AST) ≥ 56 IU/l and/or alanine transaminase (ALT) ≥ 74 IU/l and/or alkaline phosphatase (ALP) ≥ 197 IU/l in males; aspartate transaminase (AST) ≥ 47 IU/l and/or alanine transaminase (ALT) ≥ 66 IU/l and/or alkaline phosphatase (ALP) ≥ 209 IU/l in females). Liver diseases included drug induced liver injury, fatty liver, viral hepatitis, autoimmune liver disease, alcoholic liver disease, liver fibrosis, and cirrhosis. The diagnosis of liver disease was confirmed by gastroenterologist and/or was based on an imaging study (liver ultrasound, fibroscan, computerized tomography (CT) scan, magnetic resonance imaging (MRI)), viral and autoimmune serology, and histological findings on liver biopsy. The diagnosis of drug induced liver injury was based on the presence of potential drug taken at least one visit prior to detection of liver abnormality with the reasonable exclusion of other etiologies and resolution of those abnormalities after the potential drug discontinuation. Diagnosis of viral hepatitis was based on the presence of hepatitis A IgM antibody (anti-HAV IgM), hepatitis C antibody (anti-HCV), hepatitis C virus RNA detection (HCV-RNA), hepatitis B surface antigen (anti-HBs), hepatitis B core IgM antibody (anti-HBc IgM), hepatitis B virus DNA detection (HBV-DNA). Diagnosis of autoimmune hepatitis was based on the presence of anti-nuclear antibody (ANA), anti-smooth muscle antibody (SMA), anti-liver kidney microsomal antibody type 1 (anti-LKM-1), immunoglobulin G (IgG), absence of viral hepatitis or abnormal liver histology[15]. NAFLD was defined by evidence of hepatic steatosis, either by imaging or by histology when there was no other explanation such as significant alcohol consumption, medication or hereditary disorders. We defined alcohol induced hepatitis by history of significant long stranding alcohol intake during the time that abnormal transaminases were detected.

Data Collection

Demographic data were collected at the patients' first evaluation at the clinic including sex, ethnicity, year of entry, age, disease duration and comorbidities (hypertension, diabetes, hyperlipidemia, body mass index (BMI)) as well as sociodemographic variables including employment status and alcohol use. Disease activity was determined by psoriasis severity (Psoriasis Area and Severity Index (PASI), score 0-72)[16] total number of swollen joints (SJC), number of tender joints (TJC). Severity was defined by the total number of clinical damaged joints. Past and current medications, including non-steroidal anti-inflammatory drugs (NSAIDs), disease modifying anti-rheumatic drugs (DMARDs), and biologic agents were also included. Laboratory data included erythrocyte sedimentation rate (ESR), hs-CRP, CRP, and serology. Seropositivity for anti-nuclear antibody (ANA) was defined as a titer of ≥ 1:80, and seropositivity for rheumatoid factor (RF) was defined as a level > 40 IU/ml. Elevation of hs-CRP and CRP were defined as a level > 1 and 3 mg/l, respectively. Elevation of ESR was >13mm/h in males and >20mm/h in females. To identify the factors associated with liver abnormalities, these variables were also collected at the onset of the first appearance of liver test abnormality in the matched case-control study.

Statistical Analysis

Descriptive statistics were presented by mean ± standard deviation (SD) and count (%). Differences among groups for continuous variables were tested using t-test/Wilcoxon rank sum test and discrete variables were tested using Chi-square statistics. Normality assessment was done using the Shapiro-Wilk test. In the matched case-control analysis, the factors associated with liver abnormalities were evaluated at the first appearance of liver test abnormality. We performed a Generalized Estimating Equation analysis. A conditional univariate logistic regression was first

performed on each of the variables as a predictor of the binary outcome (Case vs. Control). All variables with a p-value less than 0.3 in the univariable regression analysis were selected for the multivariable regression analysis. Subsequently, backward stepwise elimination was performed to obtain a reduced model. The statistical significant difference for consideration is $p<0.05$. SAS (version 9.3; SAS Institute, Cary, NC, USA) was used for all statistical analyses.

