Dermatol Ther (Heidelb) (2023) 13:2265–2277
https://doi.org/10.1007/s13555-023-01001-2

ORIGINAL RESEARCH

Comorbidity Burden Among Patients with Vitiligo in the United States: A Large-Scale Retrospective Claims Database Analysis

Khaled Ezzedine · Ahmed M. Soliman · Chao Li · Heidi S. Camp · Amit G. Pandya

Received: June 21, 2023 / Accepted: August 2, 2023 / Published online: September 5, 2023

ABSTRACT

Introduction: Vitiligo is often associated with comorbid conditions that may increase economic burden and affect patients' health-related quality of life. No large-scale study has been published to date using claims databases to evaluate the burden of comorbidities among patients with vitiligo. Herein, we evaluate the comorbidity burden among patients diagnosed with vitiligo from the US.

Methods: This retrospective cohort analysis used the Merative MarketScan Commercial Database. Eligible patients were diagnosed with vitiligo between January 2008 and December 2020 and matched 1:4 (vitiligo:control) with control subjects with no diagnosis of vitiligo between January 2007 and December 2021. Study outcomes were the incidence of comorbidities after matching, adjusted hazard ratios of comorbidity incidence among patients with vitiligo relative to matched control subjects, and time to comorbidity diagnosis or incidence.
Results: Baseline demographics were well balanced between matched vitiligo (n = 13,687) and control cohorts (n = 54,748). Incidence rates of comorbidities were higher among patients compared with control subjects (psychiatric, 28.4% vs 22.8%; autoimmune, 13.4% vs 5.1%; and non-autoimmune, 10.0% vs 7.0%). The most common psychiatric and autoimmune comorbidities in patients with vitiligo compared with control subjects included anxiety (14.3% vs 11.0%, respectively), sleep disturbance (9.1% vs 7.1%), depression (8.0% vs 6.3%), atopic dermatitis (3.1% vs 1.1%), psoriasis (2.7% vs 0.6%), and linear morphea (1.5% vs 0.1%). The risk of developing any psychiatric (hazard ratio 1.31; $P < 0.01$), autoimmune (hazard ratio 2.77; $P < 0.01$), or non-autoimmune (hazard ratio 1.45; $P < 0.01$) comorbidity was significantly higher among patients with vitiligo. Time to diagnosis of most vitiligo

Prior Presentation Results from this study were presented at the 31st Congress of the European Academy of Dermatology and Venerology (EADV 2022), 7–10 September 2022, Milan, Italy.

K. Ezzedine (✉)
Department of Dermatology, AP-HP, Henri Mondor University Hospital, UPEC, 51 Avenue de Lattre de Tassignv, 94000 Créteil, France
e-mail: khaled.ezzedine@aphp.fr

K. Ezzedine
EA 7379 EpiDermE, Université Paris-Est Créteil (UPEC), Créteil, France

A. M. Soliman · C. Li · H. S. Camp
AbbVie Inc., North Chicago, IL, USA

A. G. Pandya
Palo Alto Foundation Medical Group, Sunnyvale, CA, USA

A. G. Pandya
University of Texas Southwestern Medical Center, Dallas, TX, USA

comorbidities was 1–3 years, although linear morphea was diagnosed at < 1 year.
Conclusion: Results of this retrospective analysis demonstrated that patients were much more likely to be diagnosed with autoimmune or psychiatric comorbidities following a vitiligo diagnosis, which likely contributed to increased economic burden and lower quality of life.

PLAIN LANGUAGE SUMMARY

Vitiligo, a long-lasting disorder in which patches of the skin lose color, is often associated with other medical conditions that may lower a patients' quality of life and increase the cost of caring for patients with the disorder. No large-scale studies are currently available that look at how other medical conditions affect patients with vitiligo. In this study, we determine the occurrence and timing of other medical conditions among patients from the US who have vitiligo. We used the Merative MarketScan Commercial Database, which captures medical and prescription drug data for 145.5 million people in the US. Patients in this study had vitiligo diagnosed between January 2008 and December 2020 and were matched with subjects who did not have vitiligo between January 2007 and December 2021. We looked at the occurrence of other medical conditions among patients with vitiligo compared with subjects without vitiligo and the time it took for another medical condition associated with vitiligo to happen. The authors found that among 13,687 patients with vitiligo and 54,748 subjects without vitiligo, patients with vitiligo were much more likely to have an autoimmune (disorders in which the body's immune system attacks healthy tissue) or psychiatric (mental, emotional, or behavioral) disorder, which likely contributed to the amount of money needed to care for the condition and reduced quality of life.

Keywords: Autoimmune; Comorbidity; Psychiatric; Retrospective; Vitiligo

Key Summary Points

Why carry out this study?
Vitiligo is associated with an increased incidence of comorbid conditions relative to the general population
This retrospective study aimed to evaluate the comorbidity burden among patients diagnosed with vitiligo from the US
What was learned from the study?
This large retrospective analysis demonstrated that patients were much more likely to be diagnosed with autoimmune or psychiatric comorbidities following a vitiligo diagnosis
These results provide further evidence that vitiligo is a complex autoimmune disorder that likely contributes to increased economic burden and lower quality of life

INTRODUCTION

Vitiligo is a chronic autoimmune disorder, characterized by skin depigmentation caused by the loss of melanocytes [1, 2]. The global prevalence of vitiligo, which varies among different geographic regions and ethnic groups, ranges from 0.5 to 2.0%, with no difference by sex, age, or race [1, 3]. Vitiligo is classified into two major forms based on the distribution of lesions as either non-segmental or segmental [4]. The etiology of vitiligo is primarily autoimmune, although it may involve multiple mechanisms, including genetic predisposition, environmental triggers, and oxidative stress [1]. Depigmentation in vitiligo is primarily mediated by an immune-mediated attack on melanocytes following the recruitment of autoreactive cytotoxic T cells by pro-inflammatory cytokines [5, 6]. This in turn induces

autologous apoptosis and loss of melanocytes [7]. Skin diseases, and vitiligo in particular, have profound effects on the quality of life of the patient [8, 9]. Unfortunately, there currently is no cure for vitiligo, although guidelines for repigmentation include courses of topical and systemic corticosteroids, topical calcineurin inhibitors, phototherapies, autologous transplantation, oral steroids, and other immunosuppressants [10].

