



Patient Reported Outcomes Measures : Depression, Anxiety and Sleep Disturbance in Vitiligo Patients Participating in the ComPaRe e-cohort

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Université Paris-Est (UPE)
Ecole Doctorale de Santé Publique (EDSP)

**Patient Reported Outcomes Measures:
Depression, Anxiety and Sleep Disturbance in Vitiligo Patients
Participating in the ComPaRe e-cohort**

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ABSTRACT

Among all skin diseases, vitiligo, a chronic acquired auto-immune depigmenting disease, is considered as the most common cause of disfiguration with a 0.5%-2% worldwide prevalence. Cut-offs of the severity assessment tools has not yet been established to reflect the patient's improvement and for the treatment's effectiveness. Furthermore, affection of visible areas in vitiligo has been associated with higher impact on the psychological health of the patient. While different studies emphasize on the psychological impact of the chronic diseases, comparative studies between chronic skin diseases and chronic non skin diseases are still lacking.

The objectives of this research were, first to show that face involvement is a good proxy for assessing the perception of global severity among vitiligo patients and to determine the minimal clinically important difference (MCID) of a patient-reported outcome measure in vitiligo; the Self-Assessment Vitiligo Extent Score (SAVES). Second, to determine correlates of depression, anxiety and quality of sleep among vitiligo patients, in addition to comparing these psychological morbidities in vitiligo to non-cutaneous chronic diseases (diabetes and hypertension).

This is a cross-sectional study in the context of the ComPaRe e-cohort. Among invited patients, 540 vitiligo, 633 diabetic, and 1153 hypertensive patients filled in electronically the initial questionnaire which included socio-demographic characteristics and lifestyle habits. The severity of vitiligo was assessed using the Self-Assessment Vitiligo Extent Score (SAVES). In order to determine the minimal clinically important difference (MCID), the SAVES was collected during the initial registration and a second collection was

performed one year after with the global assessment scale used as an anchor. In addition, patient-reported outcomes measures including ED-5Q questionnaire, Patient Health Questionnaire 7 (PHQ-7), General Anxiety Disorder 9 (GAD-9) and Pittsburgh Sleep Quality Index (PSQI) were collected.

Using the distribution based methods; the MCID and MDC were respectively equal to 7.935% and 7.864% BSA, while the Receiver Operating Characteristic (ROC) analysis revealed an MCID of 0.247% BSA increase of the total SAVES in worsened patients while an MCID equal 0.217%BSA decrease of the SAVES was determined for improved patients. Involvement of hands was not significantly associated with perceived change, while an increase in facial severity was significantly correlated with the patient's perception of deterioration (OR= 7.428; 95%CI: 1.206, 45.761; p=0.031).

The prevalence of depression in vitiligo (28.1%), diabetes (30.8%) and hypertension (29.6%) was not statistically different. Furthermore, 21.3% of vitiligo patients were anxious; while significantly higher mean GAD score was seen among vitiligo patients compared to diabetics. A significant difference in the mean PSQI was observed between vitiligo patients (7.21 ± 4.05) and hypertensive (8.45 ± 4.33), but not diabetic patients.

To conclude, our findings highlight the importance of developing a new scale for assessing repigmentation of the face is of high interest as patients' perception of their facial patches is of most importance compared to other body parts. Ultimately, this global impression of severity could correlate with an improved quality of life. Lastly, dermatologists are encouraged to consider these data because the findings of PRO instruments are critical to assisting clinicians and patients to make informed decisions regarding any intervention.

Moreover, a severity measurement scale should be developed in order to compare the impact of disease severity on the psychological morbidities and on quality of life among patients with cutaneous and non-cutaneous chronic diseases.