Ethical review and approval was obtained from the University Health Network Research Ethics Board (08-0630). Informed consent was collected from all patients at enrollment.

RESULTS

The prevalence and the incidence of liver abnormalities in PsA patients

Among the 1061 patients followed in the PsA clinic, 343 had liver abnormalities, providing a prevalence of liver abnormalities was 32%. Of those 343 patients with liver abnormalities, 256 patients developed these abnormalities after their first evaluation at the clinic. The incidence of liver abnormalities was 39/1000 patient-years. A total of 718 patients who had liver enzymes within the normal range and without any liver disease during follow-up were identified as controls.

Patient characteristics

Characteristics of PsA cases and controls at their first evaluation at the clinic are shown in **Table 1**. Most of the patients (85%) were Caucasian. There was no difference between the two groups with regards to sex, age at diagnosis of psoriasis or PsA, or duration of psoriasis or PsA at first visit. Daily alcohol intake was significantly higher in cases compared to controls. More cases were employed compared to controls. SJC, TJC and use of NSAIDs were significantly higher in cases compared to controls, and more cases had hypertension compared to controls.

Liver abnormalities in PsA patients

Among 256 PsA patients, liver abnormalities occurred after 8.3 ±7.8 years of follow-up. The mean age of PsA patients at the onset of liver abnormalities was 50.5 ±12.8 years. Eleven percent of cases took alcohol daily. The duration of psoriasis and PsA at the onset of liver abnormalities were 21.9±13.9, 13.8±10.9 years, respectively. The mean PASI score, active joint count, and clinically damage joint count were 4.0±6.4, 5.4±9.7, and 6.9±12, respectively. The average BMI was 29.7 ± 7.8 kg/m² and hypertension was found in 52% of cases. A half of cases used NSAIDs (47%) or DMARDs (51%) at the onset of liver abnormalities. Only 29 percent of cases had an identified cause of liver abnormalities or liver disease. The commonest causes of liver abnormalities were drug-induced hepatitis (14%) and fatty liver (13%). Only two cases were reported to have cirrhosis. Drug induced hepatitis occurred in 36/256 patients (MTX (18 cases), LFN (7 cases), sulfasalazine (1 case), diclofenac (2 cases), naproxen (2 cases), ibuprofen (1 case), indomethacin (1 case), celecoxib (1 case), adalimumab (1 case), acetaminophen (1 case), pravastatin (1 case)). Five cases (2%) of viral hepatitis were reported: hepatitis A (1 case), hepatitis B (1 case), hepatitis C (1 case), and Epstein-Barr virus (2 cases). Alcohol induced hepatitis was reported in 10/256 patients (4%). Further investigations were done only in 20 cases with liver biochemical abnormalities. The findings on liver fibroscan (12 cases) showed grade 0 (3 cases), grade 1 (6 cases), and grade 3 (3 cases). The liver ultrasound findings revealed fatty liver in 18 cases. Liver biopsy was performed in 5 cases and showed fatty liver in 4 cases and fibrosis in 1 case. Most of patients (151 cases) had only one visit with liver biochemical abnormalities (transient abnormalities), while 105 cases had persistent or recurrent liver biochemical abnormalities. PsA patients with transient liver biochemical abnormalities had less evidence of liver disease (23% VS 38%, $p < 0.001$) and fatty liver (5% VS 20%, $p < 0.001$) compared to PsA patients with persistent or recurrent liver biochemical abnormalities.

Factors associated with liver abnormalities in PsA patients

To determine the factors at the first appearance of liver test abnormalities which contributed to liver abnormalities we matched 204 cases to 204 controls on age, sex, and duration of follow-up. Characteristics and disease associated features at the onset of liver abnormalities in the matched case-control study are showed in **Table 2**. Duration of psoriasis and PsA were significantly longer in cases compared to controls. Cases had significantly higher clinically damage joint count and ESR compared to controls. Hypertension, hyperlipidemia and higher BMI were significantly more prevalent in cases. The use of NSAIDs was significantly less common in the cases; however, TNF inhibitors were commonly used in cases than in controls.

