

Tobacco smoking negatively influences the achievement of greater than three-quarters reduction in psoriasis area and severity index after eight weeks of treatment among patients with psoriasis: Findings from a prospective study

Yan Qiang^{1*}, Le Kuai^{2*}, Shuo Liu^{1*}, Quanruo Xu^{3*}, Lingzi Shenfan^{3*}, Rui Zhang¹, Zhongzhi Gao¹, Xiangjin Gao¹, Bin Li¹, Ruiping Wang^{1,3}

ABSTRACT

INTRODUCTION Smoking is an independent and modifiable risk factor for the onset and development of psoriasis; however, evidence on the association between tobacco smoking and psoriasis treatment efficacy is limited. This study aimed to explore the influence of smoking on treatment efficacy in a cohort of patients with psoriasis in Shanghai, China.

METHODS Patients with psoriasis were recruited from the Shanghai Skin Disease Hospital between 2021 and 2022. The treatment for patients with psoriasis includes acitretin, methotrexate, narrow-band ultraviolet/benvitimid, and biologics. Data were collected using a structured questionnaire, physical examination, and disease severity estimation at baseline, week four, and week eight. The achievement of a $\geq 75\%$ reduction in psoriasis area and severity index (PASI₇₅) score from baseline to week 8 was set as the primary outcome for treatment efficacy estimation. Data were analyzed using SAS 9.4.

RESULTS A total of 560 patients with psoriasis were enrolled in this study, who were predominantly males (72.9%). The average age of patients was 48.4 years, and 38.8% of them were current smokers, 5.0% of them were former smokers. The median score of PASI among patients changed from 11.1 (interquartile range, IQR: 7.9–16.6) at baseline to 6.2 at week 4 and 3.1 at week 8, and 13.8% and 47.3% of patients with psoriasis achieved PASI₇₅ at weeks 4 and 8, respectively. Logistic regression indicated that patients without tobacco smoking had a higher proportion of PASI₇₅ achievement at week 8. The adjusted odds ratio (AOR) was 11.43 (95% CI: 6.91–18.89), 14.14 (95% CI: 8.27–24.20), and 3.05 (95% CI: 1.20–7.76) for non-smokers compared with smokers, current smokers, and former smokers, respectively. Moreover, former smokers had higher PASI₇₅ achievement than current smokers (AOR=3.37), and patients with younger smoking initiation age, longer smoking duration, and higher smoking intensity had lower PASI₇₅ achievement.

CONCLUSIONS Tobacco smoking was negatively associated with PASI₇₅ achievement both in current and former smokers, and former smokers had higher PASI₇₅ achievement than current smokers. The implementation of tobacco control measures is beneficial for improving treatment responses.

AFFILIATION

1 Clinical Research Center, Shanghai Skin Diseases Hospital, School of Medicine, Tongji University, Shanghai, China

2 Department of Dermatology, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China

3 School of Public Health, Shanghai University of Traditional Chinese Medicine, Shanghai, China

* Contributed equally

CORRESPONDENCE TO

Ruiping Wang. Clinical Research Center, Shanghai Skin Diseases Hospital, School of Medicine, Tongji University, 1278 Baode Road, Jing'an District, Shanghai 200443, China.

E-mail: w19830901@126.com

ORCID ID: <https://orcid.org/0000-0003-4183-5795>

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INTRODUCTION

Psoriasis is a common chronic systemic inflammatory disease accompanied by severe skin damage, joint symptoms, and various comorbidities^{1,2}. Globally, psoriasis affects 0.5–11.4% of the adult population, and over 120 million people suffer from it³. Previous studies have indicated a relatively lower prevalence of psoriasis in China, but it has increased gradually in recent years, reaching 0.47% in 2012, and there are approximately 6 million patients with psoriasis in China^{4,5}. The clinical features of psoriasis are mainly erythema and silvery scale, and psoriasis can occur all over the body, with the scalp and extensor limbs being more common, usually accompanied by multifaceted comorbidities⁶. Psoriasis adversely affects patients' quality of life and work efficiency and is treated as an important public health issue worldwide because of its increased prevalence, long disease duration, recurrence, and serious disease burden^{7,8}.

Previous studies have indicated that many factors play a role in the development of psoriasis; however, the pathogenesis of psoriasis remains unclear⁹. Currently, growing evidence indicates that obesity, throat infection with streptococcus, and environmental factors (air pollution, ultraviolet radiation, tobacco smoking, etc.) are vital triggers for psoriasis initiation¹⁰⁻¹². Tobacco smoking is a modifiable risk factor for general health¹³ and has negative health impacts, resulting in increased mortality in many chronic diseases¹⁴. Moreover, recent data indicate that >50 types of diseases are associated with tobacco smoking, and >6 million people die from smoking each year^{15,16}. Smoking can induce free-radical damage and oxidative stress, increase immune cell activation, and interact with key signaling pathways in psoriasis pathogenesis¹⁷. As one of the key environmental pathogenic factors, tobacco smoking has proven to be an independent risk factor for the onset and development of psoriasis¹⁸.

In recent years, many effective therapies for psoriasis have been developed in clinical practice. For patients with mild psoriasis, treatment options include vitamin D analogs, calcineurin inhibitors, targeted phototherapy, keratolytics, and topical corticosteroids¹⁹. For patients with moderate to severe psoriasis, systemic treatments, including biological agents, oral agents, and phototherapy,

are the mainstay treatments^{20,21}. In clinical practice, clinicians widely use the psoriasis area and severity index (PASI) score to assess psoriasis severity and treat the decreased level of the PASI score as the core goal for psoriasis treatment and as a better indicator of therapeutic response, including PASI₇₅, PASI₉₀, and PASI₁₀₀^{22,23}. Currently, four classes of biologics (TNF inhibitors, IL-12/23 inhibitors, IL-17 inhibitors, and IL-23 inhibitors) represent one of the most significant therapeutic advancements in the field of dermatology, which have achieved satisfactory treatment effects (PASI₇₅, PASI₉₀, and even PASI₁₀₀) among psoriasis patients²⁴. However, psoriasis remains an incurable disease, and many patients require long-term treatment during their lifetime².