Vitiligo is associated with an increased incidence of comorbid conditions relative to the general population, with the most common including thyroid disease, especially Hashimoto's thyroiditis; psoriasis; adult-onset diabetes mellitus type 1; and alopecia areata [11–13]. Vitiligo is also associated with several psychiatric comorbidities, including depression and anxiety [1, 11]. Reported prevalence rates for comorbid autoimmune diseases are variable depending on the population. A low prevalence of comorbid autoimmune diseases, including morphea and alopecia areata, have been reported in India (3%) [14]. Higher rates have been reported in Taiwan (14%) [15], the US (23%) [16], Italy (42%) [17], and Turkey (55%) [18], with the most common comorbidities including atopic dermatitis, thyroid disease, autoimmune thyropathy, and Hashimoto's thyroiditis, respectively [15–18]. Comorbid conditions associated with vitiligo may increase the economic burden on patients and lower their health-related quality of life [1, 19]. A recent meta-analysis demonstrated that patients with vitiligo were at a significantly higher risk of depressive symptoms (approximately one-third of patients) and clinical depression (approximately one-quarter of patients) compared with those without vitiligo [20, 21]. To date, no large-scale study has been published using claims databases to evaluate the burden of comorbidity among patients with vitiligo.

This retrospective study aims to evaluate the comorbidity burden among patients diagnosed with vitiligo using data from the Merative MarketScan Commercial Database [22].

METHODS

Study Design and Data Source

This retrospective cohort analysis used the Merative MarketScan Commercial Database [22] as the data source. This database is one of the longest running and largest collections of proprietary de-identified claims data for privately and publicly insured people in the US. The database captures inpatient medical, outpatient medical, and outpatient prescription drug data for 145.5 million employees and their dependents covered by a variety of fee-for-service and managed care health plans. This retrospective cohort analysis using the Merative MarketScan Commercial Database did not require approval from an institutional review board or ethics committee nor was written informed consent required.

Study Population

The vitiligo cohort consisted of patients diagnosed with vitiligo as confirmed through one inpatient or two outpatient claims based on International Classification of Diseases, Revisions 9 and 10, Clinical Modification codes between January 1, 2008, and December 31, 2020. The control cohort consisted of those with no diagnosis of vitiligo between January 1, 2007, and December 31, 2021. The first date of diagnosis was used as the index date for patients with vitiligo. The index dates for the control cohort were randomly assigned between January 1, 2008, and December 31, 2020, based on the index date distribution among patients with vitiligo (Fig. 1).

Patients with vitiligo aged $\geq$ 12 years with $\geq$ 12 months of continuous enrollment before and $\geq$ 12 months following the index date were eligible for the study. Key exclusion criteria for patients with vitiligo included evidence of vitiligo-related treatment during a flexible pre-index period ($\geq$ 12 months to start of baseline continuous enrollment) and diagnosis of bullous disorders, dermatitis, eczema, papulosquamous disorders, disorders of skin and appendages, and other disorders of

