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ORIGINAL RESEARCH

Epidemiology and Treatment Patterns of Patients with Vitiligo: A Real-World Analysis

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ABSTRACT

Introduction: Vitiligo, a chronic autoimmune skin depigmentation disease with an unpredictable course, has been associated with several comorbid autoimmune and psychological conditions. Our current understanding of vitiligo burden and management in the real world is limited. This real-world analysis presents data on vitiligo epidemiology, comorbidities, and treatment of patients in Israel.

Methods: This retrospective study analyzed data from the Maccabi Health Services database. Prevalent patients with vitiligo in 2021 were matched to patients in the general population on the basis of age group, gender, and socioeconomic status. Patient demographics, vitiligo incidence and prevalence, comorbidities, and treatment patterns are reported. Data are presented as percentages, mean, median, *P* values, and standard mean differences (SMD).

Results: In this analysis, 11,412 patients with vitiligo were matched to patients from the general population. Incidence and prevalence rates increased over time from 2005 to 2021. Compared to the general population, patients with vitiligo were more likely to have an immune-mediated comorbidity (29.7% vs 18.4% [$P<0.001$; SMD 0.27]) or psychological comorbidity (18.7% vs 15.9% [$P<0.001$; SMD 0.07]). Comorbidities included atopic dermatitis (patients with vitiligo vs general population 12.5% vs 8.4%), psoriasis (5.8% vs 3.6%), Hashimoto's thyroiditis (2.9% vs 1.1%), alopecia areata (2.2% vs 0.9%), depression (10.8% vs 9.5%), and sleep disorder/insomnia (5.9% vs 4.4%). Only 74.8% of all patients with vitiligo had ever received treatment, with topical corticosteroids (51.5%) and calcineurin inhibitors (36.5%) most commonly prescribed. At the end of 2021, 83.7% of patients were untreated.

Conclusion: Patients with vitiligo are more likely to have various immune-related and

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psychological comorbidities, highlighting the significant impact of the condition on well-being. Nearly a quarter of patients had never received treatment, with many receiving only topical treatments, and medication persistence was low. This highlights the lack of adequate treatment in this population and the need for more effective management options.

Keywords: Comorbidities; Epidemiology; Real world; Treatment patterns; Vitiligo

Key Summary Points

Why carry out this study?

Our current understanding of vitiligo burden and management in the real world is limited.

This analysis aims to add to our understanding of vitiligo epidemiology, comorbidities, and treatment patterns using data on a large, real-world patient population derived from the Maccabi Health Services database.

What was learned from the study?

This study showed that the prevalence of vitiligo was approximately 0.5% in 2021, with nearly a quarter of patients with vitiligo having never received treatment. Moreover, this study also found that patients with vitiligo were more likely than the general population to have various immune-related and psychological comorbidities.

These findings highlight the systemic burden of disease, the lack of adequate treatment in this population, and the need for more effective management options, such as early diagnosis and appropriate intervention.

INTRODUCTION

Vitiligo is a chronic immune-mediated skin depigmentation disease characterized by chalky-white patches on the skin [1]. Depigmentation is attributed to melanocyte destruction by $CD8^+$ T cells resulting from an interplay of genetic predisposition, environmental triggers, melanocyte stress, and dysregulated innate and adaptive immune responses [2, 3]. Vitiligo can affect anywhere on the body, most commonly the face, hands, feet, and extremities [4]. The disease course of vitiligo is unpredictable, and depigmentation may progress at varying rates [5, 6].

As a systemic disease, vitiligo has been associated with several comorbid conditions, such as thyroid disease and skin, joint, and bowel conditions [7–9]. Vitiligo has been reported to have important psychosocial effects which impact many areas of life, including employment and academic performance [10–12].

The current standard of care in most parts of the world includes topical corticosteroids (CS) and topical calcineurin inhibitors (CI), along with narrowband ultraviolet B (NB-UVB) light therapy [13, 14]. Other interventions include vitamin D analogues, targeted phototherapy, melanocyte grafting, and full body depigmentation [15]. Recently, topical ruxolitinib (a Janus kinase [JAK]-1 inhibitor) was approved in the USA and Europe for patients with up to 10% body surface area (BSA) affected by vitiligo [16, 17]; there are currently no approved systemic treatments. Despite some emerging evidence, our understanding of the holistic disease burden and management of patients with vitiligo in daily practice remains limited.

This real-world analysis aims to add to our understanding of vitiligo epidemiology, comorbidities, and treatment patterns using the Maccabi Health Services (MHS) database.

METHODS

Study Design

A retrospective, cohort study assessed vitiligo incidence, and a cross-sectional study was used to describe patient characteristics and management of vitiligo. This analysis used the MHS electronic database, a large Israeli health maintenance organization accounting for 25% of the population (2.4 million people), with data

available since 1993 and less than 1% of patients lost per year.

Study Population

To be included as a vitiligo case, patients must have fulfilled ≥ 1 of the following criteria:

- ≥ 1 diagnosis code from a dermatologist
- ≥ 1 diagnosis code from a hospital plus ≥ 1 diagnosis code from any physician
- ≥ 2 diagnosis codes from any physician
- ≥ 1 diagnosis code from any physician plus purchase of a topical CS within 6 months before or 12 months after the first vitiligo diagnosis

The International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes used were 709.01 (vitiligo) and 374.53 (hypopigmentation of the eyelid). Included patients were first diagnosed between January 1, 2005 and December 31, 2021, and were MHS members ≥ 12 months before and after the first diagnosis.

Patients who met the vitiligo case definition were defined as incident patients with vitiligo. Those who were also MHS members enrolled by the last day of 2021 were defined as prevalent patients with vitiligo and matched to patients without vitiligo from the general population (GP) on the basis of age, sex, and socioeconomic status (SES).

Demographics, Comorbidities, and Vitiligo-Related Variables

Baseline demographics for patients with vitiligo and the matched GP included age (on December 31, 2021), sex, SES, smoking status, the Charlson Comorbidity Index (CCI) [18], body mass index (BMI), and vitiligo among relatives reported for patients who had ≥ 1 MHS-member relative (sibling, parent, and/or child). The two groups were categorized according to various comorbidities (Supplementary Table S1). Patients with vitiligo were further examined according to age at diagnosis, disease duration, diagnosing physician/setting, and disease severity.

As a result of a lack of clinical variables assessing disease severity within the MHS database, severity was categorized on the basis of treatment received: mild vitiligo was defined by ≥ 1 purchase of a topical CS or CI and moderate to severe disease by ≥ 1 purchase of a systemic CS and/or ≥ 1 purchase of a systemic immunosuppressant (IS), and/or ≥ 1 course of phototherapy or photochemotherapy. Phototherapy was defined as NB-UVB therapy and photochemotherapy was defined as psoralen and UVA (PUVA) therapy. Disease severity was based on categorization used for atopic dermatitis, a disease with similar treatment options [19].