In univariable analysis, the variables associated with liver abnormalities were employment (OR 0.34, 95% CI 0.22-0.55, p< 0.0001), clinically damaged joint count (OR 1.05, 95% CI 1.02-1.07, p=0.0001), duration of psoriasis (OR 1.02, 95% CI 1.01-1.04, p=0.005), duration of PsA (OR 1.08, 95% CI 1.05-1.11, p < 0.0001), ESR (OR 1.02, 95% CI 1.00-1.03, p=0.03), hypertension (OR 3.33, 95% CI 2.05-5.43, p< 0.0001), hyperlipidemia (OR 2.50, 95% CI 1.45-4.32, p=0.001), BMI (OR 1.04, 95% CI 1.00-1.09, p=0.04), use of TNF inhibitors (OR 1.67, 95% CI 1.08-2.57, p= 0.02) **(Table 3).** However, in the multivariable analysis, BMI (OR 1.07, 95% CI 1.02–1.12, p= 0.007), daily alcohol intake (OR 4.46, 95% CI 1.30-15.28, p=0.02), damaged joint count (OR 1.04, 95% CI 1.01–1.08, p= 0.01), elevated CRP (OR 2.00, 95% CI 1.04-3.85, p=0.04), use of MTX/LFN (OR 4.39, 95% CI 1.67-11.54, p=0.003), use of TNF inhibitors (OR 10.56, 95% CI 3.63-30.69, p < 0.0001) were independent factors associated with liver abnormalities in PsA patients after adjusting for others covariates**.**

DISCUSSION

In our large longitudinal cohort study, we found the prevalence and the incidence of liver abnormalities were 0.32 and 0.039 patient-years of follow-up, respectively. The prevalence is comparable with previous studies among psoriasis patients of 24-36%[1,2]. The common causes of liver abnormalities in our cohort were drug induced hepatitis and fatty liver disease which were in agreement with the findings observed in a psoriasis study[2]. Higher prevalence of liver abnormalities in PsA patients could be related to more wide-spread use of hepatotoxic agents such as MTX or LFN. Candia R. *et al* found that the risk of NAFLD was significantly higher in psoriasis patients with PsA (OR: 2.25, 95% CI: 1.37-3.71)[6]. A similar observation was noted by Ogdie et al.[17], who noted the risk for liver disease was higher among PsA patients than psoriasis alone or rheumatoid arthritis patients. In our study, most of liver biochemical abnormalities were transient and rarely lead to liver fibrosis or cirrhosis.

We demonstrated an association between higher BMI and liver abnormalities in PsA patients. This finding was noted by Rahmioglu N *et al*, who showed that the variation in the liver biochemical abnormalities were associated with BMI in both males and females in a twin pair cohort study which included 5380 subjects[18]. These results could be explained by the relationship between BMI and NAFLD. Chang Y *et al* demonstrated an increasing baseline BMI had a strong linear relationship with NAFLD among a cohort study of 77,425 metabolically healthy obese individuals (MHO) who were followed-up for 4.5 years and NAFLD determined by using ultrasound[19]. An observational cohort study of the incidence of moderate liver toxicity (≥ 1.5 x ULN) of MTX in the management of rheumatic disease also identified BMI (≥ 30 kg/m²) as a predictor of liver biochemical abnormalities[20]. A systematic review conducted by Montaudie H *et al*, revealed that

obesity was associated with a significant increased risk of liver fibrosis in psoriasis patients receiving MTX[21].

