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New-onset Bipolar Disorder in Hidradenitis Suppurativa Patients: A Multi-center, Propensity-score-matched Cohort Study

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Abstract

Background/Aim: Hidradenitis suppurativa (HS) may be linked to an elevated risk of bipolar disorder, though the precise mechanism remains unclear. This study investigated the likelihood of bipolar disorder in patients with HS.

Patients and Methods: We analyzed the electronic health records of 60,850 patients with HS and 60,850 matched controls from the TriNetX network, excluding those with a prior bipolar disorder diagnosis. Propensity score matching was conducted (1:1 ratio), and hazard ratios (HRs) were calculated to assess the risk of new-onset bipolar disorder in patients with HS compared to controls.

Results: After matching, the HR for developing bipolar disorder in patients with HS was 1.549 [95% confidence interval (CI)=1.270-1.889] after a 1-year follow-up, remaining significant in 3- and 5-year follow-ups and sensitivity analyses. Stratified by sex, female patients with HS showed a notably higher risk (HR=1.509, 95%CI=1.353-1.683), while no significant increase was seen in males.

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Conclusion: Patients with HS have a significantly elevated risk of developing bipolar disorder, especially among females. Healthcare providers should be mindful of this association when treating patients with HS.

Keywords: Hidradenitis suppurativa, bipolar disorder, cohort, epidemiology, electronic medical records.

Introduction

Patients with hidradenitis suppurativa (HS) often present lower social activities, feel anxious, depressed, and experience pain and have substantially decreased quality of life (1). Although the prevalence of this recurrent inflammatory skin follicular disease varied across studies, it was reported that among HS individuals, female, African American and biracial patients predominate (2). Real-world evidence shows that HS affects multiple organ systems, including the cardiovascular system, rheumatic and autoimmune systems, as well the nervous system (3-7).

Bipolar disorder is a severe mood disorder diagnosed by the Diagnostic and Statistical Manual 5th edition (DSM-V) with depression and hypomania appearing alternately (8). The rates of bipolar disorder varied from 0.5% to 5% in different studies. When using the DSM-V criteria, the lifetime prevalence of bipolar disorder type 1 and type 2 were found to be 0.6% and 0.4%, respectively (9, 10). With suicide rate 20-30 fold higher than the general population, bipolar disorder was more common in female (11). Having potential heritability, bipolar disorder was found to be connected with many comorbidities including anxiety, personality disorders, obesity (12), type 2 diabetes mellitus (13), irritable bowel syndrome (14) and migraine (15).

Low quality of life, often happened in patients with HS, might be a warning of mental health problems. Moreover, elevated levels of pro-inflammatory cytokines, as seen in chronic inflammatory conditions such as psoriasis, have also been confirmed to be associated with mental health problems (16). These finding suggests that HS may have a similar relationship due to its analogous inflammatory mechanisms, including the involvement of pro-inflammatory cytokines such as TNF-alpha and IL-6. Previous study also presented that bipolar disorder was more common in patients with HS than in those with psoriasis and normal individuals (17). However, the comprehensive understanding of the connection between HS and bipolar disorder has not been researched completely. Therefore, this large retrospective cohort study aimed to observe the risk of developing bipolar disorder for patients with HS compared with control cohort using TriNetX US Collaborative Network.

Patients and Methods

The TriNetX research network was used to perform this study. It collects de-identified health information from medical institutions around the world. This database has data from over 120 healthcare organizations and has been applied for many studies in the medical science field (18-21). We focused on a part of TriNetX's sub-database that includes data from greater than 60 healthcare organizations in the United States (the US collaborative network). We used the ICD-10-CM codes to identify diseases and the ATC codes to identify medications; both are listed in Table I. This study did not involve any direct contact with or treatment of patients. Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

We studied people who were recorded having medical visit between January 1, 2005, and December 31, 2018. We enrolled people with and without HS. People were included in the HS group based on the diagnosis record of ICD-10-CM L73.2. People without HS were defined as those who came for a general check-up and did not have HS before the

index date. People who died, had cancer, or had bipolar disorder before or on the index date were not included for further analysis. We performed propensity score matching to pair people with HS with people without HS who had similar characteristics, such as age, sex, race, lab results, other health conditions, medications, substance use, social and economic factors, and the utilization status of medical services. The endpoint of follow-up was defined as new-onset bipolar disorder. Incident cases of bipolar disorder occurring within 12, 24, and 36 months were excluded in different models. After matching, 60,850 patients with HS and 60,850 controls were included (Figure 1). Hazard ratios (HR) were assessed to determine the risk of new-onset bipolar disorder in patients with HS compared to controls. To evaluate the influence of sex and age on the association between HS and bipolar disorder, we conducted stratification analyses based on sex and age. Sensitivity analyses were performed contingent on different matching covariates, wash-out periods, follow-up times, claim-based algorithms, and comparators.

