

## ORIGINAL ARTICLE

# Increased prevalence of HCV and hepatic decompensation in adults with psoriasis: a population-based study in the United Kingdom

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## Abstract

**Background** The hepatitis C virus (HCV) is a major cause of global morbidity and mortality, with conflicting evidence regarding a possible association with psoriasis.

**Objective** To determine the prevalence of HCV in psoriasis patients, compared to controls, and to determine the incidence of hepatic decompensation in HCV+ psoriasis patients compared to HCV+ controls.

**Methods** Cross-sectional and cohort studies were conducted in The Health Improvement Network (THIN).

**Results** In fully adjusted models, a statistically significant increase in prevalence was seen in the adults with psoriasis (OR: 1.24, 95% CI 1.10–1.40). A “dose–response” of HCV prevalence with increasing psoriasis severity was not observed. HCV+ patients with psoriasis had a non-statistically significant increased incidence of hepatic decompensation compared to HCV+ individuals without psoriasis (aHR: 1.58, 95% CI: 0.90–2.77). The risk was highest and statistically significant, in those with moderate-to-severe psoriasis (aHR: 21.51, 95% CI: 7.58–61.03).

**Conclusions** These results demonstrate a higher prevalence of HCV in adults with psoriasis and a higher rate of hepatic decompensation in HCV+ individuals with moderate-severe psoriasis.

Received: 29 December 2016; Accepted: 27 March 2017

## Conflict of Interest/Financial Disclosures:

In the previous 12 months, Dr. Gelfand served as a consultant for Abbvie, Astrazeneca, Celgene Corp, Coherus, Eli Lilly, Janssen Biologics (formerly Centocor), Sanofi, Merck, Novartis Corp, Valeant and Pfizer Inc., receiving honoraria; and receives research grants (to the Trustees of the University of Pennsylvania) from Abbvie, Amgen, Eli Lilly, Janssen, Novartis Corp, Regeneron and Pfizer Inc.; and received payment for continuing medical education work related to psoriasis. Dr. Gelfand is a co-patent holder of resiquimod for treatment of cutaneous T-cell lymphoma. Dr. Ogdie has served as consultant for Novartis and Pfizer and has received payment for continuing medical education work related to psoriatic arthritis. Dr. Takeshita received a research grant from Pfizer, to the trustees of the University of Pennsylvania, for work that is unrelated to what is presented in this manuscript and has received payment for continuing medical education work related to psoriasis. Dr. Noe, Dr. Shin and Ms. Grewal have no financial interests to disclose.

## Funding/Support:

This work was supported by an unrestricted grant from Pfizer to the Trustees of the University of Pennsylvania (JMG), a medical dermatology fellowship from the National Psoriasis Foundation (MHN), NIH Training Grants T32-GM075766 (MHN) and T32-AR007465-32 (SKG), and K24-AR064310 36 (JMG), K23-AR063764 (AO), and K23-AR068433 (JT), from the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

## Introduction

The hepatitis C virus (HCV) causes a blood-borne infection of the liver that represents a major cause of global morbidity and mortality. Approximately 170 million people are chronically

infected with HCV worldwide, with 3–4 million new cases developing every year.<sup>1</sup> Chronic hepatitis develops in 70–80% of people with acute HCV infection and can lead to hepatic decompensation, including development of hepatocellular

carcinoma and liver failure. In addition to effects on hepatocytes, the virus localizes in skin and lymphoid tissue, leading to systemic immune dysregulation in a subset of patients.<sup>2</sup> Furthermore, recent research confirms upregulation of inflammatory cytokines in the skin of HCV+ patients with psoriasis.<sup>3</sup>

This evidence suggests a plausible mechanism for an increased prevalence of psoriasis in adults with HCV (Fig. 1); however, the precise relationship is incompletely understood. Some cross-sectional studies have shown higher rates of HCV infection in adults with psoriasis as compared to the general population; however, others have not demonstrated a statistically significant association.<sup>4–10</sup> Moreover, results of existing studies are difficult to interpret because of design limitations including small sample sizes and inability to evaluate psoriasis severity.