As mentioned previously, the pathogenesis of psoriasis is complex and not fully elucidated²⁵. Genetic factors play a critical role in the development of psoriasis, while environmental factors can exacerbate psoriasis²⁶. Because some patients cannot achieve satisfactory effects even with biological agents, and many patients encounter psoriasis recurrence², we suppose that environmental factors, especially tobacco smoking, might play a role during the treatment process. However, evidence of the association between tobacco smoking and psoriasis treatment effects, is still limited²⁷. In this study, we aimed to understand how tobacco smoking influences the achievement of PASI₇₅ after eight weeks of treatment, based on a cohort of psoriasis patients in Shanghai, China.

METHODS

Study population

This observational study was based on a cohort of patients with psoriasis established at the Shanghai Skin Diseases Hospital from 2021 to 2022. Zheng et al.²⁸ reported that the prevalence of tobacco smoking in Shanghai was 31%. In this study, psoriasis was confirmed according to the guidelines of the Chinese Clinical Dermatology, which is in line with the global guidelines for psoriasis diagnosis and treatment. Both male and female patients with moderate-to-severe psoriasis (body surface area, BSA ≥ 5 and PASI ≥ 5), aged ≥ 18 years, in the inpatient department, were included, and patients with neurological or psychiatric abnormalities or who were unable to provide informed consent were excluded. This study was reviewed and

approved by the Institutional Ethical Review Board of Shanghai Skin Disease Hospital (2021–44), and was registered in the Chinese Clinical Trial Registry (ChiCTR2200066403). This study strictly adhered to the Declaration of Helsinki.

Sample size

In this study, sample size was calculated by applying the sample size estimation formula in the observational study. Zheng et al.²⁸ reported that the prevalence of tobacco smoking was 31% in Shanghai. In this study, we set the prevalence of smoking as $p=30\%$, type I error $\alpha=0.05$, permitted error $\delta=15\%$ of p , with a 10% non-response rate during enrollment, with the sample size formula:

$$n = \mu^2_{\alpha/2} \times p(1-p) / \delta^2$$

indicating that at least 548 patients with psoriasis should be enrolled, which could ensure a 0.81 power ($1-\beta$) in this study. Finally, 560 inpatients who provided informed consent were enrolled and analyzed in this psoriasis cohort. The information that could identify individual patients after data collection was anonymized and could not be accessed by authors.

Data collection

In this study, each patient with psoriasis underwent a physical examination, BSA, PASI, and physician global assessment (PGA), evaluation administered by dermatologists, at their hospital visits. Dermatologists would then make a proper treatment plan for each patient and discuss it with them, and the individual treatment plan was finally confirmed and implemented through physician-patient shared decision-making. The treatment plan covered four options: acitretin group (25–50 mg daily), methotrexate group (MTX, 15–20 mg per week, with folic acid supplementation), narrow-band ultraviolet (NB-UVB)/benvitimod group (2–4 times weekly, plus benvitimod topical treatment concurrently), and biologics group (ustekinumab, risankizumab, secukinumab, etc.). Data were collected using a self-designed questionnaire administered by dermatologists after training. A previous pilot study demonstrated that the content validity coefficient of the questionnaire was 0.87, and the split-half reliability coefficient was 0.85. The questionnaire consisted of: 1) demographic features, including age, sex, marital status, education level, and body mass

index (BMI) etc.; 2) lifestyle habits such as tobacco smoking, physical exercise, and sleep condition etc.; 3) information on psoriasis severity (BSA, PASI, PGA), seasonality of psoriasis aggravation, and family history of psoriasis; and 4) treatment plan and PASI score evaluation at week 4 and week 8, respectively, and the records of adverse events.

Definitions and classifications

We define a smoker as a person who smoked at least 100 cigarettes in a lifetime, a current smoker someone who still smoked at the time of investigation, and a former smoker someone who had stopped smoking for at least three months at the time of investigation⁵. We defined smoking duration as the time interval (years) between the age at investigation and age at smoking initiation for current smokers, and the time interval between the age at smoking cessation and age at smoking initiation for former smokers and then classified them into <20 years and ≥ 20 years⁵. Smoking intensity was defined as the number of cigarettes smoked per day and was categorized either as <20 cigarettes or ≥ 20 cigarettes⁵. The age of the patients was classified as <45 years and ≥ 45 years. Education was recorded as completed years of schooling and categorized as 0–9 years (primary or junior high school), 10–12 years (senior high school), or >12 years (college and higher). Individual monthly income was divided into three groups: <5000, 5000–10000, and >10000 RMB (1000 Chinese Renminbi about US\$140). Daily sleep time was recorded as hours of sleep in the night plus naps in the daytime, and insufficient sleep was defined as a daily sleep time of <6 hours²⁸.

PASI was used to assess the severity of psoriasis lesions, both for lesion area and lesion severity. The score of PASI ranges from 0 to 72, with a higher score indicating greater severity of psoriasis. PASI₇₅ is defined as patients achieving $\geq 75\%$ improvement in PASI score and calculated by the formula [(PASI at baseline - PASI at week t) / PASI at baseline] $\times 100\%$ ²⁹. The efficacy of treatment was assessed by the proportion of patients achieving PASI₇₅ at week 4 and week 8, and we set PASI₇₅ achievement at week 8 as the primary outcome.

