New-onset depression among children, adolescents, and adults with hidradenitis suppurativa

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Background: Information on the risk of depression among children, adolescents, and adults with hidradenitis suppurativa (HS) is limited.

Objective: To compare the risk of new-onset depression in patients with HS with that of control individuals.

Methods: Retrospective cohort analysis of 49,280 adult and 3042 pediatric patients with HS and matched control individuals identified by using electronic health record data. The primary outcome was incident depression.

Results: The crude incidence rate was 4.8 per 100 person-years in adult patients with HS compared to 3.0 per 100 person-years in control individuals. Among pediatric patients, the crude incidence rate was 4.2 per 100 person-years in patients with HS compared with 2.3 per 100 person-years in control individuals. In adjusted analysis, adults and pediatric patients with HS had a 10% (hazard ratio, 1.10; 95% confidence interval, 1.07-1.13; $P < .001$) and 26% (hazard ratio, 1.26; 95% confidence interval, 1.10-1.44; $P < .001$), respectively, increased risk of developing depression compared to control individuals. Among patients with HS, factors associated with depression included female sex, white race, smoking, and body mass index/obesity in adults and pediatric patients and substance abuse in adults only.

Limitations: Patients not seeking care in health systems within the database were not captured.

Conclusion: Children, adolescents, and adults with HS are at an increased risk for developing depression, independent of other common risk factors for depression. (J Am Acad Dermatol 2020;83:1360-6.)

Key words: comorbidity; depression; Explorys; hidradenitis suppurativa; incidence; mood disorder; new-onset.

Hidradenitis suppurativa (HS) is a chronic inflammatory disease involving the follicular unit that results in painful nodules and draining abscesses and that causes the formation of fistulas, sinus tracts, and scarring, commonly affecting the axillae, breasts, groin, and perineum.[1] Physical symptoms associated with HS are often debilitating and can lead to significant psychosocial impairment and decreased health and skin-specific quality of life.[2-4] However, there is little information on the risk of new-onset depression in a population of either pediatric or adult patients with HS. The

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purpose of this study was to compare the incidence of depression among children, adolescents, and adults with HS with that of control individuals and to determine which clinical characteristics are most closely associated with new-onset depression in patients with HS.

METHODS

This was a retrospective cohort study using a multi—health system data analytics and research platform (Explorys) developed by IBM Corporation (Armonk, NY), Watson Health.[5] Clinical information from electronic medical records, laboratories, practice management systems, and claims systems was matched by using the single set of Unified Medical Language System ontologies to create longitudinal records for unique patients. Data are standardized and curated according to common controlled vocabularies and classifications systems, including the International Classification of Diseases (ICD), Systemized Nomenclature of Medicine—Clinical Terms,[6] Logical Observation Identifiers Names and Codes,[7] and RxNorm.[8] More than 64 million unique lives, representing approximately 15% of the population across all 4 census regions of the United States, are captured. Patients with all types of insurance and those who are self-pay are represented.

The study population was limited to patients aged 10 to 89 years old having at least 2 visits in the database between January 1, 2009, and November 18, 2019, and at least 1 year of activity in the database before study entry. We excluded patients who were missing data on age or zip code or who were missing date information for HS diagnosis, depression diagnosis, or covariates. Patients with HS were identified by at least 1 ICD-9 (705.83) or ICD-10 (L73.2) diagnosis code. In an independent validation study, we observed a positive predictive value (PPV) of 79.3% and an accuracy of 90% for diagnosis of HS with this algorithm.[9] The index date for the HS cohort was defined as the latest of the following: 1) the date of first HS diagnosis, 2) the day following a 1-year baseline period, or 3) the first encounter after January 1, 2009. For control individuals, the index date was defined as the latest of the following: 1) the day following a 1-year baseline period or 2) the first encounter after January 1, 2009. To identify new cases of depression, we excluded patients diagnosed with depression at any time before the index date. The primary outcome was new diagnosis of depression, defined as at least 1 of the ICD codes listed in Supplemental Table I (available via Mendeley at https://doi.org/10.17632/kwzghfgy7y.2). This method has been previously validated with a positive predictive value of approximately 92%.[10] Patients were followed up until the date of their first depression diagnosis or were censored on the date of their last recorded encounter in the database. Control individuals were matched to patients with HS at a ratio of 4 to 1 based on zip code and index year. Separate analyses were performed for patients aged 10 to 17 years and patients aged 18 to 89 years.