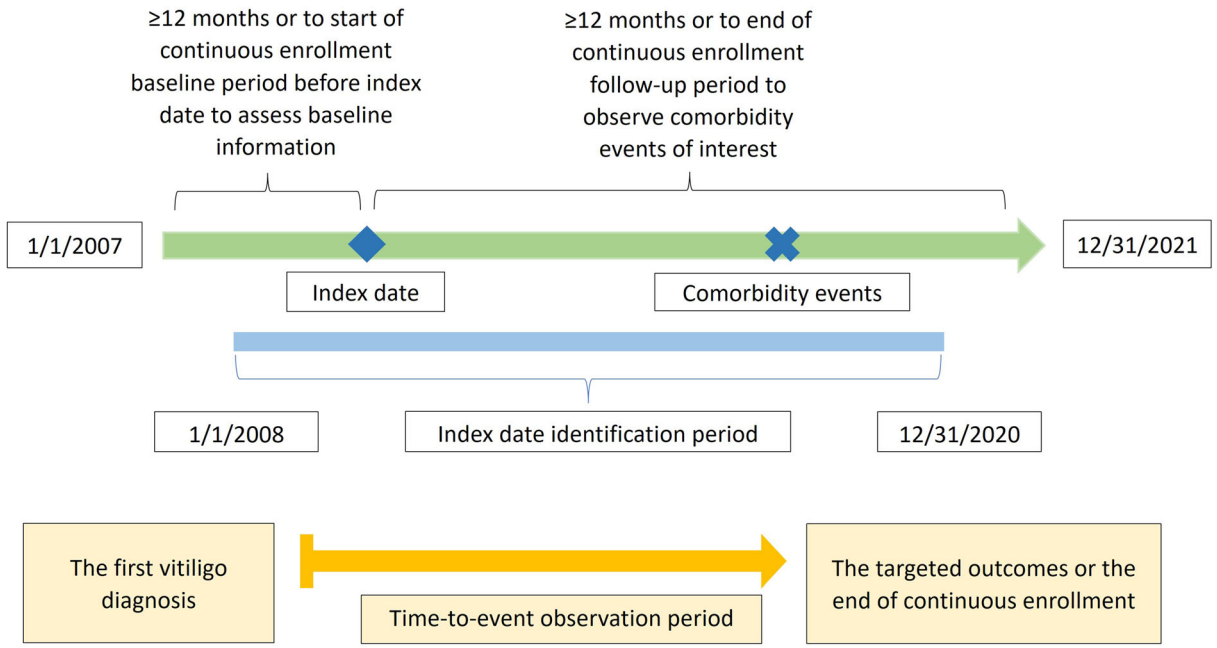


Fig. 1 Study design

pigmentation during the pre-index period. Patients who met eligibility criteria were matched 1:4 (vitiligo:control) to control participants based on age, sex, and geographic location. Matched control subjects must have had no diagnosis of vitiligo and no evidence of vitiligo-related treatment during the entire study period. For patients with vitiligo and control subjects, those with a history of or current psychiatric comorbidities, autoimmune comorbidities, and non-autoimmune comorbidities during the flexible baseline period before the index date were excluded.

Outcomes

The study outcomes were incidence of comorbidities after matching, adjusted hazard ratios (HRs) of comorbidity incidence among patients with vitiligo relative to matched controls, and time to comorbidity diagnosis/incidence.

Statistical Analysis

The HR associated with risk of developing each comorbid condition after the initial diagnosis of vitiligo in patients compared with match controls was estimated using a multivariate Cox proportional hazards model. Controlled variables in the Cox proportional hazards model included the age at index date, region of the US, baseline obesity, and baseline Charlson Comorbidity Index. The time to diagnosis of each comorbidity was also assessed and reported descriptively.

RESULTS

A total of 13,953 eligible patients with vitiligo and 1,308,073 control subjects without vitiligo were identified from the Merative MarketScan Commercial Database (Table 1). Baseline demographics were well balanced between matched cohorts (vitiligo, n = 13,687; control, n = 54,748; Table 2). Across both cohorts, the median age at index date was 39 years (range 12–64 years), and most patients were female (72.2%). Obesity rates were 2.5% and 2.2% for patients and matched control subjects, respectively. The mean Charlson Comorbidity Index was 0.1 for both cohorts. Patients were most commonly from the southern region of the US

Table 1 Attrition table identifying those included in the final study population

	Patients with vitiligo	Control subjects
Diagnosed with vitiligo (from 1 inpatient or 2 outpatient claims based on ICD-9/10-CM) 1/1/2008–12/31/2020	163,773	–
Not diagnosed with vitiligo 1/1/2007–12/31/2021	–	49,770,795
No baseline vitiligo diagnosis	161,241	–
Aged 12 years and older	139,077	42,671,647
At least 12 months continuous enrollment before and after index date	50,422	2,896,012
No baseline vitiligo-related treatment	50,090	2,892,168
No baseline diagnosis of bullous disorders, dermatitis, eczema, papulosquamous disorders, disorders of skin and appendages, or other disorders of pigmentation	22,009	1,808,652
No baseline psychiatric comorbidities	15,978	1,425,119
No baseline autoimmune comorbidities	14,987	1,378,976
No baseline non-autoimmune comorbidities	13,953	1,308,073

ICD-9/10-CM, International Classification of Diseases, Revisions 9 and 10, Clinical Modification

(39.9%), and a fee-for-service plan was the most common healthcare plan for both the vitiligo and control cohorts (82.4% and 83.5%, respectively).

Among patients, the incidence rates of any psychiatric disease and any autoimmune disease were higher among patients with vitiligo

Table 2 Baseline demographics after matching for age, sex, and geographic location

Characteristic	Vitiligo matched (*n* = 13,687)	Control matched (*n* = 54,748)
Age at index date, mean (SD), years	38.6 (14.0)	38.6 (14.0)
Median	39	39
Range	12–64	12–64
Age groups, *n* (%), years		
12–17	1327 (9.7)	5308 (9.7)
18–29	2444 (17.9)	9776 (17.9)
30–39	3205 (23.4)	12,820 (23.4)
40–49	3137 (22.9)	12,548 (22.9)
50–64	3574 (26.1)	14,296 (26.1)
Sex, *n* (%)		
Female	9880 (72.2)	39,520 (72.2)
Male	3807 (27.8)	15,228 (27.8)
Obesity[a], *n* (%)	347 (2.5)	1198 (2.2)
Charlson Comorbidity Index, mean (SD)	0.1 (0.5)	0.1 (0.4)
Median	0	0
Range	0–10	0–11
US region		
Midwest	2914 (21.3)	11,656 (21.3)
Northeast	2416 (17.7)	9664 (17.7)
South	5458 (39.9)	21,832 (39.9)
West	2899 (21.2)	11,596 (21.2)
Healthcare plan, *n* (%)		
Encounter	2403 (17.6)	9023 (16.5)
Fee-for-service	11,284 (82.4)	45,725 (83.5)
Healthcare plan type, *n* (%)		
Basic/major medical	0	1 (0)

Table 2 continued

Characteristic	Vitiligo matched (n = 13,687)	Control matched (n = 54,748)
Consumer directed health plan	1042 (7.6)	4162 (7.6)
Comprehensive	269 (2.0)	1155 (2.1)
Exclusive provider organization	178 (1.3)	657 (1.2)
High-deductible health plan	810 (5.9)	3072 (5.6)
Health maintenance organization	2326 (17.0)	8779 (16.0)
Point of service	1105 (8.1)	4745 (8.7)
Point of service with capitation	81 (0.6)	268 (0.5)
Preferred provider organization	7486 (54.7)	30,295 (55.3)
Missing/unknown	390 (2.8)	1346 (2.5)

[a]Identified by International Classification of Diseases, Revisions 9 and 10, Clinical Modification codes

compared with the matched control subjects (28.4% [n = 3892] vs 22.8% [n = 12,457] and 13.4% [n = 1830] vs 5.1% [n = 2811], respectively; Table 3). In addition, the incidence rates of non-autoimmune comorbidities were higher among patients with vitiligo (10.0% [n = 1363]) compared with the control subjects (7.0% [n = 3854]). The most common psychiatric comorbidities among patients with vitiligo and the control cohort were anxiety (14.3% vs 11.0%, respectively), sleep disturbance (9.1% vs 7.0%), and depression (8.0% vs 6.3%). The most common autoimmune comorbidities were atopic dermatitis (3.1% vs 1.1%), psoriasis (2.7% vs 0.6%), and linear morphea (1.5% vs 0.1%), and the most common non-autoimmune comorbidities were glaucoma (3.7% vs 2.8%), sensorineural hearing loss (2.7% vs 1.7%), and folate deficiency (2.7% vs 1.6%).