Statistical analysis

Data analysis was performed using SAS software

(version 9.4; SAS Institute Inc., Cary, NC, USA). Kolmogorov-Smirnov test was used to evaluate the normal data distribution for quantitative variables. Quantitative variables with a normal distribution were expressed as means and standard deviations (SD), and Student's t-test was used to examine for significance between variables. Quantitative variables with skewed distribution were expressed as medians and interquartile ranges (IQR), and the Mann-Whitney U test was used to test for significance between variables. Qualitative variables were expressed as frequencies and percentages (%), and statistical significance between groups was tested by the chi-squared test. We applied the logistic regression to calculate the odds ratios (OR) and 95% confidence intervals (CI) to explore the association between tobacco smoking and the achievement of PASI₇₅ at weeks 4 and 8 among psoriasis patients, either with current or former tobacco smoking. The generalized linear model (GLM) was used to show the trend of PASI score change from baseline to weeks 4 and week 8. Sensitivity analysis was performed to depict the association between the achievement of PASI₇₅ at week 8 and smoking initiation, smoking intensity, and smoking duration among patients with psoriasis who smoked. Subgroup analysis was performed among patients with the four aforementioned treatment plans. We set statistical significance at $p < 0.05$ (two-tailed).

RESULTS

Demographic and clinical features of patients with psoriasis

The age of 560 patients with psoriasis ranged 18–87 years, with an average age of 48.4 years, and 72.9% of them were male. The proportion of patients with psoriasis aged ≥ 45 years was 54.8%, and 81.8% of them were married; 47.7% of patients with psoriasis had college or higher education level, 22.5% had an individual monthly income > 10000 RMB, and 53.9% had non-communicable diseases (NCD) comorbidities. Five hundred sixty patients with psoriasis included 217 current smokers (38.8%), 28 former smokers (5.0%), and 315 non-smokers (56.2%), and 4.6% had daily sleep time < 6 hours. The median disease duration was 10.8 months (IQR: 2.3–20.0), and the median values of the BSA, PASI, and PGA scores were 15.0 (IQR: 10.0–28.0), 11.1 (IQR:

7.9–16.6) and 2.7 (IQR: 2.0–3.0), respectively. The proportions of patients with psoriasis in the acitretin, MTX, NB-UVB/benvitimod, and biologics groups were 13.2%, 19.3%, 21.6%, and 45.9%, respectively. Table 1 indicates that male patients with psoriasis had more NCD comorbidities, higher PASI and PGA scores, and higher prevalence of tobacco smoking than female patients, and the differences were all statistically significant ($p < 0.05$).

Demographic features of patients with different tobacco smoking conditions

Data in Table 2 give the demographic and dermatological features of psoriasis patients with different tobacco smoking status. In comparison with non-smokers, patients with tobacco smoking habit had a lower proportion of age < 45 years and a lower proportion of college and higher education level, were predominately males, and had more NCD comorbidities; the differences were all statistically significant ($p < 0.05$). Differences in age, sex, education level, and NCD comorbidities were identified between current smokers and non-smokers, as well as between former smokers and non-smokers (Table 2).

Patients with psoriasis who smoked tobacco tended to have higher PASI scores, but the disease duration, BSA score, PGA score, and treatment plan were similar to those of patients who did not smoke. In all 245 psoriasis patients with tobacco smoking, the median values of smoking initiation age, tobacco smoking years, and daily consumed cigarettes were 23.0 (IQR: 20.0–27.0), 26.0 (IQR: 15.0–40.0) and 20.0 (IQR: 10.0–20.0), respectively. Current smokers had a younger smoking initiation age, had a lower proportion of smoking duration < 20 years, and smoking intensity < 20 cigarettes/day than former smokers (Table 2).

PASI₇₅ achievement at week 4 and week 8 among patients with psoriasis

The median score of PASI among patients with psoriasis changed gradually from 11.1 (IQR: 7.9–16.6) at baseline to 6.2 (IQR: 3.4–10.3) at week 4, and 3.1 (IQR: 1.2–6.3) at week 8 after treatment, GLM analysis indicated a statistical significance for PASI score change ($F = 243.5$, $p < 0.01$). Among the 560 patients with psoriasis, 13.8% (77/560) and

Table 1. The sociodemographic and clinical characteristics, and treatment plan, among psoriasis patients in Shanghai, China (N=560)

Characteristics	Total (N=560) n (%)	Male (N=408) n (%)	Female (N=152) n (%)	χ^2	<i>p</i> *
Age (years)				0.06	0.80
<45	253 (45.2)	183 (44.9)	70 (46.1)		
≥45	307 (54.8)	225 (55.1)	82 (53.9)		
Education level				3.85	0.15
Junior high and lower	159 (28.4)	110 (27.0)	49 (32.2)		
Senior high	134 (23.9)	106 (26.0)	28 (18.4)		
College and higher	267 (47.7)	192 (47.0)	75 (49.3)		
Marital status				0.03	0.87
Unmarried	102 (18.2)	75 (18.4)	27 (17.8)		
Married	458 (81.8)	333 (81.6)	125 (82.2)		
Individual monthly income (RMB)				1.48	0.48
<5000	214 (38.2)	152 (37.2)	62 (40.8)		
5000–10000	220 (39.3)	159 (39.0)	61 (40.1)		
>10000	126 (22.5)	97 (23.8)	29 (19.1)		
Residency status				1.58	0.21
Local resident	337 (60.2)	252 (61.8)	85 (55.9)		
Non-local resident	223 (39.8)	156 (38.2)	67 (44.1)		
Non-communicable diseases (NCD)				14.47	<0.01
Yes	302 (53.9)	240 (58.8)	62 (40.8)		
No	258 (46.1)	168 (41.2)	90 (59.2)		
Tobacco smoking status				82.92	<0.01
Current smoker	217 (38.8)	199 (48.8)	18 (11.8)		
Former smoker	28 (5.00)	27 (6.6)	1 (0.7)		
Non-smoker	315 (56.2)	182 (44.6)	133 (87.5)		
Total daily sleep time (hours)				0.23	0.63
<6	26 (4.6)	20 (4.9)	6 (4.0)		
≥6	534 (95.4)	388 (95.1)	146 (96.0)		
Disease duration of psoriasis, median (IQR)	10.8 (2.3–20.0)	10.3 (2.1–19.7)	12.3 (2.9–21.9)	2.17	0.14
BSA score before treatment, median (IQR)	15.0 (10.0–28.0)	16.0 (11.0–29.0)	13.2 (8.5–23.7)	3.26	0.07
PASI score before treatment, median (IQR)	11.1 (7.9–16.6)	12.0 (8.4–18.0)	9.6 (6.8–13.8)	20.03	<0.01
PGA score before treatment, median (IQR)	2.7 (2.0–3.0)	2.7 (2.3–3.0)	2.3 (2.0–3.0)	18.14	<0.01
Treatment plan for patients				18.9	<0.01
Acitretin	74 (13.2)	62 (15.2)	12 (7.9)		
Methotrexate (MTX)	108 (19.3)	70 (17.2)	38 (25.0)		
Narrow-band ultraviolet (NB-UVB)/benvitimod	121 (21.6)	75 (18.4)	46 (30.3)		
Biologics (ustekinumab, risankizumab, etc.)	257 (45.9)	201 (49.3)	56 (36.8)		