CAPSULE SUMMARY

- Information on the incidence of depression among children, adolescents, and adults with hidradenitis suppurativa is limited.
- Pediatric and adult patients with hidradenitis suppurativa are at an increased risk for depression. Periodic screening for depression is warranted in patients with hidradenitis suppurativa, particularly among those who have additional risk factors.

The risk of depression was compared between these patients with HS and control individuals using an adjusted hazard ratio (HR) from a Cox proportional hazards regression model, controlling for age, sex, race, number of health care encounters 1 year before the index date, smoking status (ever, never), alcohol use disorder, substance use disorder, body mass index (BMI) (value closest to index date), and Charlson Comorbidity Index score (adult analysis only). A robust variance estimator was used to account for clustering within matched sets. We also performed a Cox proportional hazards regression within the pediatric and adult HS cohorts to evaluate demographic and clinical factors that are associated with depression in these groups. Multiple imputation was used to account for missing data in the primary analysis.

We performed 2 sensitivity analyses to determine whether our results were affected by changes in methodology. Patients with HS and control individuals were matched exactly on zip code and index year and were additionally matched using a propensity score based on the covariates included in the primary analysis. In the propensity score—matched sample, we compared risk of depression in patients with HS and control individuals using an unadjusted Cox proportional hazards regression model with a robust variance estimator. Second, we excluded patients with any missing data from the primary analysis and performed a complete case analysis.

The proportional hazards assumption was verified in all regression models by assessing the

Abbreviations used:

BMI: body mass index
CI: confidence interval
HR: hazard ratio
HS: hidradenitis suppurativa
ICD: International Classification of Diseases

correlation between the scaled Schoenfeld residuals and time and using graphical inspection of the Schoenfeld residuals. No departures from proportional hazards were detected.

RESULTS

A summary of patient eligibility is provided in Supplemental Table II (available via Mendeley at https://doi.org/10.17632/kwzghfgy7y.2). Of 50,124 eligible adults with HS, 49,280 (98%) were matched to 197,120 controls on zip code and index year. Of 3186 eligible pediatric patients with HS, 3042 (95%) were matched to 12,168 control individuals. Compared to control individuals, adults with HS were younger (mean age, 39.4 years) and were more often female (71%), African American (35%), and smokers (43%). Compared to control individuals, pediatric patients with HS were older (mean age, 15.0 years), and were more often female (80%) and African American (33%) (Table I).

The crude incidence of depression was 4.8 (95% confidence interval [CI], 4.7-4.9) per 100 person-years among adults with HS, compared to 3.0 (95% CI, 2.9-3.0) per 100 person-years among control individuals. Among children and adolescents with HS, the crude incidence of depression was 4.2 per 100 person-years, compared with 2.3 per 100 person-years in control individuals. In unadjusted analysis, adults and children/adolescents with HS had a 61% (HR, 1.61; 95% CI, 1.57-1.65) and an 87% (HR, 1.87; 95% CI, 1.66-2.10) increase, respectively, in the risk of developing depression relative to control individuals. In the adjusted analysis, adults and children/adolescents with HS had a 10% (HR, 1.10; 95% CI, 1.07-1.13; $P < .001$) and a 26% (HR, 1.26; 95% CI, 1.10-1.44; $P < .001$), respectively, increase in the risk of developing depression compared to control individuals (Table II). HRs for all covariates in the adjusted Cox PH models for adult and pediatric patients are provided in Supplemental Table III (available via Mendeley at https://doi.org/10.17632/kwzghfgy7y.2).