Understanding the epidemiology of HCV infection in patients with psoriasis has significant clinical implications. First, it is important to identify high risk patients so appropriate screening can be implemented to reduce transmission as well as HCV-associated morbidity and mortality which can now be prevented with curative antiviral pharmacotherapy.<sup>11</sup> Second, many systemic psoriasis treatments are either immunosuppressive or hepatotoxic; therefore, it is particularly important to determine the epidemiology of HCV in patients with more severe psoriasis who are likely to require systemic therapy.

The objective of this study was to determine the prevalence of HCV in patients with psoriasis of varying severity and to evaluate HCV-related liver outcomes among HCV+ psoriasis patients

compared to HCV+ patients without psoriasis. We hypothesize individuals with psoriasis will have higher rates of HCV compared to those without psoriasis and that HCV+ psoriasis individuals will have a higher incidence of hepatic decompensation.

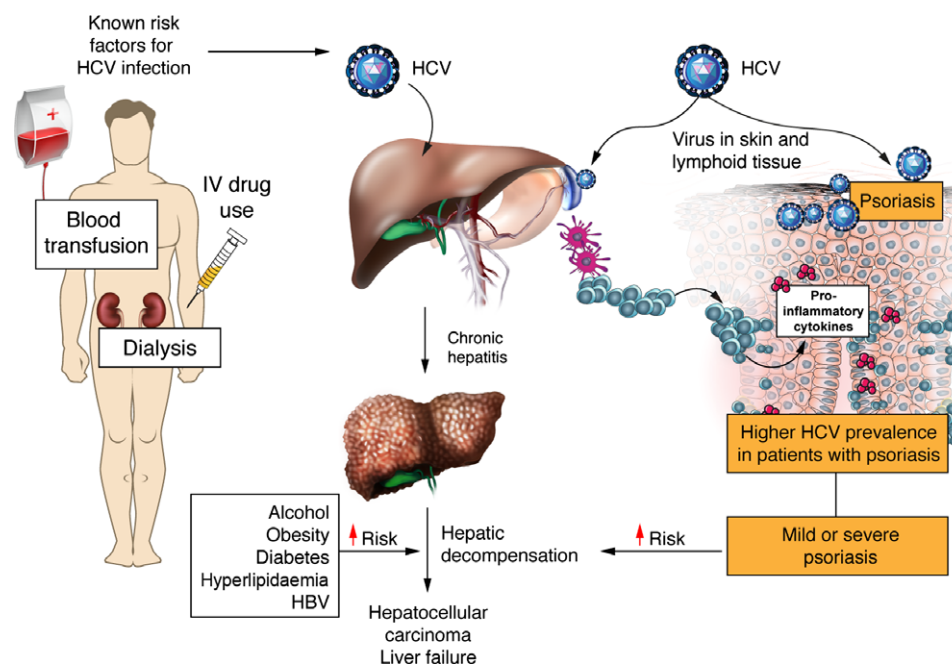
## Methods

### Study design

We conducted a population-based, cross-sectional study to investigate the lifetime prevalence of HCV in psoriasis patients compared to controls. Data were collected between 1 January 1994 and 30 June 2012. We also conducted a cohort study to examine the incidence of hepatic decompensation in HCV+ psoriasis patients compared to HCV+ patients without psoriasis. Start date was the latest of the following: registration with a clinical practice plus 180 days, date at which the clinical practice implemented Vision software, date of psoriasis diagnosis or start of therapy for psoriasis patients with moderate-to-severe psoriasis (or corresponding visit date for the control patients) and diagnosis of HCV. Censoring occurred when patients developed a diagnosis of a hepatic decompensation event, died, transferred out of the practice or reached the end of the data collection period.