We used the TriNetX research network system to deliver all statistical analyses. To compare the baseline characteristics of individuals with HS to those without, the standardized difference was calculated. If the standardized difference was greater than 0.1, we considered it to be a significant difference. We also calculated a 95% confidence interval along with the hazard ratio in each analysis to evaluate the longitudinal association between HS and bipolar disorder.

Table I. *Utilized codes.*

Description	ICD-10-CM codes
Hidradenitis suppurativa	L73.2
Neoplasms	C00-D49
Bipolar disorder	F31
Diabetes mellitus	E08-E13
Hypertension	I10
Hyperlipidemia	E78.5
Socioeconomic and psychosocial circumstances	Z55-Z65
Substance abuse	F10-F19
Chronic kidney disease	N18
Anxiety	F40-F48
Schizophrenia	F20
Suicide attempt	T14.91
Encounter for general examination	Z00
Psoriasis	L40
Atopic dermatitis	L20
Rosacea	L71
Medications	**ATC codes/RxNorm/VA codes**
Corticosteroids	ATC code: D07
Diclofenac	RxNorm: 3355
Methotrexate	RxNorm: 6851
Adalimumab	RxNorm: 327361
Infliximab	RxNorm: 191831
Lithium salts	VA:CN750

ICD-10-CM: International Classification of Diseases, Tenth Revision, Clinical Modification; ATC codes: Anatomical Therapeutic Chemical codes.

Results

Before matching, significant differences were observed in the baseline characteristics of the HS and normal cohort, including age, sex, lifestyle, socioeconomic status. After propensity score matching, the difference of covariates between two groups become insignificant (Table II). There were 60,850 patients with HS and the same number of patients without HS included in this study. The people with HS were, on average, 33 years old. Most of them were male (73.8%), followed by female (24.0%). The racial breakdown was: White (43.5%), Black or African American (34.8%), Asian (1.8%), and American Indian or Alaska Native (0.5%).

Table III shows the risk for developing future bipolar disorder in patients with HS, compared to the control cohort. The Kaplan Meier curve is shown in Figure 2. After 1-year follow-up, the HR for patients with HS developing bipolar disorder was 1.549 (95%CI=1.270-1.889). When extending to 3-year and 5-year follow-up, the HR was 1.533 (95%CI=1.360-1.729) and 1.499 (95%CI=1.361-1.652), respectively. In the sensitivity analyses, the association remained significant under various matching models. In the crude model, patients with HS exhibited a 2.909-fold risk of bipolar disorder (95%CI=2.733-3.096). The significance also presented using different washout periods and different matching algorithms. Compared to patients with psoriasis, atopic dermatitis and rosacea, the

