

CLINICAL REPORT

Increased Prevalence of Advanced Liver Fibrosis in Patients with Psoriasis: A Cross-sectional Analysis from the Rotterdam Study

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Prevalence of non-alcoholic fatty liver disease is increased in patients with psoriasis. However, it is not known how liver fibrosis correlates with psoriasis. This study investigated the association between psoriasis and liver fibrosis compared with participants without psoriasis within the population-based Rotterdam Study. All participants were screened for liver fibrosis using transient elastography. Liver stiffness >9.5 kPa suggested advanced liver fibrosis. Psoriasis was identified using a validated algorithm. A total of 1,535 participants were included (mean age ± standard deviation 70.5 ± 7.9 years; 50.8% female; median body mass index 26.4 kg/m² (interquartile range 24.2–28.9)) of whom 74 (4.7%) had psoriasis. Prevalence of advanced liver fibrosis was 8.1% in psoriasis patients compared with 3.6% in the reference group ($p=0.05$). The risk of advanced liver fibrosis in psoriasis patients remained comparable after adjustment for demographics, lifestyle characteristics and laboratory findings (odds ratio 2.57 (95% confidence interval 1.00–6.63)). This study suggests that elderly people with psoriasis are twice as likely to have advanced liver fibrosis irrespective of common risk factors. *Key words:* liver fibrosis; non-alcoholic fatty liver disease; psoriasis; comorbidity; metabolic syndrome; transient elastography.

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In psoriasis patients the prevalence of non-alcoholic fatty liver disease (NAFLD) is 46–59% (1, 2). NAFLD encompasses a wide spectrum of liver damage, ranging from simple fatty liver to advanced fibrosis including liver cirrhosis and complications, such as portal hypertension and hepatocellular carcinoma.

Remarkably, no data are available on the prevalence of advanced liver fibrosis in patients with psoriasis. Based on an increased prevalence of NAFLD in patients with psoriasis, an increased prevalence of advanced liver fibrosis is

expected. Furthermore it has been observed that patients with psoriasis are more likely to develop methotrexate (MTX)-induced liver toxicity compared with patients with rheumatoid arthritis and Crohn's disease (3, 4).

For our study, we used data from the Rotterdam Study, an on-going large prospective population-based cohort study in middle-aged and elderly participants. The specific design of the Rotterdam Study provides the opportunity to evaluate liver disease in all participants independent of their health status, using transient elastography (TE; Fibroscan[®], EchoSens, Paris, France).

The main objective of our study is to investigate whether participants with psoriasis have a higher risk of advanced liver fibrosis, as measured by TE, compared with participants without psoriasis in the population-based Rotterdam Study (5), and how this association is affected by known risk factors for liver fibrosis. In addition, we performed subgroup analyses for participants with NAFLD.

METHODS

Study population

The current study was conducted within the Rotterdam Study, which started in January 1990 (5). All inhabitants, aged 55 years and older, living in Ommoord, a district in Rotterdam, the Netherlands, were invited to participate. The study design has been described previously; its main rationale is to study factors that determine the occurrence of chronic diseases in elderly people (5). TE was added to the core protocol in January 2011 and ultrasound was included in the fifth survey of the Rotterdam Study (February 2009–February 2012), which constitutes the baseline survey for the present study. Clinical skin examinations for screening dermatological conditions started in September 2010. In addition, each participant completed an extensive interview, fasting blood was collected, and anthropometric measurements were conducted. Detailed information on drug prescriptions were derived from automated pharmacies, in which most participants (98%) are registered.

Assessment of psoriasis

Psoriasis was diagnosed either by trained physicians in dermatology at the research centre, or by records of general practitioners (GP). Among participants who were seen at the research centre a Psoriasis Area and Severity Index (PASI) was conducted. Hard copy and electronic medical records of all par-

ticipants using anti-psoriatic drugs or who had a diagnostic code for psoriasis were screened for a diagnosis of psoriasis in general practitioners' notes, medical specialist reports and hospital discharge letters. Participants with a history of possible anti-psoriatic drug use, but without a diagnosis of psoriasis, were excluded from the analysis. A more detailed description of this selection process has been described previously (6). Participants without psoriasis were defined as the reference cohort.

The date of onset of psoriasis was the date of first diagnosis of psoriasis in the medical records, first anti-psoriatic medication available in the pharmacy database, or the self-reported date of onset, whichever came first.