RMB: 1000 Chinese Renminbi about US\$140. BSA: body surface area. PASI: psoriasis area and severity index. PGA: physician global assessment. *Chi-squared test was used to derive the *p* value for the comparison between male and female patients. IQR: interquartile range.

Table 2. Sociodemographic characteristics, smoking initiation, intensity, and duration, among psoriasis patients in Shanghai, China (N=560)

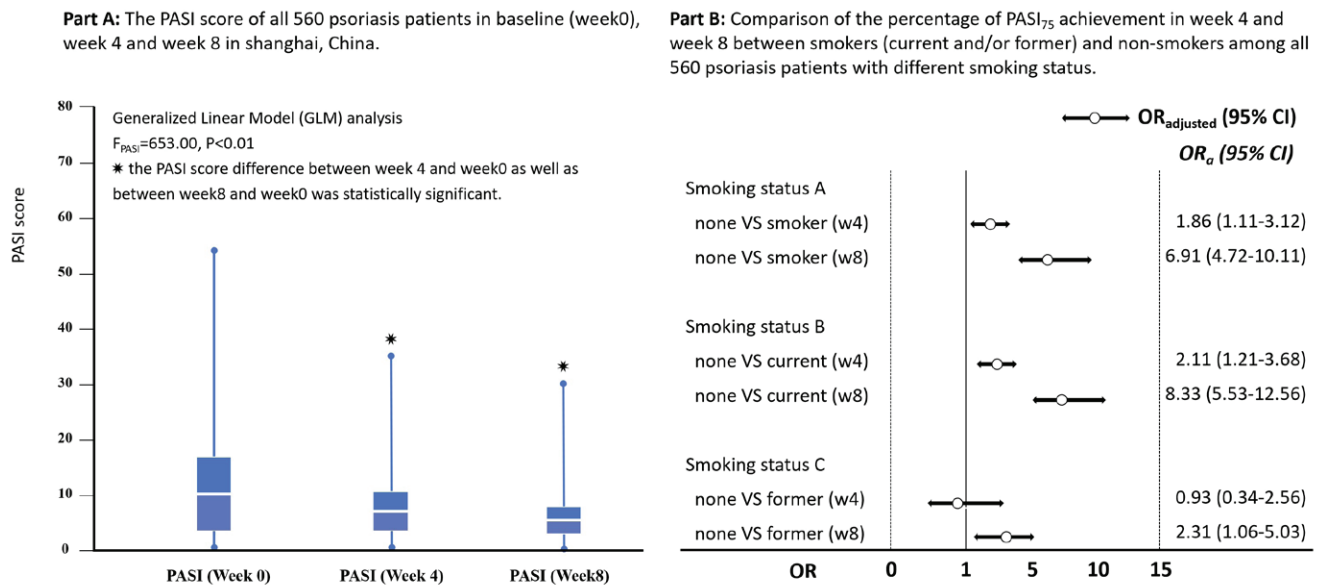
Characteristics	Tobacco smoking status			
	Smoker (N=245) n (%)	Current smoker (N=217) n (%)	Former smoker (N=28) n (%)	Non-smoker (N=315) n (%)
Age (years) <45 years ^{a-d}	89 (36.3)	83 (38.3)	6 (21.4)	164 (52.1)
Male patients ^{a-d}	226 (92.2)	199 (91.7)	27 (96.4)	182 (57.8)
Married patients ^d	208 (84.9)	185 (85.3)	23 (82.1)	250 (79.4)
Education level ^{a-d}				
Junior high and lower	78 (31.8)	65 (30.0)	13 (46.4)	81 (25.7)
Senior high	77 (31.4)	69 (31.8)	8 (28.6)	57 (18.1)
College and higher	90 (36.7)	83 (38.2)	7 (25.0)	177 (56.2)
Patients with NCD ^{a,b,d}	151 (61.6)	134 (61.8)	17 (60.7)	151 (47.9)
Daily sleep time <6 hours/day ^d	13 (5.3)	10 (4.6)	3 (10.7)	13 (4.1)
Diseases duration of psoriasis (months) ^e , median (IQR)	10.7 (2.1–19.7)	10.1 (2.0–19.1)	14.3 (10.8–22.0)	10.8 (2.6–20.9)
Scores before treatment				
BSA ^e , median (IQR)	15.0 (10.0–27.0)	15.0 (10.0–28.0)	15.0 (13.0–25.8)	15.5 (10.0–29.0)
PASI ^e , median (IQR)	11.2 (8.0–17.7)	11.2 (8.0–18.6)	10.8 (9.0–16.9)	11.0 (7.8–15.6)
PGA ^e , median (IQR)	2.7 (2.0–3.0)	2.7 (2.0–3.0)	2.7 (2.0–3.0)	2.7 (2.0–3.0)
Treatment plan for patients ^d				
Acitretin	37 (15.1)	34 (15.7)	3 (10.7)	37 (11.8)
Methotrexate	45 (18.4)	39 (18.0)	6 (21.4)	63 (20.0)
Narrow-band ultraviolet/benvitimod	51 (20.8)	46 (21.2)	5 (17.9)	70 (22.2)
Biologics (ustekinumab, risankizumab, etc)	112 (45.7)	98 (45.1)	14 (50.0)	145 (46.0)
Age of smoking initiation (years) ^e , median (IQR)	23.0 (20.0–27.0)	23.0 (20.0–27.0)	25.0 (20.0–30.0)	-
Years of tobacco smoking ^e , median (IQR)	26.0 (15.0–40.0)	25.0 (15.0–40.0)	31.5 (14.5–43.0)	-
Smoking duration <20 years ^d	78 (31.8)	69 (31.8)	9 (32.1)	-
Daily consumed cigarettes ^e , median (IQR)	20.0 (10.0–20.0)	20.0 (10.0–20.0)	12.5 (10.0–20.0)	-
Smoking intensity <20 cigarettes/day ^d	115 (46.9)	98 (45.2)	17 (60.7)	-