Factors associated with depression among adult and pediatric patients with HS are presented in Table III. Among adults with HS, the following factors were associated with depression: female sex (HR, 1.71; 95% CI, 1.61-1.80; $P < .001$), white race (HR vs black race, 1.53; 95% CI, 1.46-1.61; $P < .001$), smoking (HR, 1.85; 95% CI, 1.77-1.94; $P < .001$), BMI (HR for 5-unit increase, 1.08; 95% CI, 1.07-1.09; $P < .001$), alcohol use disorder (HR, 1.55; 95% CI, 1.33-1.81; $P < .001$), and substance use disorder (HR, 1.39; 95% CI, 1.24-1.57; $P < .001$). The highest incidence rate for depression among adult patients with HS was observed in those with a history of substance use disorder (8.8 per 100 person-years; 314 cases/3561 total person-years). Factors associated with depression among pediatric patients with HS included the following: female sex (HR, 2.13; 95% CI, 1.57-2.88; $P < .001$), white race (HR vs black race, 2.06; 95% CI, 1.63-2.61; $P < .001$), smoking (HR, 2.18; 95% CI, 1.72-2.77; $P < .001$), and obesity (HR, 1.52; 95% CI, 1.18-1.97; $P < .001$).

The results of 2 sensitivity analyses (Supplemental Materials; available via Mendeley at https://doi.org/10.17632/kwzghfgy7y.2) were consistent with the primary analysis. In complete case analysis, adult and pediatric patients with HS had 1.05 (95% CI, 1.02-1.08) and 1.24 (95% CI, 1.07-1.43) times the risk of developing depression compared to those without HS. In propensity score-matched analysis, adults and children/adolescents with HS had 1.14 (95% CI, 1.11-1.17) and 1.35 (95% CI, 1.17-1.56) times, respectively, the risk of incident depression compared to control individuals.

DISCUSSION

In this analysis, we observed that having HS is associated with an independent risk of developing depression in a population of adults, as well as children and adolescents. For every 100 HS patients without pre-existing depression, 4 new cases of depression among pediatric patients and 5 new cases of depression among adult patients would be diagnosed each year. It is speculated that pathogenesis of HS and depression may be linked through increased expression of proinflammatory cytokines, including interleukin 6 and tumor necrosis factor alpha, which have been observed at higher levels in the serum of patients with HS[11-14] and with major depression.[15] Additionally, HS has been shown to have a substantial impact on health-related quality of life,[2-4] which also likely contributes to risk of developing depression.[16]

It is also noteworthy that in the unadjusted analysis, adult and pediatric patients with HS had 61% and 87% greater risk of incident depression than those without HS, respectively. This indicates that characteristics such as obesity, smoking status, alcohol use disorder, substance use disorder and comorbidities contributed significantly to the

Table I. Characteristics of matched patients with HS and control individuals, adult and pediatric analyses