Diagnosis of liver fibrosis

Measurement of liver stiffness was performed using TE (Fibroscan, EchoSens) by a single, certified and experienced operator. The right lobe of the liver was assessed through the intercostal space in patients lying on their back with the right arm in maximal abduction. The examination lasted approximately 5–10 min. If the distance from the skin to the liver was more than 2.5 cm an XL-probe was used instead of the normal M-probe. The liver stiffness measurement (LSM) was expressed in kilopascals (kPa). TE was considered reliable if ≥ 10 validated measurements were recorded with at least 60% success rate and the interquartile range (IQR) was less than 30% of the median LSM. LSM >9.5 kPa was used as a cut-off for the presence of advanced liver fibrosis and >13 kPa was used for cirrhosis. This cut-off level was deliberately chosen because it yields a high positive predictive value for the presence of advanced fibrosis in various liver diseases, including (N)AFLD (7, 8).

Diagnosis of non-alcoholic fatty liver disease

Abdominal ultrasonography was performed by certified and experienced technicians, using Hitachi HI VISION 900 in all study participants. Images were re-evaluated by a hepatologist (JNLS) with more than 10 years experience in ultrasonography. The diagnosis of fatty liver was made based on specific ultrasound criteria according to the protocol by Hamaguchi et al. (9). Participants with any of the following possible secondary causes of fatty liver were excluded from the NAFLD analyses: (i) excessive alcohol consumption; (ii) positive hepatitis B surface antigen (HBsAg) or anti-hepatitis C virus (anti-HCV); or (iii) use of oral pharmacological agents historically associated with fatty liver (i.e. amiodarone ($n=13$), corticosteroids ($n=28$), MTX ($n=0$), and tamoxifen ($n=2$)).

Co-variables (for complete version see Appendix S1¹)

Participants were interviewed at home using a standardized questionnaire to obtain data on demographics, medical history, comorbid conditions, smoking behaviour, alcohol intake and (prior) drug use. Anthropometric measurements were performed by well-trained nurses. Body mass index (BMI) was calculated as weight (kg)/height (m²). Fasting blood samples were collected on the morning of ultrasound examination.

Metabolic syndrome was defined, according to Adult Treatment Panel III criteria, as the presence of at least 3 of 5 traits.

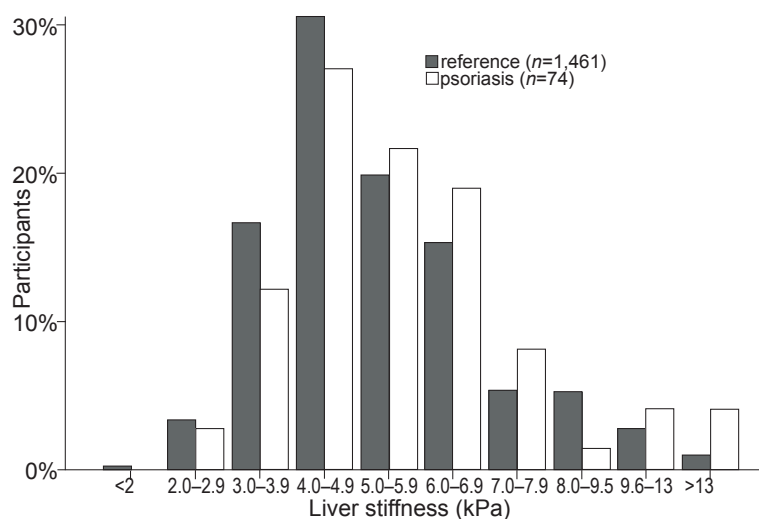


Fig. 1. Distribution of reliable measurements of liver stiffness in psoriasis and reference participants. Transient elastography (TE) was used to measure liver stiffness ($p=0.08$).

Statistical analysis

The statistical significance of differences in distribution of categorical data and continuous data between participants with and without psoriasis was determined using χ^2 tests, Student's t -tests or Wilcoxon rank-sum tests. For further details see Appendix S1¹.

RESULTS

Study population

TE and conclusive psoriasis data were available for 2,466 participants of the Rotterdam Study (flowchart Fig. S1¹). From this population 1,535 participants had a reliable TE (62.2%), which was similar between the psoriasis and reference population. Participants with a pacemaker (1.4%), an unreliable TE (27.9%) or failure of the TE (9.8%) were excluded. The proportion of overweight and obese participants was significantly higher among those with failure of the TE (88.7%, $p<0.001$) or unreliable TE (74.9% $p<0.001$) compared with those with a reliable TE (64.8%). Regarding reliability of TE, no differences were observed between the psoriasis and reference populations.