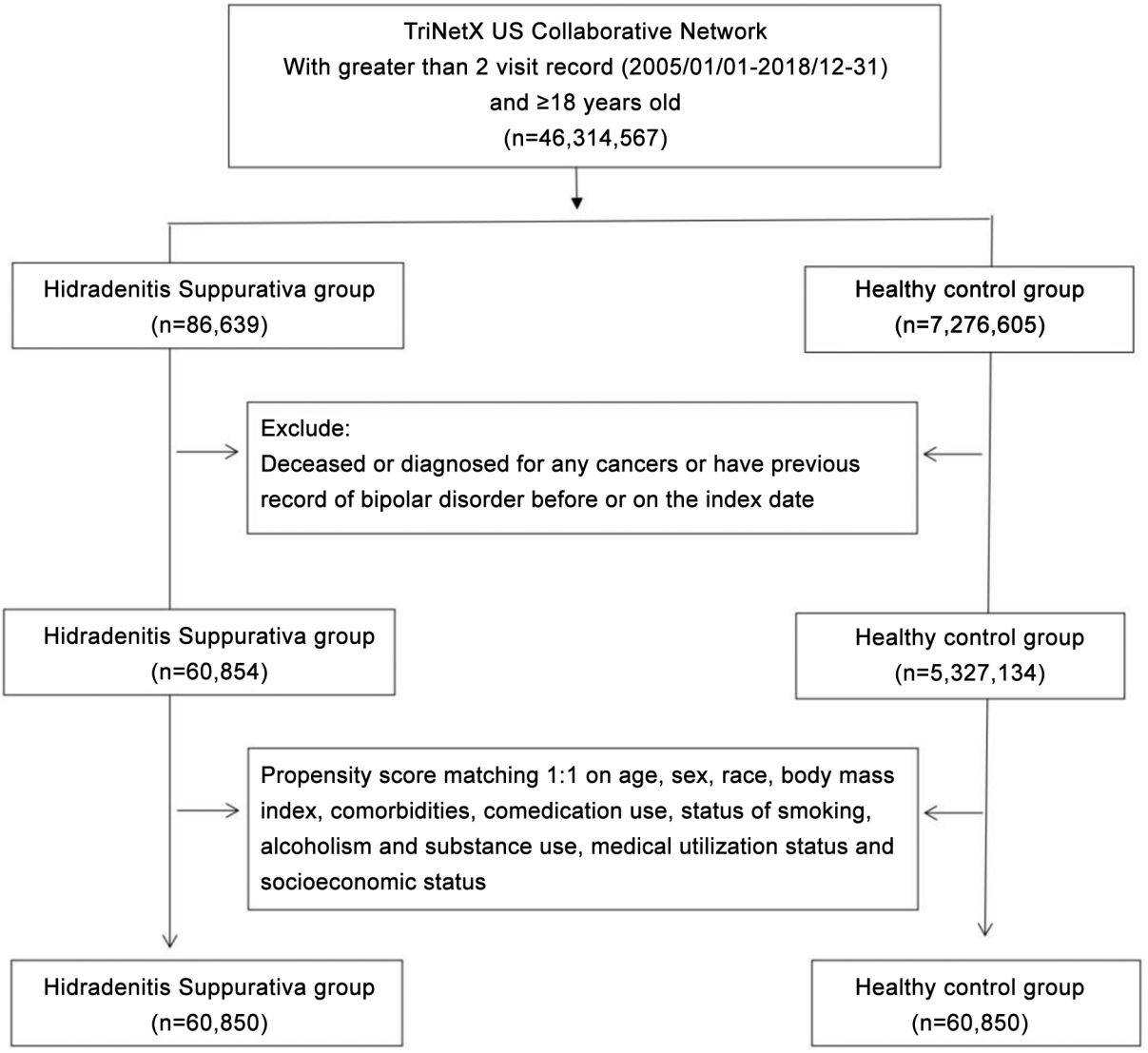

Figure 1. *Patient selection process.*

risk of bipolar disorder in patients with HS was 1.637 (95%CI=1.463-1.832), 1.471 (95%CI=1.334-1.621) and 1.988 (95%CI=1.751-2.258), respectively.

The stratification analysis demonstrated the elevated bipolar disorder risk in individuals with HS in the sex and age subgroups. For the female patients with HS, the HR for bipolar disorder was 1.509 (95%CI=1.353-1.683). However, in the male patients with HS, no significant association was observed compared to the male control subgroup. Moreover, in patients with HS aged 18-64 years, the HR was 1.554 (95%CI=1.405-1.718); whereas, in patients with HS above 65 years old, the HR was 2.627 (95%CI=1.587-4.349) (Table IV).