Characteristics	Adult analysis (ages 18-89 y)		Pediatric analysis (ages 10-17 y)	
	Patients with HS (n = 49,280)	Control individuals (n = 197,120)	Patients with HS (n = 3,042)	Control individuals (n = 12,168)
Age at index date, y, mean (SD)	39.4 (14.3)	45.3 (17.2)	15.0 (1.8)	13.7 (2.3)
Female, n (%)	35,231 (71)	107,501 (55)	2431 (80)	6205 (51)
Missing sex, n (%)	1 (<0.01)	66 (<0.1)	0 (0)	9 (<0.1)
Race, n (%)				
White	26,316 (56)	124,478 (73)	1556 (55)	7043 (69)
Black	16,519 (35)	28,565 (17)	920 (33)	1797 (18)
Other	3790 (8)	17,595 (10)	331 (12)	1325 (13)
Missing race	2655 (5)	26,482 (13)	235 (8)	2003 (16)
BMI, kg/m^2, mean (SD)	33.5 (8.7)	29.0 (7.2)	NA	NA
Underweight, n (%)*	NA	NA	29 (1)	239 (3)
Healthy weight, n (%)*	NA	NA	687 (26)	4278 (54)
Overweight, n (%)*	NA	NA	475 (18)	1536 (19)
Obese, n (%)*	NA	NA	1489 (56)	1897 (24)
Missing BMI, n (%)	5944 (12)	60,278 (31)	362 (12)	4218 (35)
Smoker (ever), n (%)	21,243 (43)	39,368 (20)	264 (9)	475 (4)
Alcohol use disorder, n (%)	1195 (2)	3058 (2)	0 (0)	4 (0.03)
Substance use disorder, n (%)	2539 (5)	3660 (2)	5 (0.2)	14 (0.1)
Charlson Comorbidity Index, n (%)				
0	29,542 (60)	162,604 (82)	NA	NA
1-2	14,960 (30)	27,328 (14)	NA	NA
3-4	2677 (5)	4197 (2)	NA	NA
≥5	2101 (4)	2991 (2)	NA	NA
Health care encounters,† median (IQR)	2 (0-5)	1 (0-2)	2 (1-4)	1 (0-2)
Follow-up time, y, median (IQR)	2.7 (1.1-5.2)	2.4 (0.9-4.9)	2.8 (1.2-5.1)	2.3 (0.9-4.6)

For categorical variables, percentages refer to the percentage of patients in each category among those who were not missing data for that variable. Percentages may not sum to 100 because of rounding.

BMI, Body mass index; *HS*, hidradenitis suppurativa; *IQR*, interquartile range; *NA*, not applicable; *SD*, standard deviation.

*BMI categories are based on percentiles relative to children and teens of the same sex and age. Underweight, less than the 5th percentile; healthy weight, 5th percentile to less than the 85th percentile; overweight, 85th to less than the 95th percentile; obese, equal to or greater than the 95th percentile.

†Number of encounters in the year before the index date.

Table II. Incidence of depression among patients with HS and control individuals, adult and pediatric analyses

Outcome measure	Adult analysis		Pediatric analysis	
	Patients with HS (n = 49,280)	Control individuals (n = 197,120)	Patients with HS (n = 3042)	Control individuals (n = 12,168)
Total person-years of follow-up	168,441	628,068	10,252	36,924
Number of new depression diagnoses	8027	18,646	433	833
Crude incidence rate per 100 person-years (95% CI)	4.8 (4.7-4.9)	3.0 (2.9-3.0)	4.2 (3.8-4.6)	2.3 (2.1-2.4)
Crude hazard ratio (95% CI)	1.61 (1.57-1.65)	Reference	1.87 (1.66-2.10)	Reference
Fully adjusted hazard ratio* (95% CI)	1.10 (1.07-1.13)	Reference	1.26 (1.10-1.44)	Reference
P value (adjusted HR)	<.001	—	.001	—

CI, Confidence interval; *HR*, hazard ratio; *HS*, hidradenitis suppurativa.

*HR was derived from a Cox proportional hazards regression model, controlling for age, sex, race, smoking, Charlson Comorbidity Index (adults), body mass index/body mass index category (pediatric), alcohol abuse, substance abuse, and number of health care encounters.

Table III. Risk factors for depression among adult and pediatric patients with hidradenitis suppurativa

Variable	HR* (95% CI) adult analysis	*P* value (adult analysis)	HR* (95% CI) pediatric analysis	*P* value (pediatric analysis)
Age	0.92 (0.90-0.94) per 10-y increase	<.001	0.97 (0.92-1.03) per 1-y increase	.29
Female (vs male)	1.71 (1.61-1.80)	<.001	2.13 (1.57-2.88)	<.001
Race				
White	1.53 (1.46-1.61)	<.001	2.06 (1.63-2.61)	<.001
Black	Reference	Reference	Reference	Reference
Other	1.25 (1.14-1.38)	<.001	1.53 (1.08-2.17)	.02
Alcohol use disorder	1.55 (1.33-1.81)	<.001	NA†	NA
Substance use disorder	1.39 (1.24-1.57)	<.001	2.77 (0.66-11.59)	.16
Ever smoker (vs never smoker)	1.85 (1.77-1.94)	<.001	2.18 (1.72-2.77)	<.001
CCI score (1-unit increase)	1.06 (1.05-1.07)	<.001	NA	NA
BMI (5-unit increase)	1.08 (1.07-1.09)	<.001	NA	NA
BMI category‡				
Underweight	NA	NA	1.30 (0.49-3.45)	.60
Healthy weight	NA	NA	Reference	Reference
Overweight	NA	NA	1.04 (0.75-1.44)	.83
Obese	NA	NA	1.52 (1.18-1.97)	<.001