Being treated for vitiligo was defined by ≥ 1 purchase/record of any of the following treatments: topical CS, topical, CI, systemic CS, systemic IS, phototherapy, photochemotherapy, vitamin D analogues, laser therapy, and skin graft. Treatment sequence was defined according to treatments used alone or as combinations. To distinguish between different lines of therapy, a new line was defined if purchased/recorded ≥ 60 days after the previous line.

Statistical Analyses

Annual incidence rates of vitiligo (overall and by subgroup) were assessed from 2005 to 2021. Prevalence rates (overall and by subgroup) were analyzed as of December 31, 2021. Incidence and prevalence were reported as rates per 100,000 patients.

Demographics, comorbidities, and vitiligo-related variables were presented as total numbers, mean ± standard deviation (SD) and median (interquartile range [IQR]) for continuous variables, and percentages for categorical variables. Comorbidities were analyzed individually and grouped by type (i.e., immune-mediated, psychological, and additional). Vitiligo-related treatments were evaluated for prevalent patients (overall and by subgroup) and by presence of comorbidities. Comparison was assessed by standardized mean differences (SMD) and Wilcoxon rank sum test, Kruskal–Wallis rank sum test, or Pearson's chi-square test, where applicable.

Logistic regression models computed the adjusted odds ratios (aOR) and 95% confidence intervals (CI) for any immune-mediated comorbidity, any psychological comorbidity, and any type of skin cancer (i.e., melanoma and non-melanoma skin cancer [NMSC]) in prevalent patients with vitiligo versus the matched GP. All models were adjusted for age (as of December 31, 2021), sex, SES, smoking status, CCI, and BMI. Statistical significance was defined as a P value < 0.05 and SMD > 0.1 or ≤ 0.1. Analyses were performed by IBM® SPSS® v.25.0 (IBM, Amrock, NY, USA) and R Foundation for Statistical Computing (Vienna, Austria).

Ethics

The study was approved by the Maccabi Health Services' Institutional Review Board, reference number MHS-0013-22, who waived the requirement to obtain any informed consent for this secondary analysis of existing data.

RESULTS

Epidemiology

From 2005 to 2021, we identified 12,709 incident patients with vitiligo. Overall incidence of vitiligo increased from 26.3 in 2005 to 36.8 per 100,000 patients in 2021 (Fig. 1). Incidence rates per 100,000 in children and adolescents rose over time from 22.5 and 13.0 in 2005 to 38.1 and 33.0 in 2021, respectively. Adult incidence remained relatively more stable over time (29.8 per 100,000 adults in 2005 and 38.2 per 100,000 in 2021).

Reported prevalence of vitiligo in the MHS population increased from 2005 to 2021 from 26.2 to 445.3 per 100,000. In 2021, the prevalence of vitiligo among children (184.1 per 100,000) was lower than in adolescents (534.8 per 100,000) and adults (511.1 per 100,000); prevalence was similar regardless of sex (Fig. 2).

Demographics and Disease Characteristics

In the 2021 prevalent population, 11,412 patients with vitiligo and 11,412 matched non-vitiligo controls were compared. Mean age in both populations was 42.3 years, with 51.1% being female patients (Table 1). In patients with vitiligo, the mean ± SD age at diagnosis was 34.8 ± 20.5 years, with a mean ± SD disease duration of 7.1 ± 4.8 years. Among patients with vitiligo included in this analysis, 95.5% received their diagnosis from a dermatologist. More patients with vitiligo than the GP had ≥ 1 relative with vitiligo (2.6% vs 1.1% [$P < 0.001$; SMD 0.11]) and were less likely to have ever smoked (11.0% vs 15.6%).

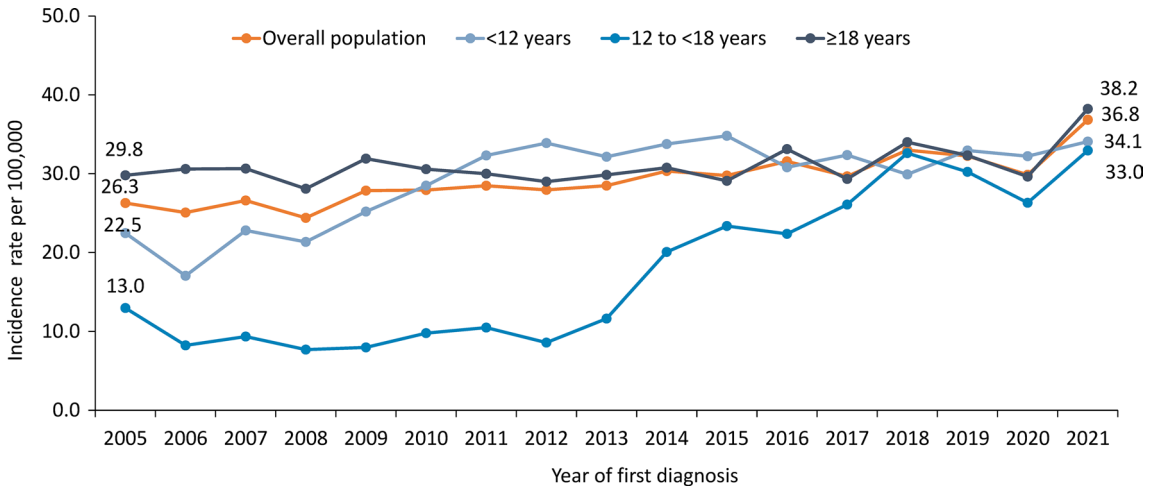


Fig. 1 Vitiligo incidence overall and by age group

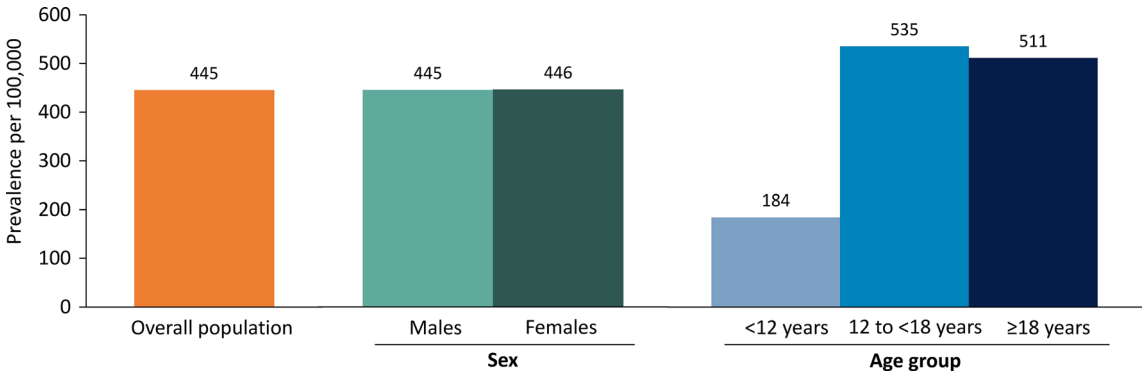


Fig. 2 Prevalence of vitiligo in 2021 in overall population, by sex, and by age group