Discussion

Studies have demonstrated the possible relationship between HS and bipolar disorder. In a cross-sectional

Table II. *Baseline characteristics.*

	Before matching			After matching[a]		
	HS cohort (n=60,854)	Control cohort (n=5,327,134)	Std diff	HS cohort (n=60,850)	Control cohort (n=60,850)	Std diff
Age at index						
Mean±SD	33.1±13.8	37.5±20.4	**0.25**	33.1±13.8	33.5±14.3	0.03
Sex						
Male	14,582 (24.0)	2,230,229 (41.9)	**0.39**	14,582 (24.0)	14,616 (24.0)	0.00
Female	44,915 (73.8)	2,905,068 (54.5)	**0.41**	44,911 (73.8)	44,991 (73.9)	0.00
Race, n (%)						
White	26,477 (43.5)	3,270,197 (61.4)	**0.36**	26,477 (43.5)	26,407 (43.4)	0.00
Black or African American	21,152 (34.8)	798,849 (15.0)	**0.47**	21,148 (34.8)	21,310 (35.0)	0.01
Asian	1,067 (1.8)	194,888 (3.7)	**0.12**	1,067 (1.8)	2,200 (3.6)	0.12
American Indian or Alaska Native	276 (0.5)	17,296 (0.3)	0.02	276 (0.5)	200 (0.3)	0.02
Socioeconomic status						
Socioeconomic/psychosocial circumstances problem	1,139 (1.9)	39,135 (0.7)	**0.10**	1,139 (1.9)	991 (1.6)	0.02
Lifestyle						
Alcohol dependence, smoking and substance use	6,850 (11.3)	176,560 (3.3)	**0.31**	6,846 (11.3)	6,956 (11.4)	0.01
Comorbidities						
Hypertension	7,429 (12.2)	557,945 (10.5)	0.05	7,428 (12.2)	7,324 (12.0)	0.01
Diabetes mellitus	4,296 (7.1)	224,010 (4.2)	**0.12**	4,295 (7.1)	4,120 (6.8)	0.01
Hyperlipidemia	3,892 (6.4)	369,166 (6.9)	0.02	3,892 (6.4)	3,623 (6.0)	0.02
Chronic kidney disease	650 (1.1)	47,137 (0.9)	0.02	650 (1.1)	590 (1.0)	0.01
Depression	5,749 (9.4)	209,221 (3.9)	**0.22**	5,745 (9.4)	5,648 (9.3)	0.01
Anxiety	6,889 (11.3)	298,714 (5.6)	**0.21**	6,885 (11.3)	6,826 (11.2)	0.00
Schizophrenia	201 (0.3)	8,686 (0.2)	0.03	201 (0.3)	171 (0.3)	0.01
Suicide attempt	26 (<0.1)	736 (<0.1)	0.02	26 (0.0)	18 (0.0)	0.01
Co-medications						
Corticosteroids	14,714 (24.2)	703,506 (13.2)	**0.28**	14,711 (24.2)	13,776 (22.6)	0.04
Diclofenac	1,685 (2.8)	69,345 (1.3)	**0.10**	1,683 (2.8)	1,325 (2.2)	0.04
Methotrexate	358 (0.6)	10,394 (0.2)	0.06	358 (0.6)	188 (0.3)	0.04
Adalimumab	317 (0.5)	3,847 (0.1)	0.08	317 (0.5)	66 (0.1)	0.07
Infliximab	176 (0.3)	2,309 (<0.1)	0.06	176 (0.3)	52 (0.1)	0.05
Lithium salts	82 (0.1)	1,587 (<0.1)	0.04	79 (0.1)	70 (0.1)	0.00
Medical utilization status						
Ambulatory visit	39,422 (64.8)	2,859,434 (53.7)	**0.23**	39,418 (64.8)	39,407 (64.8)	0.00
Inpatient visit	10,992(18.1)	605,579 (11.4)	**0.19**	10,989 (18.1)	10,934 (18.0)	0.00
Laboratory data						
BMI, n (%)						
≥25 (kg/m^2)	10,050 (16.5)	424,842 (8.0)	**0.26**	10,046 (16.5)	10,336 (17.0)	0.01

Bold font represents a standardized difference more than 0.1. HS: Hidradenitis suppurativa. [a]Matched covariates of propensity matching include age at index, sex, race, body mass index, status of comorbidities (including diabetes mellitus, hypertension, hyperlipidemia, depression, anxiety, schizophrenia, previous suicide attempt), status of comedication use (lithium salts), status of smoking, alcoholism and substance use, medical utilization status and socioeconomic status (problems related to housing and economic circumstances, persons with potential health hazards related to socioeconomic and psychosocial circumstances).

study, patients with HS were found to have a higher risk of developing bipolar disorder compared to controls (22). Furthermore, in a systematic review and meta-analysis extracting cross-sectional studies, patients with HS were found to have a significant association with schizophrenia, bipolar disorders, depression, anxiety and personality disorders (23). The current study aimed to examine a longitudinal cohort for the association