Table 3 Incidence of comorbidities in patients with vitiligo

Comorbidity[a], n (%)	Vitiligo matched n = 13,687	Control matched n = 54,748
Any psychiatric disease	3892 (28.4)	12,457 (22.8)
Anxiety	1963 (14.3)	6016 (11.0)
Sleep disturbance	1250 (9.1)	3858 (7.0)
Depression	1094 (8.0)	3470 (6.3)
Substance abuse or dependence	690 (5.0)	2598 (4.8)
Substance abuse	48 (0.4)	254 (0.5)
Substance dependence	665 (4.9)	2481 (4.5)
Adjustment disorder	510 (3.7)	1474 (2.7)
Dysthymic disorder	249 (1.8)	762 (1.4)
Panic disorder	173 (1.3)	507 (0.9)
Alcohol abuse or dependence	139 (1.0)	570 (1.0)
Alcohol abuse	103 (0.8)	456 (0.8)
Alcohol dependence	56 (0.4)	215 (0.4)
Suicidal ideation/ attempts	130 (1.0)	405 (0.7)
Bipolar disorder	107 (0.8)	350 (0.6)
Sexual dysfunction	75 (0.5)	211 (0.4)
Eating disorder	44 (0.3)	134 (0.2)
Social phobia	28 (0.2)	66 (0.1)
Agoraphobia	13 (0.1)	36 (0.1)
Personality disorder	15 (0.1)	60 (0.1)
Schizophrenia	20 (0.1)	43 (0.1)
Any autoimmune disease	1830 (13.4)	2811 (5.1)
Atopic dermatitis	422 (3.1)	581 (1.1)
Psoriasis	368 (2.7)	340 (0.6)
Linear morphea	208 (1.5)	42 (0.1)
Alopecia areata	161 (1.2)	117 (0.2)
Type 1 diabetes mellitus	105 (0.8)	303 (0.6)