RESUME (FRANÇAIS)

Parmi toutes les maladies de la peau, le vitiligo, une maladie dépigmentante chronique, auto-immune, est considérée comme la cause la plus fréquente de défiguration avec une prévalence mondiale de 0,5% à 2%. Cependant, les seuils des outils de mesure n'ont pas été déterminés pour refléter l'amélioration du patient et l'efficacité du traitement. En outre, l'affection des zones visibles dans le vitiligo a été associée avec un impact substantiel sur l'état psychologique des patients. Bien que différentes études mettent l'accent sur l'impact psychologique des maladies chroniques, des études comparatives entre les maladies chroniques de la peau et les maladies chroniques non cutanées font encore défaut.

Les objectifs de cette recherche étaient, premièrement de montrer que l'atteinte du visage est un bon paramètre pour évaluer la perception de la sévérité globale chez les patients atteints de vitiligo et de déterminer la différence minimale cliniquement pertinente (MCID) du Self-Assessment Vitiligo Extent Score (SAVES). Deuxièmement, de déterminer les corrélats de la dépression, l'anxiété et la qualité du sommeil chez les patients atteints de vitiligo, en plus de comparer ces morbidités psychologiques dans le vitiligo aux maladies chroniques non-cutanées (diabète et hypertension).

Il s'agit d'une étude transversale rétrospective dans le contexte de la cohorte électronique ComPaRe. Parmi les patients invités, 540 patients atteints de vitiligo, 633 diabétiques et 1153 hypertendus ont répondu électroniquement le questionnaire initial, évaluant les caractéristiques sociodémographiques. La gravité du vitiligo a été évaluée à l'aide des SAVES. Afin de déterminer le MCID, le SAVES a été recueilli lors de

l'enregistrement initial et une deuxième collecte a été effectuée un an après, en plus d'une échelle globale d'évaluation de l'étendu du vitiligo. De plus, des mesures reportés par les patients; la qualité de vie (questionnaire ED-5Q), Patient Health Questionnaire 7 (PHQ-7) pour la dépression, General Anxiety Disorder 9 (GAD-9) pour l'anxiété et Pittsburgh Sleep Quality Index (PSQI) pour la qualité du sommeil ont été collectées.

Les méthodes basées sur la distribution ont montré un MCID et un MDC de 7,935 % et 7,864 % de surface corporelle, tandis que l'analyse *de* la courbe des caractéristiques receveur-opérateur a révélé une valeur du MCID de 0,247 % de la surface corporelle chez les patients aggravés, et de 0,217 % de la surface corporelle chez les patients améliorés. Une augmentation de la gravité faciale était significativement corrélée à la perception de détérioration du patient (OR = 7,428; IC à 95%: 1,206, 45,761; $p = 0,031$)

La prévalence de la dépression dans le vitiligo, le diabète et l'hypertension n'était pas statistiquement différente. En outre, le score moyen GAD était significativement plus élevé chez les patients atteints de vitiligo par rapport aux diabétiques. Une différence significative de la moyenne du PSQI a été observée entre les patients atteints de vitiligo ($7,21 \pm 4,05$) et les patients hypertendus ($8,45 \pm 4,33$), mais pas les patients diabétiques.

Pour conclure, le développement d'une nouvelle échelle pour évaluer la repigmentation du visage est d'un grand intérêt car la perception des patients concernant les tâches du visage est de plus grande importance par rapport à d'autres parties du corps. En fin de compte, cette impression globale de gravité pourrait être corrélée à une amélioration de la qualité de vie. En plus, nos résultats soulignent l'importance de développer une nouvelle échelle commune de mesure de la gravité afin de pouvoir comparer l'impact de la gravité de

la maladie sur les morbidités psychologiques et sur la qualité de vie dans les maladies chroniques cutanées et non cutanées.