Table III. *Hazard ratio of bipolar disorder with 95% confidence interval under various models.*

Various matching covariates	Model 1[a]	Model 2[b]	Model 3[c]
Non-HS controls	1.00	1.00	1.00
Patients with HS	2.909 (2.733,3.096)	1.379 (1.254,1.516)	1.457 (1.324,1.605)
Various wash-out periods	Model 1[d]	Model 2[e]	Model 3[f]
Non-HS controls	1.00	1.00	1.000
Patients with HS	1.492 (1.347,1.653)	1.439 (1.288,1.607)	1.416 (1.250,1.605)
Various follow-up times	Model 1[g]	Model 2[h]	Model 3[i]
Non-HS controls	1.00	1.00	1.00
Patients with HS	1.549 (1.270,1.889)	1.533 (1.360,1.729)	1.499 (1.361,1.652)
Various claim-based algorithms	Model 1[j]	Model 2[k]	Model 3[l]
Non-HS controls	1.00	1.00	1.00
Patients with HS	1.326 (1.172,1.499)	1.964 (1.727,2.233)	1.876 (1.525,2.309)
Various comparators	Model 1[m]	Model 2[n]	Model 3[o]
Other bipolar disorder-associated inflammatory skin diseases patients	1.00	1.00	1.00
Patients with HS	1.637 (1.463,1.832)	1.471 (1.334,1.621)	1.988 (1.751,2.258)

HS: Hidradenitis suppurativa. In this table, aside from the analyses of variated matching covariates, propensity score matching was presented in all analyses, with the covariates of age at index, sex, race, body mass index, status of comorbidities (including diabetes mellitus, hypertension, hyperlipidemia, depression, anxiety, schizophrenia, previous suicide attempt), status of comedication use (lithium salts), status of smoking, alcoholism and substance use, medical utilization status and socioeconomic status (problems related to housing and economic circumstances, persons with potential health hazards related to socioeconomic and psychosocial circumstances). [a]Crude model without performing propensity score matching. [b]Covariates of propensity score matching includes age at index, sex, race, comorbidities and substance use. [c]Covariates of propensity score matching includes age at index, sex, race, comorbidities, substance use and comedications. [d]Wash-out period was set as 12 months in this model. Incident bipolar disorder occurred within 12 months were not calculated as outcome events. [e]Wash-out period was set as 24 months in this model. Incident bipolar disorder occurred within 24 months were not calculated as outcome events. [f]Wash-out period was set as 36 months in this model. Incident bipolar disorder occurred within 36 months were not calculated as outcome events. [g]Follow-up period was set as 1 year in this model. [h]Follow-up period was set as 3 years in this model. [i]Follow-up period was set as 5 years in this model. [j]Only patients diagnosed HS with more than 2 visit records and was never diagnosed of cutaneous abscess by specialists at the same time were included as HS group in this model. [k]Only patients diagnosed HS with more than 2 visit records and was limited to have at least one impatient visit due to HS were included as HS group in this model. [l]Only patients diagnosed HS with more than 2 visit records and with the record of underwent drainage and incision were included as HS group in this model. [m]Comparative arm was set as patients with psoriasis. [n]Comparative arm was set as patients with atopic dermatitis. [o]Comparative arm was set as patients with rosacea.

between HS and developing bipolar disorder and we observed an elevated risk for developing bipolar disorder in patients with HS. This notable association remained in different sensitivity analyses and models. This significance was also observed in sex and age subgroups compared with the control cohort, except for male patients.

HS is connected with many inflammatory comorbidities (24, 25). With the elevation of proinflammatory cytokines, HS may cause systemic immunological problems that have an impact on various organ systems, which would lead to cardiovascular disease, metabolic syndrome, allergic status and renal diseases (26-30). A retrospective study indicated that the risk of mental disorders is higher in patients with HS than in those with psoriasis and melanocytic nevi (31). Although the pathogenesis of HS is unclear, a complex multifactorial mechanism has been proposed (32). The pilosebaceous–apocrine unit is the center of lesion formation; whereas, follicular keratosis and hyperplasia is confirmed to occlude and plug the hair follicle. In this condition, cyst will develop and rupture, which triggers inflammation, strong immune response, abscess, and the formation of sinus tract (33-35). The volume of sebaceous glands in patients with HS is found to be decreased (36). Moreover, Th17 and Th1 pathway are reported to be activated in the immunological condition of HS (37). IL-17A and IL-17F, the key cytokines produced by Th17 cells, interact with multiple cell types, such as macrophages, to