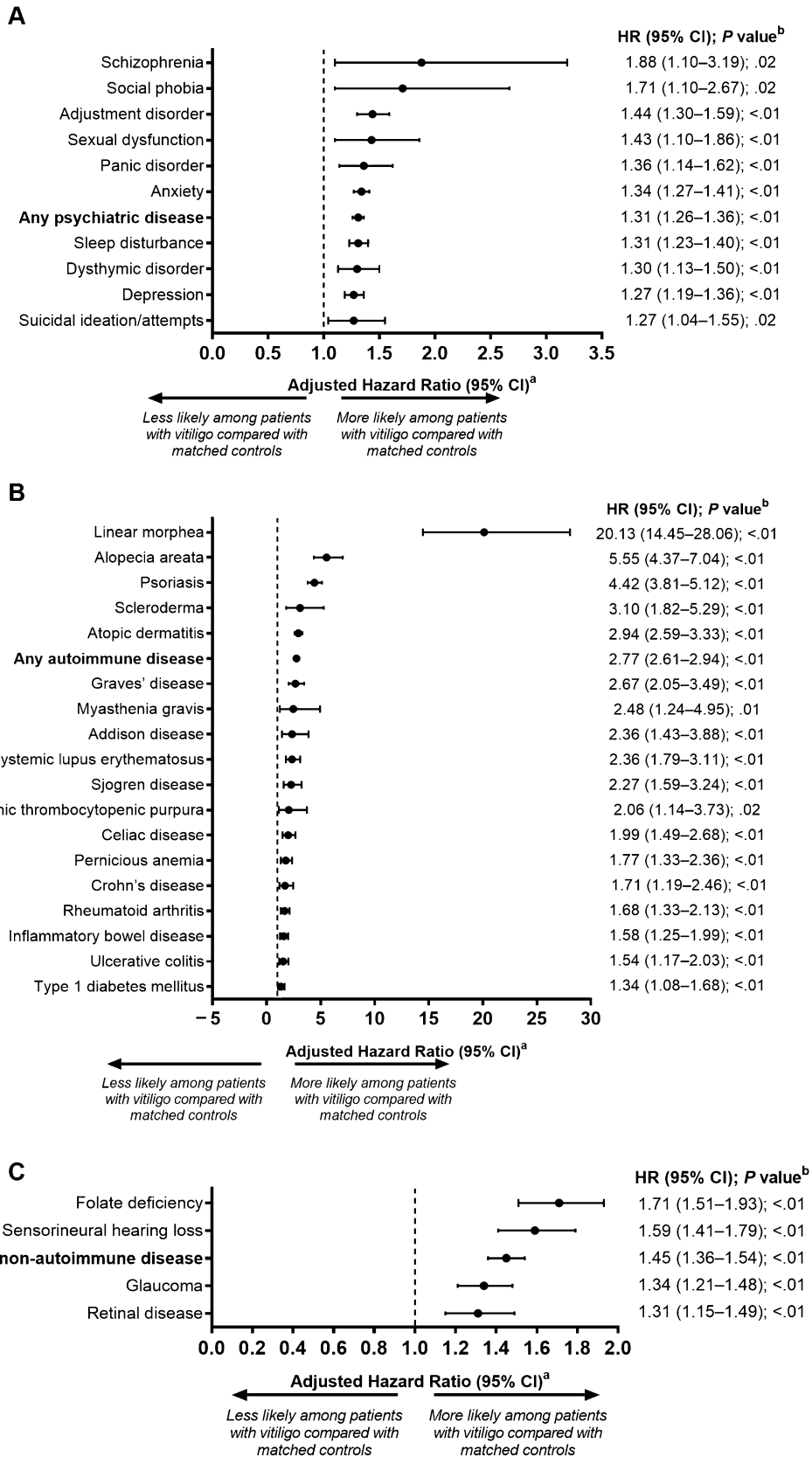
Table 3 continued

Comorbidity[a], *n* (%)	Vitiligo matched *n* = 13,687	Control matched *n* = 54,748
Graves' disease	91 (0.7)	135 (0.3)
Inflammatory bowel disease	101 (0.7)	253 (0.5)
Rheumatoid arthritis	98 (0.7)	230 (0.4)
Systemic lupus erythematosus	81 (0.6)	135 (0.2)
Celiac disease	67 (0.5)	134 (0.2)
Pernicious anemia	68 (0.5)	150 (0.3)
Ulcerative colitis	71 (0.5)	182 (0.3)
Sjogren disease	48 (0.4)	84 (0.2)
Uveitis	61 (0.4)	195 (0.4)
Crohn's disease	42 (0.3)	96 (0.2)
Addison disease	25 (0.2)	41 (0.1)
Multiple sclerosis	27 (0.2)	73 (0.1)
Scleroderma	24 (0.2)	31 (0.1)
Dermatomyositis	10 (0.1)	29 (0.1)
Idiopathic thrombocytopenic purpura	17 (0.1)	32 (0.1)
Myasthenia gravis	13 (0.1)	21 (< 0.1)
Guillain-Barré syndrome	5 (< 0.1)	10 (< 0.1)
Pemphigus vulgaris	2 (< 0.1)	8 (< 0.1)
Rheumatic fever	5 (< 0.1)	15 (< 0.1)
Any non-autoimmune disease	1363 (10.0)	3854 (7.0)
Glaucoma	505 (3.7)	1522 (2.8)
Folate deficiency	364 (2.7)	852 (1.6)
Sensorineural hearing loss	375 (2.7)	955 (1.7)
Retinal disease	307 (2.2)	930 (1.7)
Parkinson's disease	5 (< 0.1)	19 (< 0.1)

From index date to the end of the continuous enrollment of the follow-up period (≥ 12 months for every patient)
[a]Patients with a psychiatric disorder diagnosis, or an autoimmune comorbidity condition, or a non-autoimmune comorbidity condition during the pre-index period were excluded

The risk of developing any psychiatric (HR 1.31; $P < 0.01$) or any autoimmune (HR 2.77; $P < 0.01$) comorbidity was significantly higher in patients with vitiligo compared with the control cohort (Fig. 2). The greatest psychiatric comorbidity risks in patients with vitiligo included schizophrenia (HR 1.88 [95% CI 1.10–3.19]; $P = 0.02$), social phobia (1.71 [1.10–2.67]; $P = 0.02$), and adjustment disorder (1.44 [1.30–1.59]; $P < 0.01$). Patients with vitiligo had the greatest risk of being diagnosed with autoimmune comorbidities, such as linear morphea (HR 20.13 [95% CI 14.45–28.06]; $P < 0.01$), alopecia areata (5.55 [4.37–7.04]; $P < 0.01$), and psoriasis (4.42 [3.81–5.12]; $P < 0.01$) compared with the matched control subjects. A diagnosis of vitiligo versus no diagnosis was also associated with a significantly greater risk of being diagnosed with non-autoimmune conditions (HR 1.45; $P < 0.01$), including folate deficiency (HR 1.71 [95% CI 1.51–1.93]; $P < 0.01$), sensorineural hearing loss (1.59 [1.41–1.79]; $P < 0.01$), and glaucoma (1.34 [1.21–1.48]; $P < 0.01$).

Among matched patients with incident events, the mean (SD) time between the first diagnosis of vitiligo and development of comorbidities was 2.1 (2.1) years for psychiatric comorbidities, 1.8 (2.1) years for autoimmune comorbidities, and 2.7 (2.4) years for non-autoimmune comorbidities (Table 4). Mean (SD)