Among patients with vitiligo in 2021, a total of 4698 (41.2%) were categorized as having mild disease and 3824 (33.5%) were categorized as having moderate to severe disease (Table 2). Severity could not be determined in 2890 cases (25.3%) because no treatment data were available. Patients categorized as having moderate to severe versus mild disease were more likely to be older (mean ± SD 49.9 ± 20.1 vs 39.3 ± 20.5 [$P < 0.001$; SMD 0.42]), female (54.6% vs 51.0% [$P < 0.001$; SMD 0.11]), overweight (32.9% vs 27.9%) or obese (21.9% vs 14.0% [$P < 0.001$; SMD 0.28]), have a disease duration ≥ 4 years (85.5% vs 64.7% [$P < 0.001$; SMD 0.40]), and be first diagnosed later in life (mean ± SD 40.4 ± 19.6 vs 32.6 ± 20.1 [$P < 0.001$; SMD 0.32]).

Comorbidities

Patients with vitiligo versus GP had increased odds of developing ≥ 1 immune-mediated comorbidity (aOR [95% CI] 1.85 [1.73, 1.97]; $P < 0.001$). Indeed, a greater proportion of patients with vitiligo had ≥ 1 immune-mediated comorbidity versus GP (29.7% vs 18.4% [$P < 0.001$; SMD 0.27]); the most common were atopic dermatitis (12.5% vs 8.4%; SMD 0.13), Hashimoto's thyroiditis (2.9% vs 1.1%; SMD 0.13), and alopecia areata (2.2% vs 0.9%; SMD 0.11) (all $P < 0.001$) (Fig. 3). Patients with vitiligo versus GP were more likely to experience anemia (22.5% vs 17.5%; $P < 0.001$; SMD 0.12) and itch (4.2% vs 2.7%; $P < 0.001$; SMD 0.08) (Table 3). Importantly, a lower percentage of patients with vitiligo had skin cancer (2.6% vs 3.4%; $P < 0.001$; SMD 0.05) and reduced odds of developing skin cancer (aOR [95% CI] 0.67 [0.57, 0.80]; $P < 0.001$).

Patients with vitiligo versus GP had increased odds of developing ≥ 1 psychological comorbidity (aOR [95% CI] 1.23 [1.14, 1.32]; $P < 0.001$). In patients with vitiligo, 18.7% versus 15.9% of GP had ≥ 1 psychological comorbidity ($P < 0.001$; SMD 0.07); the most common included depression (10.8% vs 9.5%), sleep disorder/insomnia (5.9% vs 4.4%), and anxiety (3.7% vs 3.0%) (all $P < 0.01$; SMD < 0.1; Fig. 4). Psychological comorbidities were significantly ($P < 0.001$; SMD > 0.1) more common in adults than in children or adolescents (overall 21.8% vs 4.6% and 7.7%).

A significantly ($P < 0.001$) greater percentage of patients categorized with moderate to severe versus mild disease had ≥ 1 immune-mediated comorbidity (37.0% vs 29.7% [SMD 0.26]), or any additional comorbidity (36.1% vs 25.6%; SMD 0.22). Patients with moderate to severe versus mild disease were more likely to have any psychological comorbidity (24.8% vs 15.9%), evidenced by increased rates of depression (15.7% vs 8.5%), sleep disorder/insomnia (8.9% vs 4.6%), and anxiety (5.6% vs 2.7%) (Supplementary Table S2).

Treatment Patterns

In the 2021 prevalent vitiligo population, a total of 8537 (74.8%) had ever received any treatment, indicating that 25.2% of patients had never been treated (Table 2). Importantly,

Table 1 Demographics of prevalent patients with vitiligo in 2021 versus the matched general population

n **(%) unless otherwise stated**	**Vitiligo (*N* = 11,412)**	**General population (*N* = 11,412)**	***P*** **value**	**SMD**
Age, years[a]			0.7	0
Mean ± SD	42.3 ± 21.3	42.3 ± 21.5		
Median (IQR)	45.0 (23.0, 58.0)	45.0 (24.0, 58.0)		
Sex			> 0.9	0
Male	5579 (48.9)	5579 (48.9)		
Female	5833 (51.1)	5833 (51.1)		
CCI			< 0.001	0.04
Mean ± SD	0.7 ± 1.5	0.7 ± 1.4		
Median (IQR)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)		
Smoking status			< 0.001	0.14
Never	8483 (89.0)	7794 (84.4)		
Ever	1050 (11.0)	1442 (15.6)		
Unknown, *n*	1879	2176		
Vitiligo among relatives (≥ 1)	161 (2.6)	68 (1.1)	< 0.001	0.11
BMI			< 0.001	0.11
Underweight < 18.5	1701 (14.9)	2071 (18.1)		
Normal 18.5–25	4509 (39.5)	4205 (36.8)		
Overweight 25–30	3338 (29.2)	3102 (27.2)		
Obese ≥ 30	1864 (16.3)	2034 (17.8)		
Any immune-mediated disease	3389 (29.7)	2104 (18.4)	< 0.001	0.27
Any psychological comorbidity	2129 (18.7)	1813 (15.9)	< 0.001	0.07
Any additional comorbidity	3202 (28.1)	2495 (21.9)	< 0.001	0.14

BMI body mass index, *CCI* Charlson Comorbidity Index, *IQR* interquartile range, *SD* standard deviation, *SMD* standardized mean difference

[a]Age as of December 31, 2021

at the end of 2021, only 16.3% of patients had ever received any treatment. Mean ± SD time to first treatment was 14.7 ± 29.5 months. Patients with moderate to severe versus mild disease were more likely to have waited longer for initial treatment (mean ± SD 17.6 ± 30.7 vs 12.4 ± 28.3 [$P < 0.001$; SMD 0.30]), as was the case for adults compared with children and adolescents (Supplementary Table S3).