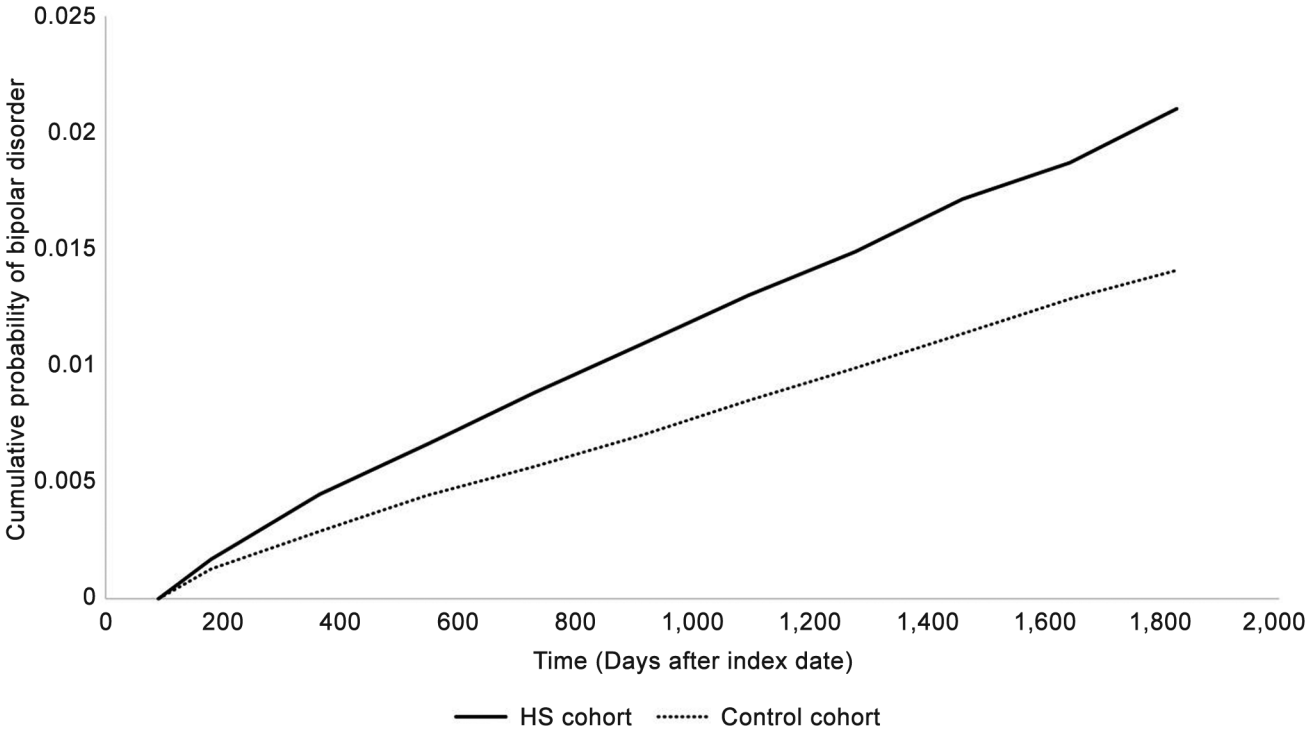

Figure 2. *Kaplan-Meier plot of new-onset bipolar disorder.*

stimulate the release of pro-inflammatory mediators. This activation initiates and propagates an inflammatory response (38). After facilitated by IL-1β, neutrophils can also migrate into the skin (39). The maturation and activation of immune pathways are also facilitated by interleukin-12 (IL-12) and interleukin-23 (IL-23), which are produced primarily by dendritic cells or other antigen-presenting cells (40). A prior translational study examining skin lesions in patients with HS revealed that macrophages infiltrating the dermis of lesioned skin exhibited high levels of IL-12 and IL-23 expression (41).