Alcohol consumption contributes to a variety of liver diseases, either by causing alcoholic liver disease or as the aggravating factor in chronic viral hepatitis, NALFD and drug induced hepatitis. We found PsA patients who took alcohol daily were more likely to have liver abnormalities than those who did not or were occasional alcohol consumers. Among rheumatoid arthritis patients receiving MTX or LFN, daily alcohol use (1-2 drinks per day) was associated with ALT/AST elevation compared to none/occasional use (OR 1.97; 95% CI 1.18-3.28).[7] Malatjalian *et al* demonstrated that occasional alcohol consumption (≤3 drinks per week) was not associated with increased risk of MTX hepatotoxicity in psoriasis patients[22]. Humphreys *et al* showed that among 11839 rheumatoid arthritis patients taking MTX and weekly alcohol consumption of less than 14 units per week was no increased risk of transaminitis[23]. However, more than 21 units per week of alcoholic drinking were associated with a significant risk of transaminitis. This result was supported by the study of Laharie, D. *et al.*[24] which found that high alcohol consumption (> 14 units per week) was associated with severe liver fibrosis among patients diagnosed with chronic inflammatory disorders who were receiving MTX.

The chronic inflammatory process from psoriatic disease itself was also associated with the increase prevalence of liver damage, NAFLD, and liver fibrosis compared with non-psoriatic patients or general population. Significant factors associated with NAFLD in psoriatic patients include longer duration of psoriatic disease and greater severity of psoriasis assessed by PASI score[3-6]. PsA patients who achieved minimal disease activity after receiving TNF inhibitors for 12 months exhibited lower incidence of worsening liver steatosis compared with PsA patients with persistently active disease[25]. We found that a higher damaged joint count and elevated CRP level

were associated with liver abnormalities. Associations between high BMI and joint damage and the presence of liver abnormalities may be mediated through Tumor necrosis factor alpha (TNF-α) and insulin resistance. TNF-α is found in skin and synovial tissue and TNF-α levels have been elevated in active, severe psoriatic disease[26,27]. Moreover, TNF-α mediates matrix metalloproteinases which lead to cartilage and joint destruction[28]. TNF-α promotes insulin resistance and induces transforming growth factor ß and connective growth factor which have been implicated in the development of NAFLD and contribute to hepatic fibrosis[29,30]. In addition, an elevation of hs-CRP, a marker of chronic inflammation, has been reported as the predictor of NAFLD[31]. This concept is supported the report by Campanati A *et al* who found that moderate-severe psoriasis patients with NAFLD receiving etanercept had significant reduction in the risk of the development of hepatic fibrosis compared with patients receiving psoralen and UVA (PUVA) therapy[32].

We found that PsA patients receiving methotrexate or leflunomide were more likely to have liver abnormalities than patients who were not taking these medications. This is not surprising since both are associated with hepatotoxicity. Previous studies showed that 14.5-35% of PsA patients receiving methotrexate had elevated AST/ALT levels and PsA patients had a 2.7-4 fold greater likelihood of these abnormalities compared to RA patients[8,9]. Furthermore, PsA patients with high cumulative dose of MTX had a prevalence of liver fibrosis of 22% which related to the number of risk factors that contributed to liver fibrosis or NAFLD (excessive alcohol consumption, diabetes, obesity, renal impairment)[33]. Higher incidence rates of elevated ALT level were found in PsA patients receiving LFN (12.5%) compared to placebo (5.4%) in a multinational, double-blind, randomized, placebo-controlled clinical trial. Only a few patients were withdrawn from the study

because of ALT levels above 3 times the ULN and no cases of severe liver toxicity were reported in leflunomide-treated patients[34].

The hepatotoxicity of TNF inhibitors is still inconclusive. Our study showed TNF inhibitors are associated with the incidence of liver abnormalities in PsA patients. However, it should be noted that the majority of the patients had had their conventional DMARDs prior to the anti-TNF agents, and it is possible that in patients with liver disease the anti-TNF agents were used instead of conventional DMARDs to avoid worsening of liver disease. Randomized clinical trials with anti-TNF agents reported few discontinuations due to increased ALT/AST[35-39]. Nonetheless, several cases of psoriasis with AIH triggered by TNF inhibitors were reported in the literature[40]. Two of the TNF inhibitors observed in the literature were infliximab and adalimumab and the onset of liver damage occurred between 4 - 26 weeks. All patients discontinued TNF inhibitors and treated with glucocorticosteroids (± azathioprine). Anti-nuclear antibody (ANA) was expressed in all patients and liver abnormalities were resolved within 3 months after treatment. However, our study did not show the association between positivity of ANA and liver abnormalities and no AIH was reported.