Among all patients, topical CS and topical CI were most common (51.5% and 36.5%, respectively), followed by systemic CS (27.1%), phototherapy (7.4%), and photochemotherapy (2.2%) (Fig. 5). Female versus male patients (77.0% vs 72.5%; SMD 0.1), and adults versus children and adolescents (77.0% vs 63.2% and 68.5%; SMD 0.20), were more likely to have ever received treatment (all $P < 0.05$).

Table 2 Demographics of prevalent patients with vitiligo in 2021 by disease severity

n **(%) unless otherwise stated**	**Overall (*N* = 11,412)**	**Not defined (*n* = 2890)**	**Mild[a] (*n* = 4698)**	**Moderate to severe[b] (*n* = 3824)**	***P*** **value**	**SMD**
Age, years[c]					< 0.001	0.42
Mean ± SD	42.3 ± 21.3	37.0 ± 21.0	39.3 ± 20.5	49.9 ± 20.1		
Median (IQR)	45.0 (23.0, 58.0)	38.0 (17.0, 53.0)	41.0 (18.0, 55.0)	52.0 (39.0, 65.0)		
Sex					< 0.001	0.11
Male	5579 (48.9)	1542 (53.4)	2300 (49.0)	1737 (45.4)		
Female	5833 (51.1)	1348 (46.6)	2398 (51.0)	2087 (54.6)		
Smoking status					0.045	0.04
Never	8483 (89.0)	1957 (87.8)	3440 (89.8)	3086 (88.8)		
Ever	1050 (11.0)	272 (12.2)	389 (10.2)	389 (11.2)		
Unknown, *n*	1879	661	869	349		
CCI					< 0.001	0.27
Mean ± SD	0.7 ± 1.5	0.5 ± 1.2	0.6 ± 1.3	1.1 ± 1.8		
Median (IQR)	0.0 (0.0, 1.0)	0.0 (0.0, 0.0)	0.0 (0.0, 1.0)	0.0 (0.0, 2.0)		
BMI					< 0.001	0.28
Underweight < 18.5	1701 (14.9)	602 (20.8)	771 (16.4)	328 (8.6)		
Normal 18.5–25	4509 (39.5)	1148 (39.7)	1961 (41.7)	1400 (36.6)		
Overweight 25–30	3338 (29.2)	770 (26.6)	1309 (27.9)	1259 (32.9)		
Obese ≥ 30	1864 (16.3)	370 (12.8)	657 (14.0)	837 (21.9)		
Disease duration, years					< 0.001	0.48
Mean ± SD	7.1 ± 4.8	5.8 ± 4.6	6.3 ± 4.6	9.0 ± 4.5		
Median (IQR)	7.0 (3.0, 11.0)	5.0 (2.0, 9.0)	6.0 (2.0, 10.0)	9.0 (5.0, 13.0)		
Disease duration					< 0.001	0.40
< 4 years	3371 (29.5)	1157 (40.0)	1659 (35.3)	555 (14.5)		
≥ 4 years	8041 (70.5)	1733 (60.0)	3039 (64.7)	3269 (85.5)		
Age at diagnosis					< 0.001	0.32
Mean ± SD	34.8 ± 20.5	30.8 ± 20.9	32.6 ± 20.1	40.4 ± 19.6		
Median (IQR)	36.0 (16.0, 50.0)	31.0 (10.0, 46.0)	34.0 (13.0, 47.0)	42.0 (29.0, 55.0)		
Diagnosing physician/setting						
Dermatologist	10,896 (95.5)	2728 (94.4)	4520 (96.2)	3648 (95.4)	0.001	0.06

Table 2 continued

n (%) unless otherwise stated	Overall (*N* = 11,412)	Not defined (*n* = 2890)	Mild[a] (*n* = 4698)	Moderate to severe[b] (*n* = 3824)	*P* value	SMD
Hospital	89 (0.8)	10 (0.3)	9 (0.2)	70 (1.8)	< 0.001	0.11
Any physician	2685 (23.5)	459 (15.9)	1005 (21.4)	1221 (31.9)	< 0.001	0.26
Received any treatment ever	8537 (74.8)	15 (0.5)	4698 (100.0)	3824 (100.0)	< 0.001	13.1
Treatment in 2021	1858 (16.3)	1 (0.0)	797 (17.0)	1060 (27.7)	< 0.001	0.59
Time to first treatment, months					< 0.001	0.30
Mean ± SD	14.7 ± 29.5	27.4 ± 40.0	12.4 ± 28.3	17.6 ± 30.7		
Median (IQR)	0.0 (0.0, 14.0)	3.0 (0.0, 41.5)	0.0 (0.0, 8.0)	2.0 (0.0, 22.0)		
Any immune-mediated disease	3389 (29.7)	577 (20.0)	1397 (29.7)	1415 (37.0)	< 0.001	0.26
Any psychological comorbidity	2129 (18.7)	432 (14.9)	749 (15.9)	948 (24.8)	< 0.001	0.17
Any additional comorbidity	3202 (28.1)	616 (21.3)	1205 (25.6)	1381 (36.1)	< 0.001	0.221

BMI body mass index, *CCI* Charlson comorbidity index, *CI* calcineurin inhibitors, *CS*, corticosteroids, *IQR* interquartile range, *SD* standard deviation, *SMD* standardized mean difference

[a]Mild vitiligo: ≥ 1 purchase of a topical CS or CI, among patients not previously defined as moderate to severe

[b]Moderate to severe vitiligo: defined by ≥ 1 purchase of a systemic corticosteroid and/or ≥ 1 purchase of a systemic immunosuppressant and/or ≥ 1 course of phototherapy or photochemotherapy

[c]Age as of December 31, 2021

Adults were more likely than children and adolescents to receive topical CS (54.9% vs 33.9% and 42.0%) and systemic treatments, including phototherapy (8.1% vs 3.6% and 5.1%) (both $P < 0.05$; SMD 0.13). In contrast, adolescents and children were more likely to receive topical CI (40.6% and 40.2% vs 35.4%; $P < 0.05$; SMD 0.07). Patients with ≥ 1 immune-mediated disease versus those without (83.0% vs 71.3%; $P < 0.001$; SMD 0.28), as well as those diagnosed with depression versus without (81.2% vs 76.3%; $P < 0.001$; SMD 0.12), were more likely to have ever received treatment (Fig. 6).