### Data source

Data were from The Health Improvement Network (THIN), an electronic medical records database in the United Kingdom



**Figure 1** Conceptual model for the increase in prevalence of psoriasis in adults with HCV infection.

(UK) which has been used extensively for epidemiological work and previously validated for the study of psoriasis<sup>12</sup> and HCV.<sup>13</sup> THIN contains information for over eleven million individuals in the UK and is broadly representative of the population.<sup>14,15</sup> A subset of psoriasis patients in THIN also belongs to a prospective cohort called the Incident Health Outcomes and Psoriasis Events (iHOPE) cohort. Patients in iHOPE have objective measures of psoriasis severity (i.e. percentage of body surface area affected) recorded by their GP, as previously described.<sup>16</sup>

### Study population

The study population in THIN included patients ages 18–89. Patients with a history of HIV or organ transplant were excluded. Up to five patients without psoriasis (e.g. unexposed controls) were randomly selected for each patient with psoriasis, matched on GP practice and start date ( $\pm 180$  days), to ensure that patients were observed by similar providers during similar time periods.

The study population in iHOPE was patients with psoriasis ages 25–64, randomly sampled from THIN. Questionnaires were sent to their GP to ascertain the severity of psoriasis by body surface area (BSA) which was categorized as mild (<3% BSA), moderate (3–10% BSA) or severe (>10% BSA). Each iHOPE patient was matched with up to ten randomly chosen controls without psoriasis, as available, and matched on practice and age category.

### Exposure definitions

Diagnoses are recorded in THIN using a READ diagnostic code scheme.<sup>17</sup> Patients were identified as having psoriasis if they had at least one READ code for psoriasis (PPV 90%<sup>12</sup>). Psoriasis severity was based on treatment. Psoriasis patients who had a code for phototherapy (ultraviolet A, ultraviolet B, and/or psoralen and ultraviolet A), methotrexate, cyclosporine, oral retinoids (acitretin or etretinate), etanercept, infliximab, adalimumab or ustekinumab were identified as having moderate-severe psoriasis. In iHOPE, psoriasis severity was determined by survey of the patients' GP regarding the body surface area affected.

### Outcomes

Patients were classified as having HCV if they received a READ diagnostic code for HCV (PPV 86%<sup>15</sup>), at any point during the study period. Hepatic decompensation was defined as one READ code for psoriasis AND at least one READ code for HCV, prior to a READ code for hepatic decompensation: ascites, variceal haemorrhage, spontaneous bacterial peritonitis, hepatic encephalopathy or hepatocellular carcinoma.<sup>15</sup>

### Statistical analyses

Statistical analysis was performed in STATA 14.0 (StatCorp, College Station, TX). Statistical significance was determined by two-

sided *P* values at a significance level <0.05. Descriptive statistics were used to summarize baseline characteristics. Chi-squared tests were used for categorical variables and one-way analysis of variance (ANOVA) for continuous variables, based on psoriasis severity groups. We descriptively reported incidence rates for hepatic decompensation. Logistic regression was used to compare the prevalence of HCV in the psoriasis groups (overall, mild and severe as defined by treatment in THIN; mild, moderate and severe as defined by % of BSA involved in iHOPE) versus patients without psoriasis. Cox proportional hazards regression was used to compare the incidence of hepatic decompensation in the psoriasis groups (overall, mild and moderate-to-severe) versus controls in THIN. Initial multivariable models included age, gender, BMI, observation time (for the cross-sectional study only), smoking history, alcohol use, Townsend score and known risk factors for the outcomes. Known risk factors for HCV infection include IV drug use, history of dialysis and history of a blood transfusion. Risk factors for hepatic decompensation include obesity, alcohol use, diabetes, hyperlipidaemia and concomitant hepatitis B infection. Each covariate was sequentially removed individually, beginning with the highest *P*-value. If the point estimate of the psoriasis variable was not altered by a minimum of 10%, the covariate was removed in order to create the most parsimonious model. Sensitivity analyses assessed the robustness of the results.

### Results

We identified 201 358 patients with psoriasis and 961 888 matched controls in THIN. Among psoriasis patients, 188 664 had mild psoriasis and 12 694 had moderate-severe psoriasis. Baseline characteristics of this study population are summarized in Table 1. Among patients with moderate-severe psoriasis, the most commonly prescribed therapies were methotrexate (69.3%), phototherapy (26.2%), cyclosporine (10.4%), oral retinoids (6.1%) and biologics (0.95%) (Table 2).