Of 1,535 participants, 74 (4.8%) had psoriasis; the remaining 1,461 were defined as the reference population. The distribution of age and sex was comparable between both groups, and the majority were Caucasian. Metabolic syndrome and obesity (BMI and waist circumference) were not significantly different between the participants with psoriasis and the reference population, although the metabolic syndrome was slightly more prevalent in the participants with psoriasis (Table I). At the time of the analyses the median disease duration of psoriasis was 11.2 years (IQR 15.8 years) and no participant was using systemic anti-psoriatic drugs. Furthermore, by then almost half of the patients with psoriasis had received a dermatological examination at the research centre, and had a median PASI score of

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2.0 (IQR 3.2), representing a population with predominantly mild psoriasis.

Liver fibrosis evaluation

The risk factors for liver fibrosis were generally comparable between participants with and without psoriasis (Table I). However, the prevalence of steatosis, diagnosed by ultrasonography, was greater in participants with psoriasis vs. the reference population (44.3% vs. 34.0%, respectively, $p=0.02$) (Fig. S1¹). The prevalence of advanced fibrosis, defined as a LSM >9.5kPa, was 8.1% in the psoriasis participants and 3.6% in the reference participants, which is an almost 2.5 times higher risk of advanced fibrosis for participants with psoriasis (crude OR 2.39; 95% CI 0.99–5.76). Distribution of reliable measurements of liver stiffness in psoriasis and reference participants (Fig. 1). The characteristics of participants with psoriasis with advanced fibrosis are summarized in Table SI¹.

After adjustment for age and sex, psoriasis remained associated with advanced liver fibrosis (LSM >9.5kPa) (adjusted OR 2.36, 95% CI 0.95–5.85). The

OR increased slightly to 2.57 (95% CI 1.00–6.63) after additional adjustment for age, sex, alcohol consumption, ALT, presence of the metabolic syndrome and steatosis in a multivariable logistic regression model (Table SII¹).

Linear regression analysis also showed that psoriasis is a predictor for the severity of fibrosis measured as log-LSM (crude β 0.04, standard error (SE) 0.02, $p=0.03$). After adjusting for age, sex, alcohol consumption, ALT and presence of the metabolic syndrome and steatosis this correlation remained the same (adjusted β 0.04, SE 0.02, $p=0.04$).

Non-alcoholic fatty liver disease population

A subgroup analysis was performed for participants with NAFLD. Of 2,502 participants, 400 were excluded because of the presence of secondary causes of liver steatosis. One-third of the remaining 2,102 participants had NAFLD ($n=704$), and of these 39 (5.5%) had psoriasis. In this subgroup analysis 395 participants had reliable TE data (56%). The psoriasis participants were significantly older (74 vs. 70 years $p=0.02$) than the

Table I. General characteristics of the study population stratified by psoriasis and non-alcoholic fatty liver disease (NAFLD)