A
HR (95% CI); P value[b]
Schizophrenia 1.88 (1.10–3.19); .02
Social phobia 1.71 (1.10–2.67); .02
Adjustment disorder 1.44 (1.30–1.59); <.01
Sexual dysfunction 1.43 (1.10–1.86); <.01
Panic disorder 1.36 (1.14–1.62); <.01
Anxiety 1.34 (1.27–1.41); <.01
Any psychiatric disease 1.31 (1.26–1.36); <.01
Sleep disturbance 1.31 (1.23–1.40); <.01
Dysthymic disorder 1.30 (1.13–1.50); <.01
Depression 1.27 (1.19–1.36); <.01
Suicidal ideation/attempts 1.27 (1.04–1.55); .02
0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5
Adjusted Hazard Ratio (95% CI)[a]
Less likely among patients with vitiligo compared with matched controls
More likely among patients with vitiligo compared with matched controls
B
HR (95% CI); P value[b]
Linear morphea 20.13 (14.45–28.06); <.01
Alopecia areata 5.55 (4.37–7.04); <.01
Psoriasis 4.42 (3.81–5.12); <.01
Scleroderma 3.10 (1.82–5.29); <.01
Atopic dermatitis 2.94 (2.59–3.33); <.01
Any autoimmune disease 2.77 (2.61–2.94); <.01
Graves' disease 2.67 (2.05–3.49); <.01
Myasthenia gravis 2.48 (1.24–4.95); .01
Addison disease 2.36 (1.43–3.88); <.01
Systemic lupus erythematosus 2.36 (1.79–3.11); <.01
Sjogren disease 2.27 (1.59–3.24); <.01
Idiopathic thrombocytopenic purpura 2.06 (1.14–3.73); .02
Celiac disease 1.99 (1.49–2.68); <.01
Pernicious anemia 1.77 (1.33–2.36); <.01
Crohn's disease 1.71 (1.19–2.46); <.01
Rheumatoid arthritis 1.68 (1.33–2.13); <.01
Inflammatory bowel disease 1.58 (1.25–1.99); <.01
Ulcerative colitis 1.54 (1.17–2.03); <.01
Type 1 diabetes mellitus 1.34 (1.08–1.68); <.01
−5 0 5 10 15 20 25 30
Adjusted Hazard Ratio (95% CI)[a]
Less likely among patients with vitiligo compared with matched controls
More likely among patients with vitiligo compared with matched controls
C
HR (95% CI); P value[b]
Folate deficiency 1.71 (1.51–1.93); <.01
Sensorineural hearing loss 1.59 (1.41–1.79); <.01
Any non-autoimmune disease 1.45 (1.36–1.54); <.01
Glaucoma 1.34 (1.21–1.48); <.01
Retinal disease 1.31 (1.15–1.49); <.01
0.0 0.2 0.4 0.6 0.8 1.0 1.2 1.4 1.6 1.8 2.0
Adjusted Hazard Ratio (95% CI)[a]
Less likely among patients with vitiligo compared with matched controls
More likely among patients with vitiligo compared with matched controls

◀**Fig. 2** Risk of developing **a** psychiatric, **b** autoimmune, and **c** non-autoimmune comorbidities among patients diagnosed with vitiligo compared with matched controls. HR, hazard ratio. [a]Adjusted HRs were estimated by Cox regressions controlling for age, obesity, Charlson Comorbidity Index, and region. [b]Only statistically significant data are presented in this figure

times to diagnosis of high-risk autoimmune comorbidities of linear morphea and alopecia areata were 0.8 (1.3) and 1.5 (2.0) years after a vitiligo diagnosis, respectively; psychiatric comorbidities of schizophrenia and social phobia were diagnosed at 4.1 (3.6) and 3.2 (2.3) years after a vitiligo diagnosis; non-autoimmune folate deficiency and sensorineural hearing loss were diagnosed 3.0 (2.6) and 3.0 (2.5) years after a vitiligo diagnosis. Although most comorbidities were diagnosed within 1–3 years of a vitiligo diagnosis, mean (SD) time to diagnosis of celiac disease was 3.9 (2.6) years and to diagnosis of myasthenia gravis was 3.5 (2.3) years after a vitiligo diagnosis.

DISCUSSION

To the best of our knowledge, this is the largest retrospective study to describe the comorbidity burden among patients diagnosed with vitiligo versus matched controls. Using data from the Merative MarketScan Commercial Database for 13,687 patients diagnosed with vitiligo from January 1, 2008, to December 31, 2020, and 54,748 matched control subjects without vitiligo, this analysis showed higher incidence rates of psychiatric, autoimmune, and non-autoimmune diseases among patients with vitiligo compared with the control cohort. For example, the incidence rates of anxiety, sleep disturbance, depression, atopic dermatitis, psoriasis, and linear morphea were higher among patients with vitiligo. Other high-incidence comorbidities included glaucoma, sensorineural hearing loss, and folate deficiency. The risk of developing psychiatric comorbidities, such as schizophrenia and social phobia, was significantly greater among patients with vitiligo

Table 4 Time to diagnosis/development of comorbidities among matched patients with vitiligo with incident events

Comorbidities, years	Mean (SD)	Median
Any psychiatric disease	2.1 (2.1)	1.4
Adjustment disorder	1.8 (1.9)	1.2
Sexual dysfunction	2.4 (2.3)	1.9
Anxiety	2.5 (2.4)	1.8
Dysthymic disorder	2.5 (2.3)	1.7
Sleep disturbance	2.8 (2.5)	2.1
Suicidal ideation/attempts	2.8 (2.5)	2.0
Depression	2.9 (2.6)	2.0
Panic disorder	2.9 (2.8)	2.0
Social phobia	3.2 (2.3)	2.8
Schizophrenia	4.1 (3.6)	3.3
Any autoimmune disease	1.8 (2.1)	1.0
Linear morphea	0.8 (1.3)	0.2
Alopecia areata	1.5 (2.0)	0.6
Addison disease	1.8 (1.6)	1.8
Graves' disease	1.8 (1.9)	1.2
Psoriasis	1.8 (2.1)	1.0
Atopic dermatitis	2.0 (2.4)	1.2
Scleroderma	2.0 (2.2)	1.1
Systemic lupus erythematosus	2.0 (2.0)	1.3
Idiopathic thrombocytopenic purpura	2.1 (2.3)	1.3
Type 1 diabetes mellitus	2.1 (2.0)	1.5
Pernicious anemia	2.3 (2.2)	1.6
Rheumatoid arthritis	2.3 (2.3)	1.8
Crohn's disease	2.5 (2.5)	2.0
Inflammatory bowel disease	2.5 (2.3)	2.1
Sjogren disease	2.5 (2.5)	1.5
Ulcerative colitis	2.5 (2.2)	2.1
Myasthenia gravis	3.5 (2.3)	3.9
Celiac disease	3.9 (2.6)	3.2

Table 4 continued

Comorbidities, years	Mean (SD)	Median
Any non-autoimmune disease	2.7 (2.4)	2.0
Retinal disease	2.6 (2.3)	1.9
Glaucoma	2.9 (2.6)	2.2
Folate deficiency	3.0 (2.6)	2.4
Sensorineural hearing loss	3.0 (2.5)	2.3

Included comorbidities are those for which patients with vitiligo were at significantly greater risk of developing compared with matched controls (matched by age at index, sex, and region)

compared with matched controls, as was the risk of developing autoimmune comorbidities, such as linear morphea and alopecia areata. Among matched patients with incident events, the time to diagnosis of most vitiligo comorbidities was within 1–3 years of the vitiligo diagnosis; however, linear morphea was diagnosed less than 1 year from the vitiligo diagnosis.