Patients with psoriasis had a higher lifetime prevalence of HCV as compared to control patients: 0.17% (95% CI: 0.16–0.19) vs 0.12% (95% CI: 0.11–0.13) ( $P < 0.001$ ). In fully adjusted models, controlling for age, sex and observation time, psoriasis overall (aOR: 1.24, 95% CI: 1.10–1.40) and mild psoriasis (aOR: 1.25, 95% CI: 1.11–1.42) were associated with an increased prevalence of HCV. The prevalence of HCV in the moderate-severe group was similar to the control group (aOR: 1.01, 95% CI: 0.63–1.63) (Fig. 2). Sensitivity analyses excluding patients with a history of any systemic therapy (methotrexate, cyclosporine, oral retinoids and biologics) increased the point estimate of the odds ratio in the moderate-severe psoriasis group (OR: 1.93, 95% CI: 0.96–3.88) (Fig. 2).

In the iHOPE cohort, we identified 8756 patients with psoriasis and 87 495 controls. Patient demographics were similar to those in THIN (Table 3). Patients with psoriasis had a higher lifetime prevalence of HCV as compared to control patients:

**Table 1** Baseline demographics in THIN\*

	Controls	Mild psoriasis	Moderate-severe psoriasis
<i>N</i>	961 888	188 664	12 694
Age, mean in years (SD)	48.39 (17.15)	45.64 (17.16)	46.20 (15.10)
Female Sex, <i>N</i> (%)	540 005 (56.14)	97 769 (51.82)	6153 (48.47)
Cohort time, years (SD)	10.10 (4.82)	8.33 (5.16)	9.35 (5.02)
Smoking History, <i>N</i> (%)			
Never	443 229 (46.08)	69 791 (36.99)	4621 (36.40)
Ever	496 096 (51.58)	114 444 (60.66)	7949 (62.62)
Missing	22 563 (2.35)	4429 (2.35)	124 (0.98)
Drinking History, <i>N</i> (%)			
Never	94 976 (9.87)	16 985 (9.00)	1210 (9.53)
Ever	762 890 (79.31)	150 053 (79.53)	10 390 (81.85)
Missing	104 022 (10.81)	21 626 (11.46)	1094 (8.62)
Body Mass Index, Mean (SD)	27.00 (5.72)	27.26 (5.90)	28.55 (6.44)
Body Mass Index, <i>N</i> (%)			
Underweight/Normal	345 580 (35.93)	64 804 (34.35)	3951 (28.29)
Overweight	300 335 (31.22)	57 815 (30.64)	4010 (31.59)
Obese	212 891 (22.13)	44 292 (23.48)	4080 (32.14)
Missing	103 082 (10.72)	21 751 (11.53)	1013 (7.98)
Townsend Score, <i>N</i> (%)			
1st Quintile	241 061 (25.06)	43 677 (23.15)	3049 (24.02)
2nd Quintile	203 781 (21.19)	38 297 (20.30)	2659 (20.95)
3rd Quintile	192 114 (19.97)	38 274 (20.29)	2575 (20.29)
4th Quintile	168 741 (17.54)	34 331 (18.20)	2235 (17.61)
5th Quintile	115 859 (12.04)	24 721 (13.10)	1613 (12.71)
Missing	40 332 (4.19)	9364 (4.96)	563 (4.44)
History of IVDU†, <i>N</i> (%)	133 (0.01)	45 (0.02)	4 (0.03)
History of dialysis‡, <i>N</i> (%)	946 (0.10)	151 (0.08)	23 (0.18)
History of blood transfusion, <i>N</i> (%)	7887 (0.82)	1397 (0.74)	138 (1.09)

\*All *P* values are <0.001 unless otherwise reported.