Treatment Sequencing

Topical CS and topical CI were the most commonly prescribed first-line treatments in the total population (42.4% and 27.8%, respectively) (Fig. 7). Second- and third-line treatments included higher percentages of systemic CS (36.9% vs 32.0%, respectively) and systemic IS (1.2% vs 12.2%), as well as phototherapy (7.8% vs 14.5%). Combination therapy

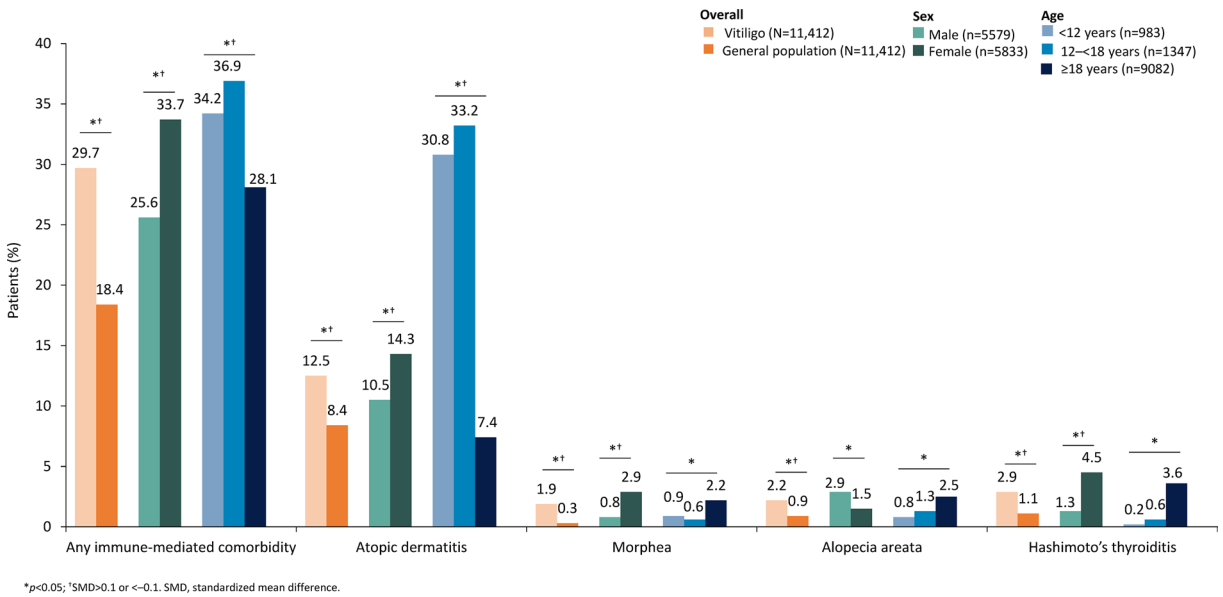


Fig. 3 Immune-mediated comorbidities overall, by sex, and by age group. *$P < 0.05$; †SMD > 0.1 or < −0.1. *SMD* standardized mean difference

(covering any combination of systemic and/or topical agents) was more commonly prescribed as a first-line treatment and was less common as second- and third-line therapy (13.7%, 4.3%, vs 1.2%, respectively). Similarly, in first-line therapy, more children and adolescents than adults were treated with topical CI (43.6% and 40.6% vs 24.7%) and had less use of systemic treatments (systemic CS 28.2% and 21.4% vs 38.7%; systemic IS 0.6% and 0.3% vs 1.3%) (Supplementary Fig. S1).

DISCUSSION

The findings of this analysis provide a broad view of the epidemiology, disease characteristics, comorbidities, and treatment patterns of patients with vitiligo in Israel. The results demonstrate that the prevalence of vitiligo in 2021 was approximately 0.5%, with some expected differences across age groups. Increasing incidence over time could be due to increasing awareness of the disease and introduction of new treatment modalities, making it easier for healthcare providers to treat vitiligo. Approximately one-third of patients were considered to have moderate to severe disease. To the best of our knowledge, this is one of the first studies in vitiligo to use prescribed treatments as a proxy for disease severity within a payer/provider database.

In this analysis, patients categorized as having moderate to severe vitiligo had longer disease duration, suggesting a potentially progressive disease course. In a study of patients with vitiligo where lesions were compared on the basis of their response to a combination of phototherapy and a topical CI, the results demonstrated that patients with a shorter disease duration had better responses to treatment [20]. Increased time to diagnosis and first treatment in patients with moderate to severe vitiligo suggest that early diagnosis and intervention could be important factors to modulate disease progression.

Regarding the holistic burden of vitiligo, our results show that close to 30% of patients with vitiligo have at least one immune-mediated comorbidity, a percentage that is slightly higher than other literature has reported. In studies from the USA and Belgium, 23% and 15% of patients with vitiligo, respectively, had comorbid autoimmune conditions [8, 21]. Differences in

Table 3 Comorbidities in 2021 prevalent patients with vitiligo versus the matched general population

n (%)	Vitiligo (*N* = 11,412)	General population (*N* = 11,412)	*P* value	SMD
Immune-mediated comorbidities				
Skin and subcutaneous tissue				
Atopic dermatitis	1421 (12.5)	955 (8.4)	< 0.001	0.13
Dermatitis herpetiformis	1 (0.0)	1 (0.0)	> 0.9	0
Pemphigus vulgaris	7 (0.1)	5 (0.0)	0.8	0.01
Discoid lupus erythematosus	34 (0.3)	19 (0.2)	0.054	0.03
Psoriasis	658 (5.8)	415 (3.6)	< 0.001	0.1
Lichen sclerosus	0 (0.0)	0 (0.0)	–	0
Prurigo nodularis	251 (2.2)	146 (1.3)	< 0.001	0.07
Morphea	214 (1.9)	37 (0.3)	< 0.001	0.15
Alopecia areata	251 (2.2)	101 (0.9)	< 0.001	0.11
Hidradenitis suppurativa	56 (0.5)	44 (0.4)	0.3	0.02
Musculoskeletal system and connective tissue				
SLE	30 (0.3)	15 (0.1)	0.037	0.03
Scleroderma	40 (0.4)	7 (0.1)	< 0.001	0.06
Sjorgen's syndrome	46 (0.4)	36 (0.3)	0.3	0.01
Dermatomyositis	3 (0.0)	3 (0.0)	> 0.9	0
Rheumatoid arthritis	121 (1.1)	72 (0.6)	< 0.001	0.05
Ankylosing spondylitis	31 (0.3)	25 (0.2)	0.5	0.01
Endocrine, nutritional and metabolic diseases, and immunity disorders				
Grave's disease	152 (1.3)	72 (0.6)	< 0.001	0.07
Hashimoto's thyroiditis	336 (2.9)	129 (1.1)	< 0.001	0.13
Addison's disease	13 (0.1)	2 (0.0)	0.01	0.04
Autoimmune polyglandular syndrome	4 (0.0)	0 (0.0)	0.13	0.03
Selective IgA deficiency	14 (0.1)	11 (0.1)	0.7	0.01
Digestive system				
IBD	206 (1.8)	160 (1.4)	0.018	0.03
Celiac disease	114 (1.0)	64 (0.6)	< 0.001	0.05
Nervous system				
Guillain-Barré syndrome	6 (0.1)	5 (0.0)	> 0.9	0
Myasthenia gravis	14 (0.1)	9 (0.1)	0.4	0.01