BSA: body surface area. PASI: psoriasis area and severity index. PGA: physician global assessment. **a** The differences between smoker and non-smoker was statistically significant ($p < 0.05$). **b** The differences between current smoker and non-smoker was statistically significant ($p < 0.05$). **c** The differences between former smoker and non-smoker was statistically significant ($p < 0.05$). **d** The chi-squared test was used to derive the p value for the comparison between groups. **e** Mann-Whitney U tests was used to derive the p value for the comparison between groups. IQR: interquartile range.

47.3% (265/560) achieved PASI₇₅ at weeks 4 and 8, respectively. Figure 1 indicates that patients with psoriasis who did not smoke had higher PASI₇₅ achievement in week 4 (OR=1.86; 95% CI: 1.11–3.12) and week 8 (OR=6.91; 95% CI: 4.72–10.11) than

those who smoked; the findings were consistent in week 4 and week 8 for non-smokers compared with current smokers, but was only in week 8 for non-smokers compared to former smokers (OR=2.31; 95% CI: 1.06–5.03) (Figure 1).

Figure 1. The psoriasis area and severity index (PASI) score evaluation among psoriasis patients at baseline, week 4 and week 8, and comparison of the percentage of PASI₇₅ achievement from baseline to week 4 and week 8 among patients with different tobacco smoking status in Shanghai, China (N=560)



Association between tobacco smoking and PASI₇₅ achievement in week 8

Patients with psoriasis who smoked tobacco had a lower PASI₇₅ achievement in week 8 than those without tobacco smoking ($p < 0.05$). Female patients, patients with an education level of college and higher, without NCD comorbidities, with daily sleep time ≥ 6 hours, and with biologics treatment, tended to have a higher PASI₇₅ achievement at week 8; the differences were statistically significant ($p < 0.05$). Multivariable logistic regression analysis with potential confounders adjustment (age, sex, education level, NCD, daily

sleep time, and treatment plan) indicated that patients without tobacco smoking had a higher proportion of PASI₇₅ achievement at week 8, the adjusted odds ratio (AOR) was 11.43 (95% CI: 6.91–18.89), 14.14 (95% CI: 8.27–24.20), and 3.05 (95% CI: 1.20–7.76), for non-smokers compared with smokers, current smokers and former smokers, respectively (Table 3).

Subgroup and sensitivity analysis

Subgroup analysis was performed to demonstrate the association between tobacco smoking and PASI₇₅ achievement at week 8 for patients with different

Table 3. Factors associated with the achievement of PASI₇₅ after 8 weeks of treatment among psoriasis patients in Shanghai, China (N=560)

Variables	PASI ₇₅ in Week 8 n (%)	Model A		Model B		Model C	
		OR	95% CI	OR	95% CI	OR	95% CI
Smoking status A^a							
Smoker ⊗	55 (22.5)	1		-	-	-	-
Non-smoker	210 (66.7)	11.43	6.91–18.89	-	-	-	-
Smoking status B^a							
Current smoker ⊗	42 (19.4)	-	-	1		-	-
Non-smoker	210 (66.7)	-	-	14.14	8.27–24.20	-	-

Continued

Table 3. Continued

Variables	PASI ₇₅ in Week 8 n (%)	Model A		Model B		Model C	
		OR	95% CI	OR	95% CI	OR	95% CI
Smoking status C^a							
Former smoker [®]	13 (46.4)	-	-	-	-	1	
Non-smoker	210 (66.7)	-	-	-	-	3.05	1.20–7.76
Age (years)^a							
<45	131 (54.8)	1.52	0.93–2.49	1.32	0.79–2.19	1.50	0.79–2.83
≥45 [®]	134 (46.7)	1		1		1	
Sex^a							
Male	177 (43.4)	0.84	0.51–1.39	0.89	0.54–1.49	1.10	0.72–3.36
Female [®]	88 (57.9)	1		1		1	
Education level^a							
Junior high and lower [®]	60 (37.7)	1		1		1	
Senior high	61 (45.5)	1.61	0.89–2.90	1.99	1.06–3.72	1.56	0.72–3.36
College and higher	144 (53.9)	1.30	0.74–2.27	1.38	0.77–2.47	1.30	0.65–2.62
NCD^a							
Yes [®]	128 (42.4)	1		1		1	
No	137 (53.1)	1.32	0.86–2.03	1.29	0.82–2.03	1.14	0.67–1.97
Daily sleep time (hours)^a							
<6 [®]	7 (26.9)	1		1		1	
≥6	258 (48.3)	1.87	0.70–4.99	2.52	0.83–7.66	2.81	0.89–8.83
Treatment plan^a							
Acitretin [®]	14 (18.9)	1		1		1	
Methotrexate	37 (34.3)	2.37	1.08–5.19	2.31	1.04–5.14	1.83	0.80–4.22
NB-UVB/benvitimid	46 (38.0)	2.98	1.36–6.54	2.59	1.16–5.78	2.26	0.97–5.25
Biologics	168 (65.4)	13.37	6.38–28.02	12.59	5.89–26.91	13.05	5.72–29.74