†*P* = 0.002

‡*P* = 0.001

0.21% (95% CI: 0.11–0.30%) vs 0.11% (95% CI: 0.09–0.14%, *P* = 0.02). Based on disease severity, patients with mild psoriasis (BSA <3%) had a prevalence of 0.24%, (95% CI: 0.21–0.43) and those with moderate psoriasis (BSA 3–10%) had a prevalence of 0.22%, (95% CI: 0.09–0.46%). There were no cases of HCV in the severe psoriasis (BSA >10%) group (95% CI: 0–0.34%). In fully adjusted models, controlling for age, sex, smoking status and observation time, only mild psoriasis (aOR: 1.88, 95% CI: 1.01–3.51%) was associated with an increased prevalence of HCV. The prevalence did not reach statistical significance in the overall psoriasis group (aOR: 1.52, 95% CI: 0.92–2.51%) or the moderate group (aOR: 1.57, 95% CI: 0.73–3.39%); however, point estimates of association were consistent with an increased prevalence of HCV as well. These results remained robust to sensitivity analyses.

In THIN, among HCV+ individuals, 338 psoriasis patients and 1193 controls developed hepatic decompensation (Table S1). The incidence of hepatic decompensation was 6.19 events per 1000 person-years in controls and 9.33 events per

1000 person-years in patients with psoriasis. After adjusting for age and sex, the hazard ratios for hepatic decompensation were 1.58 (95% CI: 0.90–2.77) in all patients with psoriasis, 1.23 (95% CI: 0.66–2.28) in mild psoriasis and 21.51 (95% CI: 7.58–61.03) in moderate-severe psoriasis (Table 4).

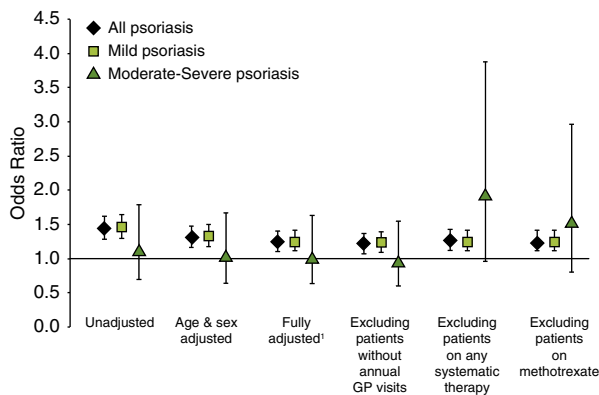
## Discussion

Results from our large, population-based study in the U.K. demonstrate a higher prevalence of HCV in patients with psoriasis compared with those without psoriasis (OR: 1.24, 95% CI: 1.10–1.40). A statistically significant relationship between HCV and psoriasis severity was not observed. Importantly, the background prevalence of HCV infection in our study (0.12–0.17%) is consistent with what has been previously reported for the general population in THIN, providing an external measure of validity.<sup>13</sup> Our study is, to our knowledge, the largest population-based analysis of HCV prevalence in adults with psoriasis and the first to evaluate the impact of psoriasis severity on HCV prevalence and HCV outcomes such as hepatic decompensation.

**Table 2** Treatment characteristics of patients with moderate-severe psoriasis

Treatment	N* (%)
Any	12 694
<b>Phototherapy</b>	
Any	3329 (26.22)
UVA/UVB	2395 (18.87)
PUVA	934 (7.36)
<b>Oral systemic</b>	
Any	9984 (78.65)
Methotrexate	8796 (69.29)
Cyclosporine	1315 (10.36)
Oral Retinoids	778 (6.13)
<b>Biologic</b>	
Any	121 (0.95)
Etanercept	47 (0.37)
Adalimumab	60 (0.47)
Infliximab	14 (0.11)
Ustekinumab	2 (0.02)

\*All treatments reported for any patient are included.

**Figure 2** Prevalence of HCV infection in psoriasis patients compared to matched controls in THIN. <sup>1</sup>. Adjusted for age, sex and cohort time.