Table 3 continued

n (%)	Vitiligo (*N* = 11,412)	General population (*N* = 11,412)	*P* value	SMD
Vogt-Koyanagi-Harada disease	2 (0.0)	1 (0.0)	> 0.9	0.01
Other immune-mediated comorbidities				
Sarcoidosis	37 (0.3)	20 (0.2)	0.034	0.03
Rheumatic fever	12 (0.1)	5 (0.0)	0.15	0.02
Idiopathic thrombocytopenic purpura	43 (0.4)	24 (0.2)	0.028	0.03
Psychological comorbidities				
Depression	1235 (10.8)	1084 (9.5)	0.001	0.04
Anxiety	421 (3.7)	347 (3.0)	0.007	0.04
Suicide tendency/attempt	30 (0.3)	34 (0.3)	0.7	− 0.01
Sleep disorder/insomnia	668 (5.9)	497 (4.4)	< 0.001	0.07
Sexual dysfunction	36 (0.3)	38 (0.3)	> 0.9	0
Agoraphobia	52 (0.5)	64 (0.6)	0.3	− 0.01
Social phobia	27 (0.2)	26 (0.2)	> 0.9	0
Personality disorder	133 (1.2)	136 (1.2)	> 0.9	0
Schizophrenia	46 (0.4)	68 (0.6)	0.049	− 0.03
Episodic mood disorders	59 (0.5)	68 (0.6)	0.5	− 0.01
Attention deficit and hyperactivity disorder	162 (1.4)	117 (1.0)	0.008	0.04
Eating disorder	84 (0.7)	57 (0.5)	0.028	0.03
Alcohol dependency and complications	2 (0.0)	3 (0.0)	> 0.9	− 0.01
Drug addiction	17 (0.1)	25 (0.2)	0.3	− 0.02
Additional comorbidities				
Diabetes mellitus (type 1 and 2)	989 (8.7)	995 (8.7)	> 0.9	0
Photosensitivity	33 (0.3)	14 (0.1)	0.009	0.04
Pernicious anemia (vitamin B_{12} deficiency)	50 (0.4)	9 (0.1)	< 0.001	0.07
Multiple sclerosis	28 (0.2)	22 (0.2)	0.5	0.01
Ocular abnormalities (uveitis, iris/retinal pigmentary changes, glaucoma)	440 (3.9)	392 (3.4)	0.1	0.02
Hearing loss	5 (0.0)	4 (0.0)	> 0.9	0
Anemia	2562 (22.5)	1993 (17.5)	< 0.001	0.12
Itch (unspecified pruritic disorder)	478 (4.2)	304 (2.7)	< 0.001	0.08
Cerebellar ataxia	6 (0.1)	6 (0.1)	> 0.9	0

Table 3 continued

n (%)	Vitiligo (*N* = 11,412)	General population (*N* = 11,412)	*P* value	SMD
Helicobacter pylori infection	0 (0.0)	0 (0.0)	–	–
Any skin cancer	301 (2.6)	393 (3.4)	< 0.001	0.05
Melanoma	60 (0.5)	66 (0.6)	0.6	0.01
Nonmelanoma skin cancer	254 (2.2)	354 (3.1)	< 0.001	0.01

IBD inflammatory bowel disease, *IgA* immunoglobulin A, *SLE* systemic lupus erythematosus, *SMD* standardized mean difference

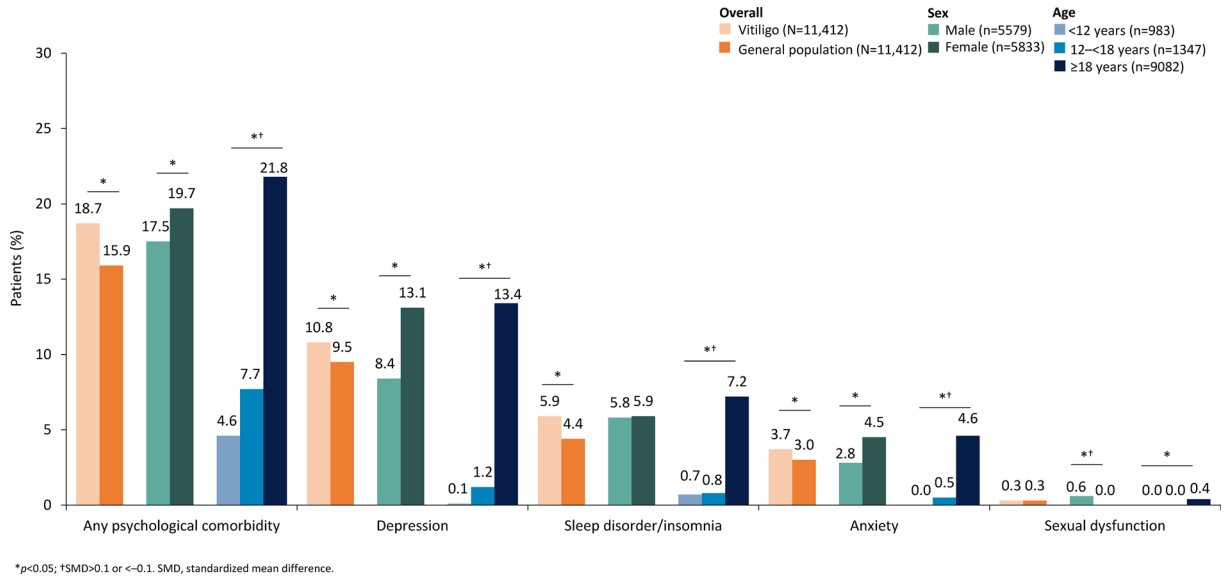


Fig. 4 Psychological comorbidities overall, by sex, and by age group. *$P < 0.05$;†SMD > 0.1 or < −0.1. *SMD* standardized mean difference

the study population, sample size, data sources, methodology, symptom underreporting, and geographic or temporal variations may account for differences between our study and others. Similar to our study, Ezzedine et al. showed that significantly greater proportions of patients with vitiligo versus controls had atopic dermatitis (12% vs 10%) and alopecia areata (4% vs 2%) [22]. Furthermore, in this study, patients with moderate to severe disease were more likely to have immune-mediated comorbidities, as were female patients, children, and adolescents, indicating a disproportionate burden. As such, the requirements for monitoring and intervention may vary depending on the patient population.