^a The differences of PASI₇₅ achievement in week 8 between groups was statistically significant ($p < 0.05$). Model A: Multivariable logistic regression to explore association between tobacco smoking and the achievement of PASI₇₅ in week 8 among smokers (N=245) and non-smokers (N=315). Model B: Multivariable logistic regression to explore association between tobacco smoking and the achievement of PASI₇₅ in week 8 among current smokers (N=217) and non-smokers (N=315). Model C: Multivariable logistic regression to explore association between tobacco smoking and the achievement of PASI₇₅ in week 8 among former smokers (N=28) and non-smokers (N=315). NCD: non-communicable diseases. NB-UVB: Narrow-band ultraviolet. [®] Reference categories.

treatment plans. Figure 2 indicates that smokers had lower PASI₇₅ achievement at week 8 than non-smokers in the acitretin, MTX, NB-UVB/benvitimid, and biologics groups, especially among current smokers. Current smokers tended to have lower PASI₇₅ achievement at week 8 than non-smokers, but the difference was not statistically significant ($p > 0.05$).

We also explored the association between PASI₇₅ achievement at week 8 and tobacco smoking habits

among 245 patients with psoriasis who smoked tobacco. The data in Table 4 show that former smokers had higher PASI₇₅ achievement at week 8 than non-smokers (OR=3.61; 95% CI: 1.60–8.16), even after adjusting for potential confounders (AOR=3.37; 95% CI: 1.40–8.10). The findings also showed that psoriasis patients with a younger smoking initiation age, longer smoking duration, and higher smoking intensity had lower PASI₇₅ achievement at week 8, but the difference was not statistically significant ($p > 0.05$).

Figure 2. The comparison of PASI₇₅ achievement from baseline to week 8 among patients with different tobacco smoking status based on the logistic regression model and in different treatment groups (Acitretin, MTX, NB-UVB/benitimid and biologics) in Shanghai, China (N=560)