RESUME SUBSTANTIEL

Le vitiligo, une maladie dépigmentante chronique, auto-immune, est la cause la plus fréquente de dépigmentation avec une prévalence mondiale de 0,5% à 2%. En 2015, une étude internationale a permis d'établir les domaines essentiels et importants pour l'évaluation du succès thérapeutique lors des essais cliniques en soulignant l'importance de création d'outils d'évaluation de la sévérité de la maladie qui soient validés. Depuis 2015, de nombreux scores d'évaluation de la sévérité de la maladie aient été développés et validés partiellement, même si les seuils cliniquement signifiants de ces outils de mesure restent à déterminer en prenant en compte non seulement l'amélioration du patient mais également l'aggravation de la maladie dans la mesure de l'efficacité du traitement. En outre, l'atteinte des zones visibles dans le vitiligo a été associée avec un impact substantiel sur l'état psychologique des patients. Dans ce contexte, la repigmentation du visage et des mains a été considéré comme le critère de jugement le plus approprié dans les essais cliniques pour les patients atteints de vitiligo. De plus, bien que différentes études mettent l'accent sur l'impact psychologique des maladies chroniques cutanées, peu d'études comparant entre l'impact du vitiligo par rapport à celui des maladies chroniques non cutanées existent.

Les objectifs de cette recherche étaient premièrement de montrer que l'atteinte du visage est un bon paramètre pour évaluer la perception de la sévérité globale chez les patients atteints de vitiligo et de déterminer la différence minimale cliniquement pertinente (MCID) du *Self-Assessment Vitiligo Extent Score* (SAVES). Deuxièmement, de déterminer le lien entre dépression, anxiété et qualité du sommeil chez les patients atteints de vitiligo et de

comparer l'impact de ces morbidités psychologiques dans le vitiligo à celui de deux maladies chroniques non-cutanées fréquentes ; le diabète et l'hypertension artérielle.

Il s'agit d'une étude transversale prospective dans le contexte de la cohorte électronique ComPaRe, une cohorte de plus de 50.000 participants atteints de maladie chronique. Les patients atteints de vitiligo, de diabète et d'hypertension ont été sélectionnés. Au total, 540 patients vitiligo, 633 diabète et 1153 hypertendus ont répondu électroniquement le questionnaire initial, évaluant les caractéristiques sociodémographiques (âge, sexe, taille, poids, scolarité, état matrimonial, situation de travail, nombre de comorbidités, résidence, date du premier diagnostic, etc.), les habitudes de vie (tabagisme, consommation d'alcool entre autres. La sévérité du vitiligo a été évaluée à l'aide des SAVES. Afin de déterminer le MCID, le SAVES a été recueilli lors de l'enregistrement initial et une deuxième collecte a été effectuée un an plus tard, en plus d'une échelle globale d'évaluation de l'étendue du vitiligo. L'échelle globale est un score de Likert en 5 points évaluant l'étendue du vitiligo ; « Depuis l'année dernière, pensez-vous que l'étendue (la zone touchée) de votre vitiligo? ». Par ailleurs, tous les patients devaient avoir répondu à des questionnaires incluant la qualité de vie (questionnaire ED-5Q), la dépression (*Patient Health Questionnaire 7*, PHQ-7), l'anxiété (*General Anxiety Disorder 9*, GAD-9) et la qualité du sommeil (*Pittsburgh Sleep Quality Index*, PSQI).

Une corrélation moyenne significative a été détectée entre le score global et la différence du SAVES indiquant que la question d'ancrage était adéquate pour l'évaluation. En utilisant les méthodes basées sur la distribution; le MCID et le MDC étaient respectivement égaux à 7,935% et 7,864% de la surface corporelle, alors que les résultats de la surface sous la courbe ont révélé MCID de 0,247 % chez les patients aggravés tandis

qu'une MCID égale à 0,217 % a été déterminée pour les patients améliorés. En outre, les résultats ont montré que le SAVES des mains n'était pas significativement associé à la question d'ancrage, tandis qu'une augmentation de la sévérité de l'atteinte faciale était significativement corrélée à la perception de détérioration du patient indiquant que l'évaluation du visage est un critère important dans l'évaluation de la perception de la gravité du vitiligo.