Although we studied a large number of PsA patients in our cohort, we could only identify an etiology for the liver biochemical abnormalities in 30%. Only NAFLD was identified in only 13% of PsA cases which is less than the previous studies of psoriasis[4-7].

In conclusion, liver abnormalities are commonly found in PsA patients. We found that higher BMI, daily alcohol intake, higher damaged joint count, elevated CRP, use of MTX/LFN or TNF inhibitors are associated with the development of liver abnormalities in PsA patients. We recommend monitoring liver function tests in these high risk PsA patients. This is important in the

management of patients with PsA as many of the therapeutic options may aggravate or even lead to liver abnormalities in this patient population.

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Contributors: All authors were involved in the study conception and design, acquisition of data as well as analysis and interpretation of data. All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Gladman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1. **Characteristics and disease related features and treatment profiles of psoriatic arthritis (PsA) case and control populations at the first evaluation at the clinic.**

Variables	Case, n = 256	Control, n = 718	P-value
Sex, n (%)			0.36
Female	111 (43)	335 (47)	
Male	145 (57)	383 (53)	
Ethnicity, n (%)			0.97
Caucasian	217 (85)	608 (85)	
Other	39 (15)	110 (15)	
Decade of study, n (%)			<0.001
1978-1987	43 (17)	188 (27)	
1988-1997	59 (23)	89 (13)	
1998-2007	92 (36)	186 (27)	
2008-2016	61 (24)	232 (33)	
Age at baseline (mean ± SD, year)	42.6 (11.9)	43.1 (13.5)	0.58
Age at diagnosis of psoriasis (mean ± SD, year)	28.4 (13.9)	27.7(14.6)	0.50
Age at diagnosis of PsA (mean ± SD, year)	36.6 (12.5)	37.3 (13.9)	0.48
Duration of psoriasis (mean ± SD, year)	14.1 (12.6)	15.4 (12.6)	0.15
Duration of PsA (mean ± SD, year)	6 (8)	5.9 (7.9)	0.87
Daily alcohol intake, n (%)	30 (13)	43 (8)	0.04
Employment, n (%)	142 (55)	323 (45)	0.004
PASI score (mean ± SD)	4.5 (8.9)	3.4 (6.1)	0.03
Active (swollen or tender) joint count (mean ± SD)	10.4 (10.1)	8.7 (10.1)	0.02
Clinically damage joint count (mean ± SD)	2.8 (7.5)	2.0 (5.6)	0.08
Erythrocyte sedimentation rate (mean ± SD, mm/h)	22.5 (20.1)	21.0 (19.8)	0.31
Elevated CRP, n (%)	56 (22)	161 (22)	0.86
Positive rheumatoid factor, n (%)	13 (5)	63 (10)	0.025

Positive anti-nuclear antibody, n (%)	**24 (9)**	**52 (7)**	**0.27**
Hypertension, n (%)	**127 (50)**	**163 (23)**	**<0.001**
Hyperlipidemia, n (%)	**17 (7)**	**37 (5)**	**0.37**
Diabetes, n (%)	**14 (5)**	**35 (5)**	**0.71**
Body mass index (mean ± SD, kg/m²)	**29.0 (7.8)**	**27.9 (6.9)**	**0.10**
Use of NSAIDs, n (%)	**198 (77)**	**491 (68)**	**0.01**
Use of non-biological DMARDs, n (%)	**122 (48)**	**314 (44)**	**0.28**
Use of biologic, n (%)	**26 (10.2)**	**59 (8.2)**	**0.35**

PASI: Psoriasis Area and Severity Index; SJC: swollen joint count; TJC: tender joint count; hs-CRP: High-sensitivity C-reactive protein; NSIADs: non-steroidal anti-inflammatory drugs; DMARDs: disease-modifying anti-rheumatic drugs.