Cohen *et al.*<sup>7</sup> previously reported a significant association between HCV and psoriasis using a population-based sample of 12 502 patients with psoriasis and 24 287 controls from Israel. This risk differed by smoking status: OR = 1.93 (95% CI: 1.30–2.67) in smokers and OR = 2.22 (95% CI: 1.63–3.04) in non-smokers. Kanada *et al.*<sup>9</sup> examined 6532 adults, including 162 with psoriasis, from the National Health and Nutrition Examination Survey in the United States and did not find a significant association between HCV and psoriasis (OR = 0.24, 95% CI: 0.03–2.01). Other studies assessing this relationship were single-institutional case series, limiting generalizability of results.<sup>4–6,8,10</sup>

We also found a statistically significant, increased rate of hepatic decompensation in HCV+ individuals with moderate-severe psoriasis (HR: 21.51, 95% CI: 7.58–61.03), a finding that has not

previously been reported. The overall rate of hepatic decompensation in our study was 6.19 events per 1000 person-years in controls and 9.33 events per 1000 person-years in patients with psoriasis, which is consistent with previous reports of approximately 3–53 per 1000 person-years.<sup>18–20</sup> This increased risk of hepatic decompensation in patients with moderate-severe psoriasis suggests recognition and treatment of HCV in this population is important to reduce risk of subsequent liver failure.

Our study has several strengths compared to previous research. Our analysis of more than 200 000 psoriasis patients and almost 1 000 000 controls is orders of magnitude greater in size than prior studies. This large sample with practice-matched, date-matched controls and extensive series of sensitivity analyses minimizes observation bias that may be more apparent in other observational studies. Using THIN, we were also able to examine known risk factors for HCV infection (IV drug use, dialysis, blood transfusion) and hepatic decompensation (obesity, alcohol use, diabetes, hyperlipidaemia and concomitant hepatitis B infection). Moreover, psoriasis and HCV diagnoses have been previously validated in THIN, minimizing misclassification.<sup>12,13</sup>

There are also some limitations. Given the cross-sectional design of the HCV prevalence study, we are unable to determine the directionality of the relationship between HCV infection and psoriasis; however, the exact timing of HCV infection is often difficult to determine, because many people are diagnosed years after being infected. In general, the pathophysiology of concordant HCV infection and psoriasis is not well understood, but it has been previously proposed HCV infection may lead to the development of psoriasis in genetically susceptible individuals.<sup>3</sup> Furthermore, blocking tumour necrosis factor, a well-established treatment mechanism for psoriasis, has also been shown to be an effective adjuvant treatment for HCV infection,<sup>21</sup> further suggesting a shared inflammatory pathway. Also, it is difficult to know whether the lack of relationship between HCV infection and severity of psoriasis is real or due to the low prevalence of HCV in the UK, resulting in limited statistical power to detect a relationship. One previous study of 90 adults with untreated psoriasis did show an association between Psoriasis Area Severity Index (PASI) and quantity of HCV-mRNA,<sup>22</sup> but additional and larger studies are needed to better understand the association between psoriasis severity and HCV infection.

In summary, HCV is a viral infection of the liver that leads to significant morbidity, including liver failure and hepatocellular carcinoma. In this study, HCV was more prevalent among psoriasis patients. Our study also suggests that more severe psoriasis is associated with an increased risk of hepatic decompensation among HCV+ individuals. Further research is necessary to better understand the pathophysiology and shared immunology between HCV and psoriasis. Dermatologists should be aware of this increased prevalence of HCV to screen all psoriasis patients with HCV risk factors prior to initiation of hepatotoxic or immunosuppressive medications. Earlier identification of HCV+