La prévalence de la dépression dans le vitiligo (28,1 %), le diabète (30,8 %) et l'hypertension (29,6 %) n'était pas statistiquement différentes. Le sexe féminin, la conjugalité (marié/en couple), le niveau d'études (ne pas avoir un diplôme universitaire), le nombre de comorbidités, l'IMC, la consommation d'alcool (2 à 4 fois par semaine) étaient positivement corrélés à un score de dépression plus important. De la même manière, une qualité de vie et une qualité de sommeil détériorées étaient également associées à la dépression chez les patients vitiligo. L'analyse multivariée a montré qu'être célibataire, obtenir un diplôme universitaire, fumer régulièrement et avoir un sommeil perturbé étaient corrélés à la dépression. De plus, les patients dont la peau est plus foncée étaient plus déprimés.

Bien que les scores moyens du GAD-7 soient significativement plus élevés chez les patients vitiligo comparativement aux patients hypertendus ou diabétiques. Parmi les patients vitiligo, 21,3 % étaient anxieux; cette prévalence n'était pas statistiquement différente de celle des patients hypertendus (19,3 %) ou diabétiques (19,5 %). Enfin, chez les patients atteints de vitiligo, une mauvaise qualité de vie et de sommeil étaient fortement corrélées à l'anxiété.

Pour conclure, nous avons déterminé pour SAVES le MCID. Par ailleurs, l'atteinte du visage semble être le meilleur proxy de la perception globale de la sévérité du vitiligo par les patients. En ce sens, il semble nécessaire de développer des scores de sévérité ciblant plus spécifiquement cette partie du corps qui pourrait être corrélé à la qualité de vie. Un tel score de sévérité doit absolument prendre en compte le point de vue du patient puisque la perception de la sévérité du vitiligo peut être différente entre patients et médecins. Enfin, les travaux de cette thèse ont permis de montrer l'impact psychologique du vitiligo sur la vie des patients, cet impact étant comparable à celui d'autres maladies chroniques non dermatologiques comme l'hypertension artérielle ou le diabète.

SCIENTIFIC PUBLICATIONS

Published articles

- Samar MERHI, Pascale SALAMEH, Peter KAPLAN, Shayak BANERJEE, Mohamad LAJNEF, Emmanuel L. P. DUMONT and Khaled EZZEDINE. “An Ecological Study Indicates the Importance of Ultraviolet A Protection in Sunscreens.” *Acta dermato-venereologica* vol. 101,6 adv00480. 28 Jun. 2021, doi:10.2340/00015555-3788

Submitted article

- Samar Merhi, Pr. Pascale Salameh, Mounya Abboud, Pr. Viktoria Eleftheriadou, Isabelle Pane, Viet-Thi Tran, Jason Shourik, Pr. Khaled Ezzedine. “Facial SAVES is reflective of global perception of severity in vitiligo patients”

Article in progress

- Samar Merhi, Pascale Salameh, Isabelle Pane, Viet-Thi Tran, Pr. Khaled Ezzedine. “Depression, anxiety and sleep disturbances in vitiligo: A comparative study with diabetes and hypertension”

Accepted Posters

- Samar MERHI, Pascale SALAMEH, Peter KAPLAN, Shayak BANERJEE, Mohamad LAJNEF, Emmanuel L. P. DUMONT and Khaled EZZEDINE. “An Ecological Study Indicates the Importance of Ultraviolet A Protection in Sunscreens.”

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DEDICATIONS

I dedicate this work to my beloved husband who supported me every step of the way despite all the challenges. To my three children, I hope one day you will understand why I was working almost all afternoons when you needed me most. To my family, for always encouraging me. I, also, dedicate this work to my second family, my colleagues and friends at the Faculty of Nursing and Health Sciences at Notre Dame University- Louaize (NDU)- Lebanon, especially Dr. Jessy El Hayek and Ms. Maya AbouJaoude, for their endless support. Thank you all for your unconditional love!