Co-variables	All participants			Participants with NAFLD		
	Reference ($n=1,461$; 95.3%)	Psoriasis ($n=74$; 4.7%)	p^a -value	Reference ($n=375$; 94.9%)	Psoriasis ($n=20$; 5.1%)	p^a -value
Age, years, mean \pm SD	70.5 \pm 8.0	71.2 \pm 6.5	0.34	69.6 \pm 7.6	73.6 \pm 6.5	0.02
Female, %	51.1	44.6	0.27	50.4	60.0	0.40
Caucasian, %	95.4	98.6	0.21	94.5	94.7	0.72
Body mass index (kg/m ²), median interquartile range (IQR)	26.4 (24.2–28.9)	26.6 (24.1–28.5)	0.47	29.0 (26.9–31.2)	28.5 (26.7–32.5)	0.74
Alcohol intake (drinks/week), median (IQR)	5.0 (0.6–7.5)	7.5 (0.9–7.5)	0.07	2.63 (0.56–7.5)	4.97 (0.23–7.5)	0.75
Alcoholic more than 14 units/week, %	13.2	17.8	0.26	n/a	n/a	n/a
Viral hepatitis, %	0.8	1.4	0.57	n/a	n/a	n/a
Hepatotoxic medication, %	2.8	2.7	0.96	n/a	n/a	n/a
Smoking, %			0.45			
Never	34.6	27.4		33.3	25.0	
Former	53.9	60.3		59.7	70.0	
Current	11.5	12.3		6.9	5.0	
Metabolic syndrome, % ^b	46.5	52.1	0.36	68.5	83.3	0.18
Fasting glucose >100 mg/dl or drug treatment for elevated blood glucose, %	47.0	41.4	0.40	66.3	60.0	0.62
Waist circumference >88 cm (♀) or >102 cm (♂), %	34.2	45.8	0.07	61.6	81.2	0.12
Triglycerides >150 mg/dl or drug treatment for elevated triglycerides, %	41.7	41.1	0.93	52.5	64.3	0.39
HDL-C <40 mg/dl (♂) or <50 mg/dl (♀) or drug treatment for low HDL-C, %	37.3	37.5	0.97	47.4	42.9	0.74
BP \geq 130/85 mmHg or drug treatment for elevated BP, %	91.7	88.1	0.34	96.0	93.8	0.66
Alanine aminotransferase (U/l), median (IQR)	18 (14–24)	18 (14–24)	0.89	22 (16–28)	22 (17–25)	0.94
Aspartate aminotransferase (U/l), median (IQR)	25 (22–29)	24 (21–31)	0.67	25 (22–29)	25 (21–30)	0.63
Gamma glutamyl transferase (U/l), median (IQR)	23 (17–34)	25 (19–37)	0.20	26 (19–37)	26 (21–40)	0.55
Bilirubin, median (IQR)	8 (6–11)	9 (6–12)	0.52	8.0 (6.0–11.0)	6.5 (5.8–11.0)	0.24
Platelet count (g/l), median (IQR)	258 (217–301)	271 (231–332)	0.008	255 (211–311)	271 (186–323)	0.98
HOMA-IR, median (IQR)	2.5 (1.6–3.7)	2.5 (1.8–3.7)	0.66	3.9 (2.6–5.9)	4.2 (2.9–5.4)	0.90
Steatosis on ultrasound, %	34.0	44.3	0.016	n/a	n/a	n/a
Cirrhosis on Fibroscan, %	1.1	3.4	0.13	1.6	8.6	0.005
Advanced liver fibrosis on Fibroscan, %	3.6	8.1	0.045	4.0	15.0	0.022
Fibroscan stiffness (kPa), median (IQR)	4.9 (4.1–6.2)	5.4 (4.4–6.6)	0.10	5.3 (4.4–6.7)	6.3 (4.9–7.3)	0.066

^aSignificance level between reference population and psoriasis. Based on t -test, Wilcoxon rank-sum test or χ^2 test. ^bMetabolic syndrome was defined as the presence of at least 3 of the 5 traits.

HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; HDL-C: high-density lipoprotein cholesterol; BP: blood pressure; N/A: not applicable.

reference participants, but the distribution of the other co-variables, such as sex, BMI, the metabolic syndrome and liver enzyme tests, were comparable. Using TE, a significantly greater prevalence of advanced fibrosis was demonstrated in participants with psoriasis vs. the reference population (15% vs. 4%, $p=0.02$). Moreover, more participants with psoriasis had a LSM >13 kPa, suggesting liver cirrhosis, than the reference population (8.6% vs. 1.6%, $p=0.005$) (Table I).

Logistic regression analyses in this NAFLD population showed that participants with psoriasis had a 4 times greater risk of advanced liver fibrosis compared with the reference population (crude OR 4.2, 95% CI 1.1–16.0). This risk remained 4 times increased after adjustment for age, sex, alcohol consumption, ALT and presence of the metabolic syndrome in a multivariable logistic regression model (fully adjusted OR=4.1, 95% CI 1.01–17.0).

Furthermore, in a linear regression analysis, the association between psoriasis and liver fibrosis (continuous LSM) was also confirmed (crude and fully adjusted β 0.07, SE 0.04 $p=0.04$).

DISCUSSION

This is the first large population-based cohort study of middle-aged and elderly people to demonstrate that participants with psoriasis have a 2-fold higher risk of advanced liver fibrosis than participants without this skin disease. This risk increases up to 4 times among the subgroup of participants with NAFLD and is independent of systemic anti-psoriatic drugs and other known risk factors associated with liver fibrosis. Previous studies focused on liver fibrosis in the context of MTX-induced hepatotoxicity, but were limited in sample size and restricted to patients with severe psoriasis who were eligible for liver biopsy in tertiary centres (12, 13). In contrast to the 8.1% of patients with psoriasis who had advanced liver fibrosis based on TE, the prevalence of advanced liver fibrosis in MTX-treated patients ranged from 6.9% to 69.5% (13). The prevalence of liver fibrosis in our non-psoriatic reference population (3.6%) is similar to that observed in other population-based studies confirming the validity of the ascertainment of liver fibrosis using TE (14).