**Table 3** Baseline demographics in iHOPE\*

	Controls	Mild psoriasis	Moderate psoriasis	Severe psoriasis
<i>N</i>	87 495	4538	3132	1086
Age, mean in years (SD)†	45.31 (11.08)	45.67 (11.22)	45.26 (11.02)	44.50 (10.86)
Female Sex, <i>N</i> (%)	46 304 (52.92)	2369 (52.20)	1481 (47.29)	478 (44.01)
Cohort time, years (SD)‡	13.53 (6.75)	13.42 (6.77)	13.79 (6.61)	13.75 (6.70)
Smoking History, <i>N</i> (%)				
None	42 548 (48.63)	1751 (38.59)	1072 (34.23)	384 (35.36)
Current	21 295 (24.34)	1344 (29.62)	1040 (33.21)	364 (33.52)
Former	22 289 (25.47)	1404 (30.94)	992 (31.67)	331 (30.48)
Missing	1363 (1.56)	39 (0.86)	28 (0.89)	7 (0.64)
Drinking History, <i>N</i> (%)				
None	8640 (9.87)	386 (8.51)	255 (8.14)	92 (8.47)
Current	63 475 (72.55)	3393 (74.77)	2301 (73.47)	786 (72.38)
Former	5191 (5.93)	297 (6.54)	214 (6.83)	81 (7.46)
Missing	10 189 (11.65)	462 (10.18)	362 (11.56)	127 (11.69)
Body Mass Index, Mean (SD)	27.06 (5.72)	27.61 (6.00)	28.02 (6.13)	29.06 (6.68)
Body Mass Index, <i>N</i> (%)				
Underweight/Normal	31 569 (36.08)	1529 (33.69)	956 (30.52)	270 (24.86)
Overweight	27 289 (31.19)	1430 (31.51)	980 (31.29)	317 (29.19)
Obese	19 450 (22.23)	1170 (25.78)	874 (27.91)	365 (33.61)
Missing	9187 (10.50)	409 (9.01)	322 (10.28)	134 (12.34)
Townsend Score, <i>N</i> (%)				
1st Quintile	21 260 (24.30)	1014 (22.34)	714 (22.80)	224 (20.63)
2nd Quintile	17 786 (20.33)	934 (20.58)	585 (18.68)	199 (18.32)
3rd Quintile	17 399 (19.89)	923 (20.34)	652 (20.82)	211 (19.43)
4th Quintile	15 130 (17.29)	787 (17.34)	572 (18.26)	221 (20.35)
5th Quintile	11 052 (12.63)	604 (13.31)	449 (14.34)	176 (16.21)
Missing	4868 (5.56)	276 (6.08)	160 (5.11)	55 (5.06)
History of IVDU, <i>N</i> (%)‡	26 (0.03)	2 (0.04)	1 (0.03)	0 (0.00)
History of dialysis, <i>N</i> (%)‡	25 (0.03)	1 (0.02)	0 (0.00)	1 (0.09)
History of blood transfusion, <i>N</i> (%)‡	343 (0.39)	17 (0.37)	8 (0.26)	4 (0.37)

\*All *P* values are <0.001 unless otherwise reported.

†*P* = 0.012

‡*P* > 0.05.

**Table 4** Incidence of hepatic decompensation in THIN

	Controls	All psoriasis	Mild psoriasis	Moderate – severe psoriasis
Mean follow-up time, years (SD)	5.89 (4.64)	5.26 (4.52)	5.34 (4.60)	3.64 (2.15)
Median (IQR)	4.67 (1.91, 9.17)	3.74 (1.57, 7.61)	3.74 (1.56, 7.74)	4.05 (1.98, 4.72)
Total person-years	7091	1822	1764	59
New events, <i>N</i> (%)	49 (4.02)	17 (4.83)	13 (3.88)	4 (23.53)
Incidence per 1000 person years (95% CI)	6.91 (5.22–9.14)	9.33 (5.80–15.01)	7.37 (4.28–12.69)	68.30 (25.63–181.98)
Hazard Ratio* (95% CI)	Reference	1.58 (0.90–2.77)	1.23 (0.66–2.28)	21.51 (7.58–61.03)

\*Adjusted for age and sex.

individuals will give more patients access to curative therapy, reducing the complications of chronic infection and decreasing transmission.

### Acknowledgements

We are indebted to Vincent Lo Re, MD MSCE, Assistant Professor of Medicine and Senior Scholar in the Center for Clinical

Epidemiology at the University of Pennsylvania for his assistance in conceptualizing this study design and expertise in hepatitis.

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### Supporting information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Baseline characteristics of patients with incidence hepatic decompensation among HCV+ patients in THIN.