Table 2. **Characteristics and disease related features and treatment profiles of the cases and their matched controls (204 pairs) at the onset of liver abnormalities.**

Variables	Case (N= 204)	Control (N=204)	P-value
Caucasian, n (%)	168 (82)	168 (82)	1.00
Duration of psoriasis (mean ± SD, year)	25.1 (14.7)	21.3 (13.8)	0.009
Duration of psoriatic arthritis (mean ± SD, year)	16.5 (11.2)	10.4 (10.3)	<0.001
Daily alcohol intake, n (%)	19 (10)	12 (6)	0.14
Employment, n (%)	89 (44)	135 (66)	< 0.001
PASI score (mean ± SD)	4.0 (7.3)	3.5 (5.3)	0.40
Active (swollen or tender) joint count (mean±SD)	4.8 (8.6)	3.4 (6.1)	0.06
Clinically damage joint count (mean ± SD)	8.3 (13.1)	3.4 (7.8)	<0.001
Erythrocyte sedimentation rate (mean ± SD, mm/h)	16.9 (17.4)	13.8 (12.4)	0.04
Elevated CRP, n (%)	77 (38)	67 (33)	0.30
Positive rheumatoid factor, n (%)	6 (3)	3 (2)	0.36
Positive anti-nuclear antibody, n (%)	31 (15)	27 (13)	0.57
Hypertension, n (%)	115 (56)	66 (32)	<0.001
Hyperlipidemia, n (%)	51 (26)	25 (12)	<0.001
Diabetes, n (%)	25 (13)	16 (8)	0.12
Body mass index (mean ± SD, kg/m²)	30.1 (6.5)	28.7 (5.6)	0.03
Use of NSAIDs, n (%)	41 (20)	59 (29)	0.04
Use of non-biological DMARDs, n (%)	83 (41)	71 (35)	0.22
Use of TNF inhibitors, n (%)	92 (45)	70 (37)	0.03

PASI: Psoriasis Area and Severity Index; hs-CRP: High-sensitivity C-reactive protein; NSIADs: non-steroidal anti-inflammatory drugs; DMARDs: disease-modifying anti-rheumatic drugs; TNF inhibitors: tumor necrosis factor inhibitors.

Table 3. **Univariate analysis of factors associated with liver abnormalities in the matched case-control study in psoriatic arthritis (PsA) cohort.**

Variables	OR (95%CI)	p-value
Duration of psoriasis (year)	1.02 (1.01-1.04)	0.005
Duration of PsA (year)	1.08 (1.05-1.11)	<0.0001
Daily alcohol intake	1.70 (0.78-3.71)	0.18
Employment	0.34 (0.22-0.55)	<0.0001
PASI score	1.01 (0.98-1.04)	0.41
Active (swollen or tender) joint count	1.03 (0.99-1.06)	0.06
Clinically damage joint count	1.05 (1.02-1.07)	0.0001
Erythrocyte sedimentation rate	1.02 (1.00-1.03)	0.03
Elevated CRP	1.27 (0.83-1.95)	0.28
Positive rheumatoid factor	2.50 (0.49-12.89)	0.27
Positive anti-nuclear antibodies	1.18 (0.67-2.09)	0.56
Hypertension	3.33 (2.05-5.43)	<0.0001
Hyperlipidemia	2.50 (1.45-4.32)	0.001
Diabetes	1.64 (0.85-3.19)	0.14
Body mass index	1.04 (1.00-1.09)	0.04
Use of NSAIDs	0.63 (0.40-0.99)	0.05
Use of MTX/LFN	1.28 (0.86-1.91)	0.23
Use of TNF inhibitors	1.67 (1.08-2.57)	0.02

PASI: Psoriasis Area and Severity Index; SJC: swollen joint count; TJC: tender joint count; hs-CRP: High-sensitivity C-reactive protein; NSIADs: non-steroidal anti-inflammatory drugs; MTX: methotrexate; LEF: leflunomide; TNF inhibitors: tumor necrosis factor inhibitors.