It is known that ALT is a poor diagnostic marker for NAFLD and liver fibrosis. Other diagnostic tests including TE, FibroTest, Procollagen III N-Terminal Propeptide, and the Enhanced Liver Fibrosis (ELF™, Siemens Healthcare, The Netherlands) test are more accurate in detecting liver fibrosis and seem more appropriate in monitoring drug-induced effects in the follow-up of patients with psoriasis, if indicated.

In clinical practice it could therefore be considered appropriate to refer patients with psoriasis and an increased baseline hepatic risk profile to a hepatologist

for a TE before commencing potentially hepatotoxic medication. During systemic therapy TE may be repeated at regular intervals, depending on the baseline TE, to monitor for signs of liver fibrosis. A liver biopsy may be considered in patients with a LSM of >9.5 kPa depending on the patients' clinical background and is strongly recommended in patients with a LSM of >13 kPa (14).

Conventional explanations for the association of NAFLD, advanced liver fibrosis and psoriasis are the increased presence of components of the metabolic syndrome, increased alcohol intake, and the use of hepatotoxic medication, but the distribution of these factors was comparable between the patients with psoriasis and the reference population. The low-grade chronic inflammatory state, seen both in psoriasis and NAFLD, may play a role in the development of advanced fibrosis, but this needs to be studied in more detail to determine whether it is the missing link in the relationship between these diseases (15, 16). However, inflammation does not explain the fact that MTX toxicity is seen more often in patients with psoriasis than in patients with rheumatic or Crohn's disease (3, 4). Other hypotheses for the increased prevalence of advanced liver fibrosis in psoriasis are possible genetic similarities, lifestyle factors, such as nutrition, that were not included in the analyses or another still unknown common pathway for psoriasis and liver fibrosis.

Study strengths and limitations

The strengths of this study are its population-based design, the large number of participants, and the extensive availability of demographic, pharmacological, disease and lifestyle factors and serological markers of liver damage. In the adjusted models, we were able to include most of the known confounders that could influence the association of both advanced liver fibrosis and NAFLD with psoriasis. The study was performed in a district of Rotterdam that was highly representative of the Dutch elderly general population. Notwithstanding the large number of participants, the available cases with psoriasis and liver fibrosis was small, which explains the borderline significance often found in this study and the wider range of the confidence interval in the NAFLD subpopulation. However, the different analytic approaches and subgroup analysis all show the same trend suggesting the validity of the findings in this study population of predominantly mild cases without systemic anti-psoriatic medication. An intrinsic limitation of the cross-sectional study design is that a direct causal relationship between psoriasis and advanced liver fibrosis cannot be established.

The case definition (i.e. psoriasis) is based on an algorithm, which included a clinical examination by a trained physician, with a high specificity and sensitivity (both 98%) (6). Since the population consisted of elderly participants, the results may not be generalized

to younger subjects with psoriasis. This also explains the high prevalence of psoriasis compared with other population-based studies.

At present, liver biopsy remains the gold standard for the assessment of liver fibrosis (17). However, different non-invasive methods have been evaluated in recent years, including TE (18). A recent meta-analysis concluded that a higher stage of liver fibrosis (a higher cut-off value) improves the test accuracy of TE (7). We used a cut-off value of 9.6 kPa (\leq F3), which is the highest value to detect liver fibrosis next to liver cirrhosis ($>$ 13 kPa; F4). Another shortcoming of our study is the failure rate or unreliable TE in one-third of the participants, which mostly affected overweight and obese patients irrespective of using an XL probe. This may have led to a selection bias and underestimation of the prevalence of advanced liver fibrosis in our study. However, the failure rate of TE was equally distributed amongst participants with and without psoriasis, suggesting a non-differential misclassification bias.

Conclusion

These results suggest that middle-aged and elderly people with predominately mild psoriasis and no systemic anti-psoriatic medication have an increased risk of advanced liver fibrosis, independent of other known risk factors, especially if they have pre-existing NAFLD. In clinical practice this may lead to a reconsideration of the current role of ALT in monitoring the development of liver fibrosis, and may stimulate the use of other diagnostic approaches, such as TE, especially in psoriasis patients with (components of) the metabolic syndrome that are being screened prior to and during potentially hepatotoxic therapies.

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