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ABBREVIATIONS

Abbreviation	Definition
AUC	Area Under the Curve
BDI	Beck's Depression Inventory
BMI	Body Mass Index
BSA	Body Surface Area
CES-S	Center for Epidemiologic Studies Depression Scale
ComPaRe	Community of Patients for Research
DLQI	Dermatology Life Quality Index
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
ED-5D	EuroQol-5D
EQ VAS	EQ Visual Analog Scale
ES-Q	Emotional State Questionnaire
FTU	Fingertip Unit
F-VASI	Facial Vitiligo Area Scoring Index
GAD-7	General Anxiety Disorder 7
GHQ	General Health Questionnaire
HADS	Hospital Anxiety and Depression Scale
HAMD	Hamilton Depression Rating Scale
INFO	International Initiative for Outcomes
MCID	Minimal Clinically Important Difference
NSV	Non-Segmented Vitiligo
PHQ-9	Patient Health Questionnaire 9
PROM	patient reported outcome measures
PSQI	Pittsburgh Sleep Quality Index
QoL	Quality of Life
ROC	Receiver Operating Characteristic
SAVASI	Self-Assessment Vitiligo Area Scoring Index
SAVES	Self-Assessment Vitiligo Extent Score
SRQ-24	Self-Reporting Questionnaire-24
SV	Segmented vitiligo
VASI	Vitiligo Area Scoring Index
VDAS	Vitiligo Disease Activity Score
VDIS	Vitiligo Disease Improvement Score
VES	Vitiligo Extent Score
VES-plus	Vitiligo Extent Score-Plus
VESTA	Vitiligo Extent Score for a Target Area

VETF	Vitiligo European Task Force
VETI	Vitiligo Extent Tensity Index
VIPs	Vitiligo Impact Patient Scale
VIS	Vitiligo Impact Scale
VitQol	vitiligo Quality of Life Score
VNS	Vitiligo Noticeability Scale
VSAS	Vitiligo Signs of Activity Score
VTI	Vitiligo Treatment Impact

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CHAPTER I- INTRODUCTION

1 THESIS PROGRESS

My PhD candidacy project was initially about knowledge, attitude and practice towards sunscreen use. The study was in the context of the NutriNet-Santé e-cohort managed by the “Equipe de Recherche en Epidémiologie Nutritionnelle”-EREN University Paris 13. Since I am not residing in France, the plan was to travel three to four times per year from Lebanon to Paris to work on the analysis. The first article consisted on analyzing data from 4 different countries, and checking the association between sunscreen use and melanoma. The article was published in the *Acta dermato-venereologica* in 2021; “An Ecological Study Indicates the Importance of Ultraviolet A Protection in Sunscreens” (1). I travelled to France three times, and then the COVID-19 pandemic started and the travel restrictions were set. A communication was sent to EREN to request a remote access to the data, but the request was rejected. Hence, the project was cancelled and a new study on vitiligo within the context of the ComPaRe cohort was initiated.

2 INTRODUCTION

Among all skin diseases, vitiligo, a chronic acquired auto-immune depigmenting disease, is considered as the most common cause of disfiguration with a 0.5%-2% worldwide prevalence (2–5). Multiple assessment tools were developed to monitor the severity and extent of vitiligo, making the comparison of the outcomes of different studies very difficult (6–9). Therefore, a consensus was developed aiming to create an international set of core outcomes acceptable for healthcare givers and patients (10). The consensus concluded that repigmentation and maintenance of gained repigmentation are essential outcomes for both