Findings on comorbidities in this analysis included lower odds of skin cancer in patients with vitiligo, as consistent with published literature [23, 24]. One study demonstrated that patients with vitiligo have up to a threefold decreased probability of developing NMSC [24]. Another comorbidity to note is the proportion of patients reporting itch (4.2%), as it is generally believed that the disease is not linked to physical discomfort. However, one study showed that 48.1% of patients reported experiencing itch prior to the appearance of new vitiligo lesions [25].

Regarding psychological comorbidities, the significant increase in patients with vitiligo

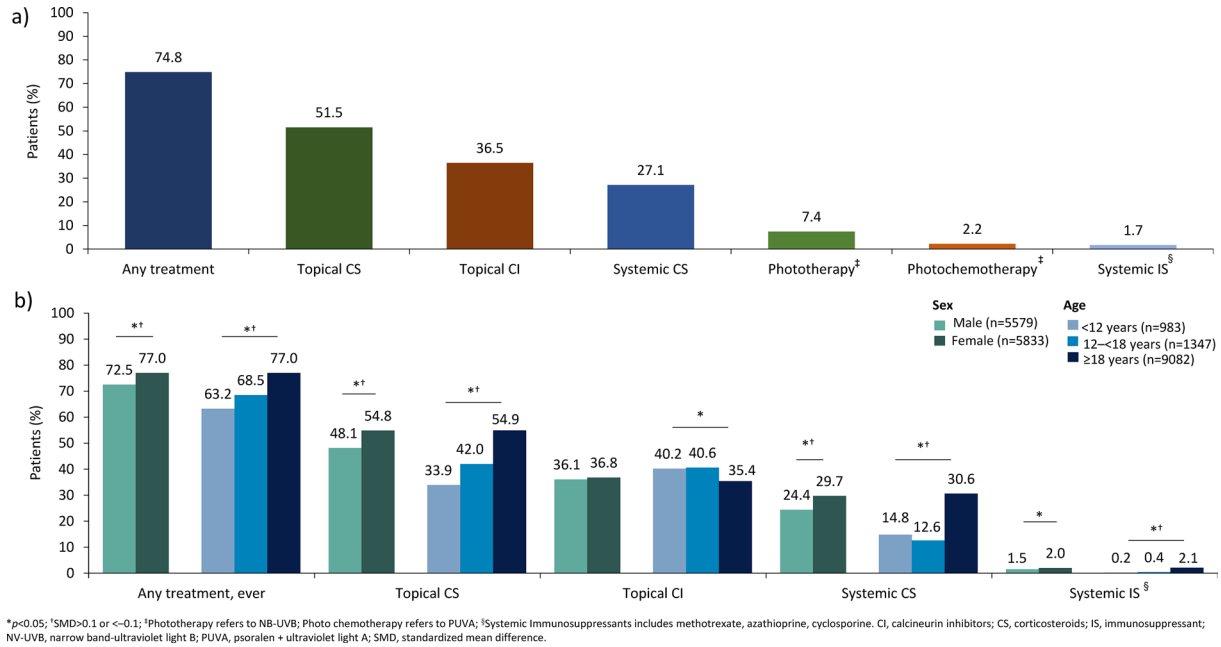


Fig. 5 Treatment patterns **a** overall and **b** by sex, and by age group. *$P < 0.05$; †SMD > 0.1 or < −0.1; ‡Phototherapy refers to NB-UVB; Photochemotherapy refers to PUVA; §Systemic Immunosuppressants includes methotrexate, azathioprine, cyclosporine. *CI* calcineurin inhibitors, *CS* corticosteroids, *IS* immunosuppressant, *NV-UVB* narrowband ultraviolet B light, *PUVA* psoralen + ultraviolet A light, *SMD* standardized mean difference

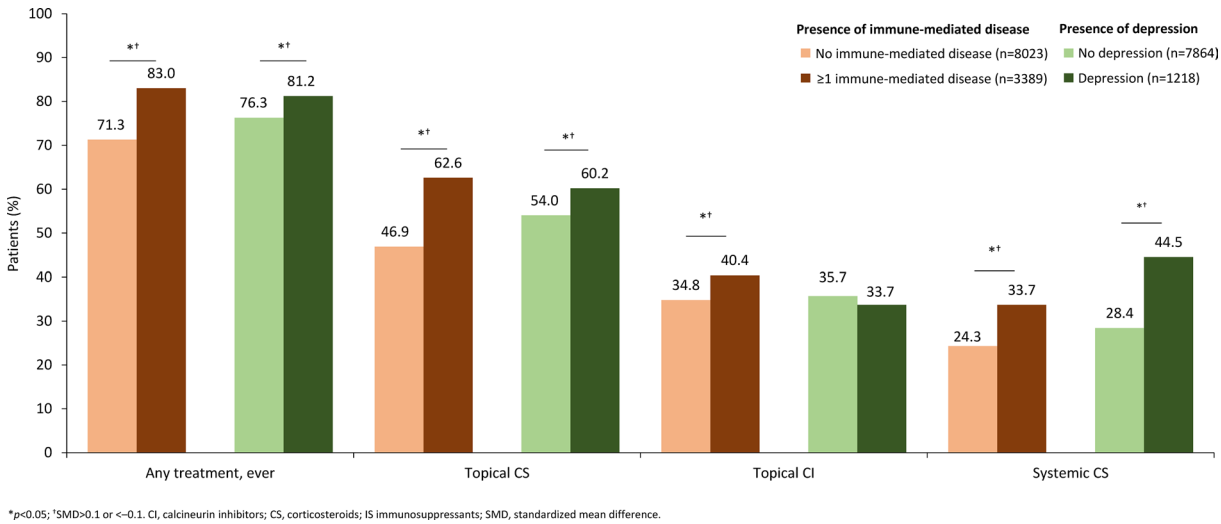
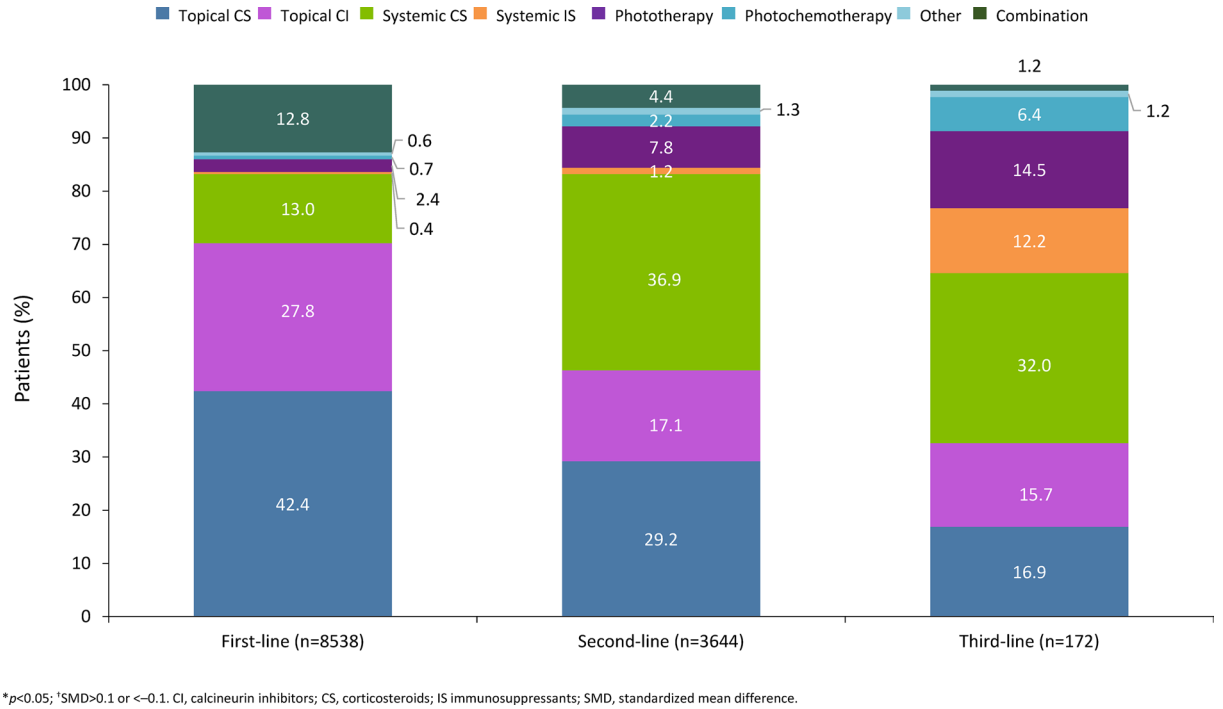