BMI, Body mass index; *CCI*, Charlson Comorbidity Index; *CI*, confidence interval; *HR*, hazard ratio; *NA*, not applicable because the variable was not included in the regression model.

*HR derived from a Cox proportional hazards regression model, controlling for age, sex, race, BMI, smoking status, alcohol abuse (adult analysis), substance use disorder, CCI (adult analysis), and number of health care encounters.

†Alcohol use disorder was not included in the regression model for pediatric patients because no pediatric patients with HS had a history of alcohol use disorder.

‡BMI categories are based on percentiles relative to children and teens of the same sex and age. Underweight, less than the 5th percentile; healthy weight, 5th percentile to less than the 85th percentile; overweight, 85th to less than the 95th percentile; obese, equal to or greater than the 95th percentile.

development of depression within the HS cohort, as they do in the general population.[17-28] Accordingly, in addressing depression among patients with HS, it is important to recognize and manage the independent increase in risk attributable to HS, as well as the risk attributable to other common factors predisposing patients with HS to depression.

The literature to date describing depression among patients with HS has primarily focused on prevalence estimates in the adult population, with the frequency of depression ranging from 1.6% to 42.9%.[16,29-35] To our knowledge, only 1 other study has evaluated the incidence of depression in a population of adult patients with HS. In a Danish cohort of 7732 patients with HS, the incidence rate for depression was 0.68 per 1000 person-years among patients with HS compared with 0.35 per 1000 person-years in the general population.[35] Although incidence rates among Danish patients with HS and control individuals were lower than that of the present study, the incidence rate among patients with HS was nearly double that of control individual, which is consistent with our findings. However, the fully adjusted HR in the Danish analysis did not reach statistical significance (HR, 1.12; 95% CI, 0.58-2.17). Furthermore, the results of the Danish analysis may not be generalizable to the US population, where the prevalence of depression is higher.[36-38] To our knowledge, this is also the first population analysis describing the risk of depression in a population of children and adolescents with HS.

There are limitations to the present study that warrant consideration when interpreting the results. We could not capture patients who did not seek care in health systems included in the database. There is potential for misclassification of HS diagnosis, depression diagnosis, or covariates due to erroneous documentation or misdiagnosis. To mitigate the influence of possible misclassification bias, we used validated case definitions to identify patients with HS and depression. Data on potentially relevant covariates, such as socioeconomic status, that are not typically collected in the course of routine health care are generally unavailable in electronic medical records or claims data. Despite these limitations, this population-based analysis reports important data on the risk of depression among pediatric and adult patients with HS. Our study is strengthened by the inclusion of a wide range of relevant comorbidities that may confound the relationship between HS and depression. In sensitivity analyses, our findings were robust to changes in methodology. Given the size

and demographic heterogeneity of our cohort, we believe these results may be generalized to the US health care–seeking population.

In conclusion, both pediatric and adult patients with HS are at increased risk of developing depression, independent of other common risk factors for depression that also affect patients with HS. Periodic screening for depression among patients with HS may be warranted, particularly among women, smokers, and those with substance use disorder. The Patient Health Questionnaire 2 is a validated, 2-question assessment that can be administered by dermatologists to patients with HS to screen for new depressive symptoms with high sensitivity,[39-41] and those who screen positive may be referred for further evaluation.

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