The association between HS and bipolar disorder could potentially be attributed to the mediation of the immune system. Bipolar disorder is substantially associated with the morphological changes of the frontal cortex, hippocampus and amygdala (42). It can influence various levels of our lives, including psychosocial functioning and behavior, and quality of life (43). Although the pathogenesis and inflammatory mechanism of bipolar disorder are still unclear, some studies present the relationship between bipolar disorder and the inflammatory response. Compared to normal individuals, patients with bipolar disorder have heightened serum levels of pro-inflammatory cytokines, including IL-6, TNF-α, IL-1β, interleukin-10 (IL-10), soluble interleukin-2 receptor (sIL-2R), C-C chemokine ligand 2 (CCL-2), soluble receptor of TNF-α type 1 (sTNFR1), IL-12 and CRP (44-47). A meta-analysis reported a significantly increased weighted mean difference (WMD) of 1.78 pg/ml for IL-6 and 3.97 pg/ml for TNF-α, highlighting a notable link between elevated pro-inflammatory cytokines and the presence of depression (48). The involvement of pro-inflammatory cytokines, commonly observed in both HS and psychiatric disorders, may help explain the elevated risk of psychiatric comorbidities, such as bipolar disorder, in patients with HS.

Table IV. *Stratification analysis of bipolar disorder risk in patients with HS in 5-year follow-up.*

Subgroups	Cases occurring new-onset bipolar disorder		HR (95%CI)[a]
	HS cohort No. of outcome event (%)	Control cohort No. of outcome event (%)	
Sex			
Male	175 (1.2)	154 (1.1)	1.163 (0.936,1.444)
Female	806 (1.8)	535 (1.2)	1.509 (1.353,1.683)
Age at index date			
18-64 years old	966 (1.7)	622 (1.1)	1.554 (1.405, 1.718)
≥65 years old	54 (1.1)	21 (0.4)	2.627 (1.587,4.349)

[a]Propensity score matching was presented in all analyses, with the covariates of age at index, sex, race, body mass index, status of comorbidities (including diabetes mellitus, hypertension, hyperlipidemia, depression, anxiety, schizophrenia, previous suicide attempt), status of comedication use (lithium salts), status of smoking, alcoholism and substance use, medical utilization status and socioeconomic status (problems related to housing and economic circumstances, persons with potential health hazards related to socioeconomic and psychosocial circumstances).

Additionally, quality of life can be a possible reason in this relationship. HS, as a chronic skin disease, will seriously impair quality of life of patients and have a profound impact on daily life (49). Quality of life could also be reduced in patients with bipolar disorder (50). Furthermore, lithium is suggested to be the main treatment of bipolar disorder (51). However, the use of lithium may lead to dermatological diseases, encompassing psoriasis and folliculitis (52). This result could be taken into consideration in clinical work while treating patients with bipolar disorder and skin disease.

Study limitations. First, although we did our best to balance the baseline characteristics of participants in our study, most of them were White or Black/African American, with fewer Asian and Native American people. Because different health conditions may affect different racial groups in different ways, we were not able to conclude whether racial disparity exist in the observed HS-bipolar disorder association. Moreover, the use of administrative codes, although frequently employed in numerous real-world and database-derived studies, has inherent limitations that may affect the precision of defining diseases, medications, or intervention (53, 54). Second, since this is an observational study, the causation between HS and bipolar disorder cannot be established. Third, our research database design includes data of only for five years follow-up, which means long-term risk of developing bipolar disease in patients with HS cannot be estimated in our cohort. Fourth, notwithstanding the propensity score matching and sensitivity analyses eliminate confounding bias, some misclassification bias and confounders may still present in the study (55), such as misdiagnosis of HS. Hence, our study results should be interpreted cautiously.

Conclusion

In this study, we report the elevated risk of patients with HS for developing bipolar disorder. This significant observation may be taken into account in the clinical practice while treating patients with HS.

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Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

All the Authors were involved in drafting or revising the article and approved of the submitted version. Study conception and design: Wu MC, Li YF, Lin CY, Lin NH, Lee

CY, Su YJ, Chang HC, Gau SY. Data acquisition: Chang HC and Gau SY. Data analysis and demonstration: Wu MC, Li YF and Gau SY. Original draft preparation: Wu MC, Li YF, Lin CY, Lin NH, Lee CY, Su YJ, Chang HC, Gau SY.

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