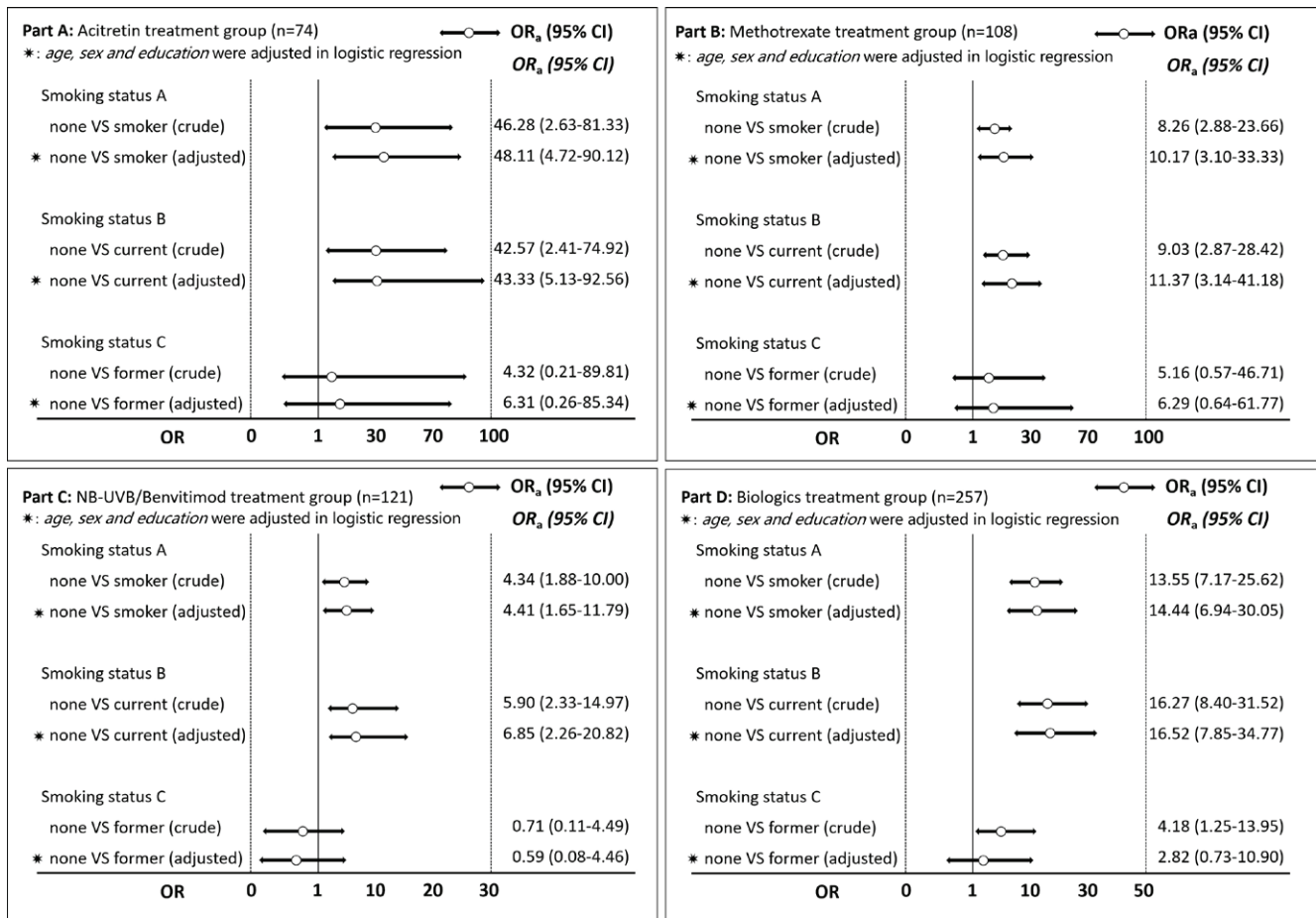


Table 4. The association between the achievement of PASI₇₅ after 8 weeks of treatment and smoking initiation age, smoking intensity and smoking duration among psoriasis patients with smoking in Shanghai, China (N=245)

Variables	PASI ₇₅ in Week 8 n (%)	Model 1		Model 2	
		OR	95% CI	AOR	95% CI
Tobacco smoking status					
Current ®	42 (19.4)	1		1	
Former	13 (46.4)	3.61	1.60–8.16	3.37	1.40–8.10
Smoking initiation age (years)					
<18 ®	4 (15.4)	1		1	
18–25	28 (23.9)	1.73	0.55–5.45	1.72	0.52–5.66
>25	23 (22.6)	1.60	0.50–5.12	1.25	0.36–4.26
Smoking duration (years)					
<20 ®	18 (23.1)	1		1	
≥20	37 (22.2)	0.95	0.50–1.80	0.52	0.17–1.66
Smoking intensity (cigarettes/day)					
<20 ®	27 (23.5)	1		1	
≥20	28 (21.5)	0.90	0.49–1.63	0.85	0.44–1.61

Model 1: Univariable logistic regression to explore association between tobacco smoking and the achievement of PASI₇₅ in week 8 among psoriasis patients with smoking habit. Model 2: Multivariable logistic regression to explore association between tobacco smoking and the achievement of PASI₇₅ in week 8 among psoriasis patients with smoking habit, with the adjustment of age, sex, and education level. AOR: adjusted odds ratio. PASI: psoriasis area and severity index. ® Reference categories.

DISCUSSION

This study recruited 560 patients with psoriasis in Shanghai to explore the influence of tobacco smoking on the efficacy of systemic treatments based on real-world clinical data. This study showed that tobacco smoking was negatively associated with PASI₇₅ achievement, both for patients with current and former tobacco smoking habits. Moreover, former smokers had higher PASI₇₅ achievement than current smokers, and patients with a younger smoking initiation age, longer smoking duration, and higher smoking intensity had lower PASI₇₅ achievement at week 8.

In practice, the decreased PASI score was treated as the core goal for psoriasis treatment, and the levels of PASI₇₅, PASI₉₀, and PASI₁₀₀ were viewed as better indicators of therapeutic response than the absolute decreased value of PASI score^{22,23}. In this study, the overall PASI₇₅ achievement was 13.8% at week 4 and 47.3% at week 8, which is consistent with previous studies²⁹⁻³¹. Griffiths et al.²⁹ reported a <20% improvement of at least 75% in the PASI score among patients with psoriasis receiving etanercept or ustekinumab treatment at week 4, and approximately 40% and 58% of PASI₇₅ achievement for etanercept and ustekinumab treatment at week 8, respectively. In a randomized clinical trial by Gordon et al.³⁰, adalimumab treatment targeted for TNF_α neutralization achieved <80% PASI reduction on average at week 8, and approximately 60% of patients with psoriasis achieved PASI₇₅ at week 8 with infliximab treatment, which was reported by Kristian et al.³¹. The American Academy of Dermatology National Psoriasis Foundation guidelines recommend the concurrent use of biologics, oral agents, and phototherapy for patients with moderate-to-severe psoriasis²⁶. In this study, patients treated with biologics achieved better efficacy (65.4% achieved PASI₇₅ at week 8) than those treated with acitretin, methotrexate, or NB-UVB. Previous studies have reported that immunosuppressive agents such as methotrexate and acitretin are effective in the treatment of psoriasis, and biologics that selectively block the steps in the inflammatory cascade provide additional therapies for psoriasis and have better treatment efficacy³².

Tobacco smoking is a well-established modifiable

risk factor¹³ and is positively associated with the initiation and severity of psoriasis¹⁸. In this study, we noticed that tobacco smoking was negatively associated with the PASI₇₅ achievement at week 8 during systemic treatment. Patients without tobacco smoking had a 14.14 (95% CI: 8.27–24.20) and 3.05 (95% CI: 1.20–7.76) times higher chance of achieving PASI₇₅ at week 8 than patients with current or former tobacco smoking, respectively. Moreover, this study also indicated that patients with younger smoking initiation age, longer smoking duration, and higher smoking intensity had lower PASI₇₅ achievement at week 8; the findings were in line with previous studies. Zhou et al.³³ reported that psoriasis disease improvement at six months in former smokers was poorer than in non-smokers (OR=0.80; 95% CI: 0.67–0.95) in a meta-analysis. Gupta et al.³⁴ found a lower percentage of tobacco smokers achieving PASI₇₅ at three months compared to conventional drug therapy for plaque psoriasis. Previous studies have indicated that excessive activation of the adaptive immune system is the kernel of psoriasis pathogenesis, and a variety of cell types, including keratinocytes, natural killer T cells, and macrophages, secrete cytokines that activate myeloid dendritic cells and play a role in the initiation and development of psoriasis²⁵. Tobacco smoking may trigger the initiation and development of psoriasis through oxidative, inflammatory, and genetic mechanisms. Nicotine also stimulates innate immune cells, and these cells release cytokines that activate T lymphocytes and perpetuate a cycle of chronic inflammation¹⁷, which is integral to the pathogenesis of psoriasis and might contribute to the lower treatment efficacy than in patients with a smoking habit.