Vitiligo has often been classified as a cosmetic disease [19], but these results provide further evidence that vitiligo is a complex autoimmune disorder that can have multiple associated autoimmune and psychiatric comorbid conditions. A combination of genetic susceptibility, inflammation, and autoimmune response is believed to contribute to the etiology of vitiligo [23]. Several genes and genetic abnormalities of specific loci have been identified that appear to mediate vitiligo susceptibility and are shared with several other autoimmune diseases, which supports a shared pathogenesis of autoimmune comorbidities associated with vitiligo [24].

The results from this study are consistent with previous studies identifying a high prevalence of autoimmune diseases among patients diagnosed with vitiligo. A chart review of 1873 patients with vitiligo in the US identified comorbid psoriasis in 2.2% of patients with vitiligo and linear morphea in 0.2% and found that patients with at least one comorbid autoimmune disease tended to have more extensive vitiligo disease by body surface area compared with those without comorbid autoimmune disease [12]. In addition, a retrospective population-based study of 14,883 patients with vitiligo in Taiwan identified high rates of atopic dermatitis (8.0%) and psoriasis (2.8%) and found that patients with vitiligo had a fourfold higher risk of having three or more associated autoimmune or atopic diseases compared with controls [15]. A study of 2624 patients with vitiligo in North America and the UK reported a twofold higher incidence of inflammatory bowel disease and an eightfold higher incidence of any autoimmune thyroid disease in patients with vitiligo compared with the general population [25]. Our results are consistent with a previous population-based study observing higher rates of Graves' disease in patients with vitiligo (0.3%) compared with the general population (0.1%) [15]. That study also noted marked increased rates of another autoimmune thyroid disease (Hashimoto's thyroiditis) in patients with vitiligo (1.26%) compared with the general population (0.24%) [15].

Recent reviews have identified anxiety and depression to be highly prevalent in patients with vitiligo and have identified an unmet need to quantify and manage psychological symptoms and disorders in these patients [20, 21, 26]. Our analysis is congruent with these findings and provides further evidence of the associations between vitiligo and psychiatric diseases.

Melanocytes in the cochlea have been shown to play a key role in hearing [27], and it has been speculated that patients with vitiligo may be at an increased risk of developing sensorineural hearing loss due to melanocyte depletion in the cochlea. This hypothesis is supported by our observations as well as a population-based cohort study examining the association between sensorineural hearing loss and vitiligo from Taiwan, which showed a 2.2-fold increased risk of developing sensorineural hearing loss in patients with vitiligo compared with the general population [28].

A strength of this analysis includes the consideration of patients who were diagnosed with vitiligo before any other autoimmune disease.

However, the retrospective nature of this study is a limitation that does not allow causation to be firmly established; prospective long-term clinical studies and registries are needed in the future to confirm these results. In addition, although the study matched patients and controls on several important characteristics, there might be unmeasured confounding and selection biases that cannot be eliminated. Consequently, these results may not be generalizable to populations outside the US.

CONCLUSION

Patients with vitiligo were much more likely to be diagnosed with autoimmune or psychiatric comorbidities compared with matched controls. In addition, comorbid conditions likely contributed to the increased economic burden and the lower quality of life experienced by patients with vitiligo.

ACKNOWLEDGEMENTS

AbbVie and the authors thank the patients, the personnel at the study sites, and the investigators who participated in this study

Medical Writing, Editorial, and Other Assistance Medical writing support was provided by Lisa R. Denny, PhD, and Janet E. Matsuura, PhD, of ICON (Blue Bell, PA, USA) and was funded by AbbVie.

Author Contributions. All authors had access to relevant data and participated in the drafting, review and editing, and approval of this publication. K. Ezzedine, A.G. Pandya, and A.M. Soliman contributed to conceptualization and K. Ezzedine, A.G. Pandya, A.M. Soliman, and H.S. Camp to methodology. Formal analysis was performed by C. Li. A.M. Soliman oversaw funding acquisition, investigation, project administration, resources, supervision, and validation.

Funding. AbbVie funded this study and the Rapid Service Fee and participated in the study design, research, analysis, data collection, interpretation of data, reviewing, and approval of the publication. No honoraria or payments were made for authorship.

Data Availability. All data generated or analyzed during this study were derived from the privately held Merative MarketScan Commercial Database and are not a publicly available.

Declarations

Conflict of Interest. K. Ezzedine is a consultant for AbbVie, Incyte, La Roche-Posay, Pfizer, Pierre Fabre, Sanofi, and Viela Bio. A.M. Soliman, C. Li, and H.S. Camp are full-time employees of AbbVie Inc. and may hold AbbVie stock and/or stock options. A.M. Soliman is also a co-inventor on AbbVie patents. A.G. Pandya has served as an investigator for Immune Tolerance Network, Incyte, and Pfizer. He is a consultant for AbbVie, Arcutis, Avita Medical, Immune Tolerance Network, Incyte, Pfizer, Trifecta, TWi, Viela Bio, Vyne, and Villaris and holds stock options for Tara Medical and Zerigo Health.