Fig. 6 Treatment patterns by presence of other immune-mediated disease and depression. *$P < 0.05$; †SMD > 0.1 or < −0.1. *CI* calcineurin inhibitors, *CS* corticosteroids, *IS* immunosuppressants, *SMD* standardized mean difference

versus GP is consistent with other research and highlights the broader impact of disease on patients' daily lives [26]. Indeed, one study found that patients with vitiligo had a 25% increased risk of recurrent depressive disorder, and a 23% increased risk of anxiety disorder, compared with a control group [26]. The study also found that those with a psychological



*p<0.05; †SMD>0.1 or <–0.1. CI, calcineurin inhibitors; CS, corticosteroids; IS immunosuppressants; SMD, standardized mean difference.

Fig. 7 Treatment sequencing. *$P < 0.05$; †SMD > 0.1 or < −0.1. *CI* calcineurin inhibitors, *CS* corticosteroids, *IS* immunosuppressants, *SMD* standardized mean difference

comorbidity were twice as likely to be absent from work and unemployed [26]. Another study showed higher levels of depression and worse sleep quality in patients with vitiligo versus a control group [27]. Furthermore, the psychological impact of vitiligo can affect quality of life and social integration [28, 29], especially among patients with greater than 5% BSA, darker skin types, or lesions on the face [30]. As a result of these debilitating effects of vitiligo, it is important that providers routinely assess patients' quality of life along with treatment efficacy.

Patients with any immune-mediated comorbidity or depression were more likely to have received any treatment than patients without these comorbidities. These findings suggest that the increased impact of additional physical or psychosocial burden may potentially drive treatment decision-making.

Despite the current lack of formally approved medications for re-pigmentation in Israel, it is encouraging to see that 74.8% of patients had received ≥ 1 treatment; half of patients received topical CS, followed by topical CI and systemic CS. These treatment patterns are consistent with guidelines recommending topical treatments as first- and second-line therapies in vitiligo [4, 14, 31]. Unfortunately, many of these treatments are frequently only effective in a minority of patients and the broad use of topical treatments does not align with the growing understanding of vitiligo as a systemic disease.

Although 74.8% of all patients with vitiligo were treated at some point, our results show that at the end of 2021, more than 80% of patients were untreated, suggesting a lack of medication persistence. This may be due to potential safety concerns with long-term use of therapies, such as steroids, and/or could be an indicator of treatment dissatisfaction by patients and physicians [14, 32–34].

Our findings highlight several unmet needs for patients with vitiligo, such as the lack of efficacious and approved treatment options, in particular, systemic therapies. These results also show an important comorbid burden that should be assessed and treated as part of a comprehensive patient management plan. There is

a clear need for further research regarding disease course and factors affecting progression in vitiligo.

A strength of this analysis is that it is, to the best of our knowledge, the largest real-world assessment of patients with vitiligo and one of few analyses on vitiligo outside of the US population. The attrition rate of the MHS database is low, allowing for a comprehensive and longitudinal view of the patient's experience. Limitations of this analysis included disease severity being defined by treatments recorded. While treatment is a reasonable proxy that has been employed in similar diseases, it may underestimate the proportion of patients with moderate to severe vitiligo due to frequent undertreatment [35, 36]. Moreover, defining severity by treatment inherently excludes patients who have not received treatment and relies on such treatment being administered as prescribed. Furthermore, the absence of disease-specific measures, such as BSA, Vitiligo Area Scoring Index, Vitiligo Extent Score, or location of vitiligo lesions impedes potentially more granular conclusions.

CONCLUSIONS

This real-world analysis of patients in Israel showed that the prevalence of vitiligo was approximately 0.5% in 2021. The results highlight the systemic burden of disease, showing that patients with vitiligo were significantly more likely to have a range of immune-mediated and psychological comorbidities. The data on treatment patterns highlight the undertreatment and lack of treatment continuity for many patients with vitiligo, suggesting a need for more effective treatment options. Further research is needed to better understand how timely diagnosis and early treatment may impact disease progression and development of comorbidities.

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Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available since the data that support the findings of this study originate from Maccabi Healthcare Services and restrictions apply to the availability of these data. However, these data may be accessed through written request to the authors and/or Maccabi Healthcare Services.

Declarations

Conflict of Interest. Y Ramot received speaker honoraria, consultancy fees or travel support from Pfizer, AbbVie, Novartis, Janssen, Sanofi, BI, Neopharm, Dexcel Pharma, Taro, and Lilly. V Rosenberg has nothing to declare. L Zhou and S Harbers are employees of AbbVie and may own AbbVie stock and/or options.

Ethical Approval. The study was approved by the Maccabi Health Services' Institutional Review Board, reference number MHS-0013-22, who waived the requirement to obtain any informed consent for this secondary analysis of existing data.

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