Smoking cessation is the most powerful and cost-effective intervention available in clinical settings for the prevention of disease, disability, and death⁵, but currently, studies assessing the impact of smoking cessation on psoriasis are limited³³. In this study, former smokers had a significantly weaker association between smoking and PASI₇₅ achievement than current smokers (AOR=3.05 and 14.14) compared with non-smokers. In subgroup analysis among psoriasis patients with tobacco smoking, former smokers had higher PASI₇₅ achievement at week 8 than current smokers (OR=3.61), even after adjusting

for potential confounders (AOR=3.37). Zhou et al.³³ reported that smoking cessation benefits patients with psoriasis under treatment, based on a pooled analysis. Therefore, implementing tobacco control measures among patients with psoriasis is beneficial for improving the treatment response. Moreover, illness can be a powerful motivation to quit. The provision of cessation guides and bedside support and delivery of effective patient-centered, culturally sensitive tobacco cessation services can forestall the discomfort of nicotine withdrawal and permit the chance of successful quitting.

Previous studies have indicated that tobacco smoking is associated with the initiation and severity of psoriasis^{5,18}. In this study, patients with psoriasis and tobacco smoking had a higher median score of PASI than those without tobacco smoking, but the difference was not statistically significant. This might be due to selection bias because psoriasis patients enrolled in this study were all patients with moderate to severe psoriasis, who tended to have higher scores of BSA and PASI, even without tobacco smoking, which diminished the association between tobacco smoking and psoriasis severity. We also observed in the subgroup analysis that patients with psoriasis who smoked tobacco had a lower proportion of PASI₇₅ achievement at week 8, and the findings were consistent regardless of their treatment plan. However, the influence of tobacco smoking on PASI₇₅ achievement among patients with psoriasis was stronger in the acitretin treatment group (OR=48.11) than in the MTX (OR=10.17), NB-UVB (OR=4.41) and biologics (OR=14.44) treatment groups, this might be due to the small sample size in the acitretin treatment group; however, the true reason for these differences should be explored in future studies.

Strengths and limitations

A key strength of this study was the longitudinal design for data collection among 560 enrolled patients during their treatment based on real-world clinical circumstances, and the eight weeks of follow-up time ensured 100% compliance among patients with psoriasis. Moreover, the clinical data of patients with psoriasis were extracted from the Health Information System (HIS) directly without recall bias, which resulted in high data quality, which is another

strength of this study.

This study has some limitations. First, all 560 patients were enrolled in one hospital, which ensured high internal validity; however, the generalization of the findings to patients with psoriasis in China or even in Shanghai was limited. Second, tobacco smoking status among patients with psoriasis is self-reported, which might lead to recall bias, and the missing information on secondhand smoke exposure might underestimate the influence of tobacco smoking on treatment efficacy to some degree. The self-designed questionnaire for data collection might also lead to some information bias. Third, the time points for treatment efficacy assessment were set at weeks 4 and 8, with week 8 as the primary outcome in this study. Week 12 is more commonly used for efficacy assessment; therefore, the rate of PASI₇₅ achievement at week 8 in this study had limited comparability with other studies, so the incorporation of more assessment time points should be considered. Fourth, only tobacco smoking habits were assessed in this study, and the influence and interaction of other lifestyle habits, including alcohol consumption, lack of physical exercise, and high-fat diet and beverage consumption, should be considered in future studies^{35,36}. Fifth, we applied a logistic regression model in this study to explore the association between tobacco smoking and the achievement of PASI₇₅ among patients with psoriasis. Considering the longitudinal measurement of PASI, mixed models would be more appropriate to show the association and the interaction, which should be used in future studies. Finally, the quality-of-life assessment is another indicator of treatment efficacy but was not included in this study; therefore, the Dermatology Life Quality Index (DLQI), Short-Form-36 (SF-36), and Dermatology Quality of Life Scale (DQOLS) should be incorporated in future studies.

CONCLUSIONS

Tobacco smoking was negatively associated with the proportion of PASI₇₅ achievement among patients with psoriasis, both for those with current or former tobacco smoking habits. Moreover, former smokers had a higher proportion of PASI₇₅ achievement than current smokers. We recommend the implementation of tobacco control measures, the provision of patient-

centered, culturally sensitive cessation guides, and bedside support to improve the treatment response among patients with psoriasis.

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CONFLICTS OF INTEREST

The authors have each completed and submitted an ICMJE form for disclosure of potential conflicts of interest. The authors declare that they have no competing interests, financial or otherwise, related to the current work. R. Wang reports that since the initial planning of the work this study was supported through numerous grants, as listed under Funding.

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ETHICAL APPROVAL AND INFORMED CONSENT

Ethical approval was obtained from the Institutional Ethical Review Board of Shanghai Skin Diseases Hospital, Shanghai, China (Approval number: 2021-44; Date: 7 January 2021). Participants provided informed consent.

DATA AVAILABILITY

The data supporting this research are available from the authors on reasonable request. The request should state the title and aim of the research for which the data are requested.

AUTHORS' CONTRIBUTIONS

RW, YQ and BL: designed this study. QX, SL, LS, ZG, XG and RZ: collected data. LK and RW: performed statistical analyses. LK and YQ: drafted the manuscript. BL: supervised the study. RW: revised the manuscript. All authors read and approved the final version of the manuscript.

PROVENANCE AND PEER REVIEW

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