Ethical Approval. This retrospective cohort analysis using the Merative MarketScan Commercial Database did not require approval from an institutional review board or ethics committee nor was written informed consent required.

REFERENCES

1. Bergqvist C, Ezzedine K. Vitiligo: a review. Dermatology. 2020;236(6):571–92.

2. Ezzedine K, Lim HW, Suzuki T, et al. Revised classification/nomenclature of vitiligo and related issues: the Vitiligo Global Issues Consensus Conference. Pigment Cell Melanoma Res. 2012;25(3):E1-13.

3. Silverberg N. The epidemiology of vitiligo. Curr Dermatol Rep. 2015;4(1):36–43.

4. Taieb A, Picardo M, VETF Members. The definition and assessment of vitiligo: a consensus report of the Vitiligo European Task Force. Pigment Cell Res. 2007;20(1):27–35.

5. van den Boorn JG, Konijnenberg D, Dellemijn TA, et al. Autoimmune destruction of skin melanocytes by perilesional T cells from vitiligo patients. J Invest Dermatol. 2009;129(9):2220–32.

6. Ogg GS, Rod Dunbar P, Romero P, Chen JL, Cerundolo V. High frequency of skin-homing melanocyte-specific cytotoxic T lymphocytes in autoimmune vitiligo. J Exp Med. 1998;188(6):1203–8.

7. Wu J, Zhou M, Wan Y, Xu A. CD8+ T cells from vitiligo perilesional margins induce autologous melanocyte apoptosis. Mol Med Rep. 2013;7(1):237–41.

8. Ongenae K, Dierckxsens L, Brochez L, van Geel N, Naeyaert JM. Quality of life and stigmatization profile in a cohort of vitiligo patients and effect of the use of camouflage. Dermatology. 2005;210(4):279–85.

9. Radtke MA, Schäfer I, Gajur A, Langenbruch A, Augustin M. Willingness-to-pay and quality of life in patients with vitiligo. Br J Dermatol. 2009;161(1):134–9.

10. Taieb A, Alomar A, Böhm M, et al. Guidelines for the management of vitiligo: the European Dermatology Forum consensus. Br J Dermatol. 2013;168(1):5–19.

11. Dahir AM, Thomsen SF. Comorbidities in vitiligo: comprehensive review. Int J Dermatol. 2018;57(10):1157–64.

12. Gill L, Zarbo A, Isedeh P, Jacobsen G, Lim HW, Hamzavi I. Comorbid autoimmune diseases in patients with vitiligo: a cross-sectional study. J Am Acad Dermatol. 2016;74(2):295–302.

13. van Geel N, Speeckaert M, Brochez L, Lambert J, Speeckaert R. Clinical profile of generalized vitiligo patients with associated autoimmune/autoinflammatory diseases. J Eur Acad Dermatol Venereol. 2014;28(6):741–6.

14. Poojary SA. Vitiligo and associated autoimmune disorders: a retrospective hospital-based study in Mumbai, India. Allergol Immunopathol (Madr). 2011;39(6):356–61.

15. Chen YT, Chen YJ, Hwang CY, et al. Comorbidity profiles in association with vitiligo: a nationwide population-based study in Taiwan. J Eur Acad Dermatol Venereol. 2015;29(7):1362–9.

16. Sheth VM, Guo Y, Qureshi AA. Comorbidities associated with vitiligo: a ten-year retrospective study. Dermatology. 2013;227(4):311–5.

17. Ingordo V, Cazzaniga S, Raone B, et al. Circulating autoantibodies and autoimmune comorbidities in vitiligo patients: a multicenter Italian study. Dermatology. 2014;228(3):240–9.

18. Akay BN, Bozkir M, Anadolu Y, Gullu S. Epidemiology of vitiligo, associated autoimmune diseases and audiological abnormalities: Ankara study of 80 patients in Turkey. J Eur Acad Dermatol Venereol. 2010;24(10):1144–50.

19. Ezzedine K, Sheth V, Rodrigues M, et al. Vitiligo is not a cosmetic disease. J Am Acad Dermatol. 2015;73(5):883–5.

20. Lai YC, Yew YW, Kennedy C, Schwartz RA. Vitiligo and depression: a systematic review and meta-analysis of observational studies. Br J Dermatol. 2017;177(3):708–18.

21. Osinubi O, Grainge MJ, Hong L, et al. The prevalence of psychological comorbidity in people with vitiligo: a systematic review and meta-analysis. Br J Dermatol. 2018;178(4):863–78.

22. Merative. Real-world evidence. 2022. https://www.merative.com/real-world-evidence?ref=ibm. Accessed 5 December 2022.

23. Chang WL, Ko CH. The role of oxidative stress in vitiligo: an update on its pathogenesis and therapeutic implications. Cells. 2023;12(6):936.

24. Spritz RA. The genetics of generalized vitiligo and associated autoimmune diseases. Pigment Cell Res. 2007;20(4):271–8.

25. Alkhateeb A, Fain PR, Thody A, Bennett DC, Spritz RA. Epidemiology of vitiligo and associated autoimmune diseases in Caucasian probands and their families. Pigment Cell Res. 2003;16(3):208–14.

26. Kussainova A, Kassym L, Akhmetova A, et al. Vitiligo and anxiety: a systematic review and meta-analysis. PLoS One. 2020;15(11): e0241445.

27. Steel KP, Barkway C. Another role for melanocytes: their importance for normal stria vascularis development in the mammalian inner ear. Development. 1989;107(3):453–63.

28. Li CL, Ma SH, Wu CY, Chang PH, Chang YT, Wu CY. Association between sensorineural hearing loss and vitiligo: a nationwide population-based cohort study. J Eur Acad Dermatol Venereol. 2022;36(7): 1097–103.