clinicians and patients, followed by quality of life from the patients' perspective which is considered as the main impact of vitiligo (20,21). Moreover, a workshop was held to determine the best outcome measures from a physician's perspective. The workshop deduced that the best scoring tools to assess vitiligo were the Vitiligo Area Scoring Index (VASI) and Vitiligo Extent Score (VES); however, the VES seemed quicker, easier and simpler (12). Furthermore, the International Initiative for Outcomes (INFO) for vitiligo held a workshop for vitiligo patients, during which, from the patients' point of view, a rate of 80% repigmentation was considered as a treatment success, whereas face, hands and neck were reported as the most important parts of the body for achieving satisfactory treatment results. In addition, patients considered that the assessment of repigmentation should be done through a subjective scale (Vitiligo Noticeability Scale (VNS) for patches noticeability after treatment) and an objective measure (VES for extent of patches) (13). In spite of the fact that many studies were performed on the appropriate assessment tools, and core outcomes have been determined, however, cut-offs has not yet been established to reflect the patient's improvement and for the treatment's effectiveness.

Even though vitiligo does not affect life expectancy, the disease has a substantial impact on the quality of life (14,15) and the psychological status of patients, including depression, anxiety and reduced quality of sleep (16–21). From another hand, diabetes and hypertension are leading causes of death worldwide (22) with respective global rates of 422 million and 1.13 billion (23,24). Similarly to other chronic diseases, patients with diabetes and hypertension have higher risks of depression, anxiety and sleeping disorders. In fact, studies have showed higher scores of depression and anxiety in diabetic patients and higher sleep disorders, which affects the prognosis, treatment and quality of life and increases the

mortality among these patients (25–30). However, this situation is inversed in hypertension; studies showed that depression, anxiety and sleep disorders are risk factors for hypertension (31–35). Despite the severe consequences of anxiety and depression on the patients, these can be prevented by providing psychological care. In fact, improving patients' quality of life (36,37), and optimizing sleep duration has been correlated with a better outcome in patients with chronic diseases (38,39). While different studies emphasize on the psychological impact of the chronic diseases, comparative studies between chronic skin diseases and chronic non skin disease are still lacking.

3 VITILIGO: AN OVERVIEW

3.1 Definition

Melanocytes are pigment producer cells present in the epidermis, hair follicle and in the eyes (40). Vitiligo is a chronic auto-immune disease resulting in the depigmentation of the skin due to the destruction of melanocytes (41). The loss of melanocyte leads to a reduced pigmentation of the affected areas characterized by a complete amelanotic, nonscaly, chalky white patches with distinct margins (44). The disease is mediated by genetic and environmental factors along with a complex inflammatory process (42) (43).

3.2 Historical background

The first description of a disease similar to vitiligo dates back more than 3000 years in Hindu sacred writings and in ancient Egyptian papyrus; both texts referred to the disease as presence of depigmented spots. However, vitiligo was long confused with other disorders such as Leprosy (44). The Latin term *vitiligo* was first used by Celsus in his medical classic

De Medicina in the first century AD, while the name is thought to be derived from Latin *vitium* meaning defect or flaw, or *vitelus* comparing to the white patches in vitiligo to those observed in calves (45–47).

3.3 Epidemiology

Vitiligo is the most common cause of skin disfiguration with a prevalence 0.1%-2% in both adults and children (48–51) , without preferences to ethnicities, gender and skin types (2,41,48,50).

The largest epidemiological study was done in 1977 in Denmark, in which the prevalence of vitiligo was estimated to be 0.38% (52).

Vitiligo may develop at all ages, but usually occurs in young people aged 10 to 30 years (51,53–55). The most recent epidemiological study on vitiligo age-of-onset in Caucasians showed delays in the age of occurrence of the disease, ranging from 54% in people born between 1951 and 1969 to 26% in those born from 2005 to 2013 most probably due to environmental triggers (56). Even though vitiligo affects males and females equally; girls and females tend to consult more frequently (3,57).

3.4 Histopathology

Lesional skin biopsies show complete or almost-complete absence of melanocytes with the infiltration of lymphocytes of type CD8+ in the epidermis. The infiltration occurs in parallel to the inflammatory response and lymphocytes will be cleared by the time the skin becomes visibly depigmented (Figure 1) (5,48).

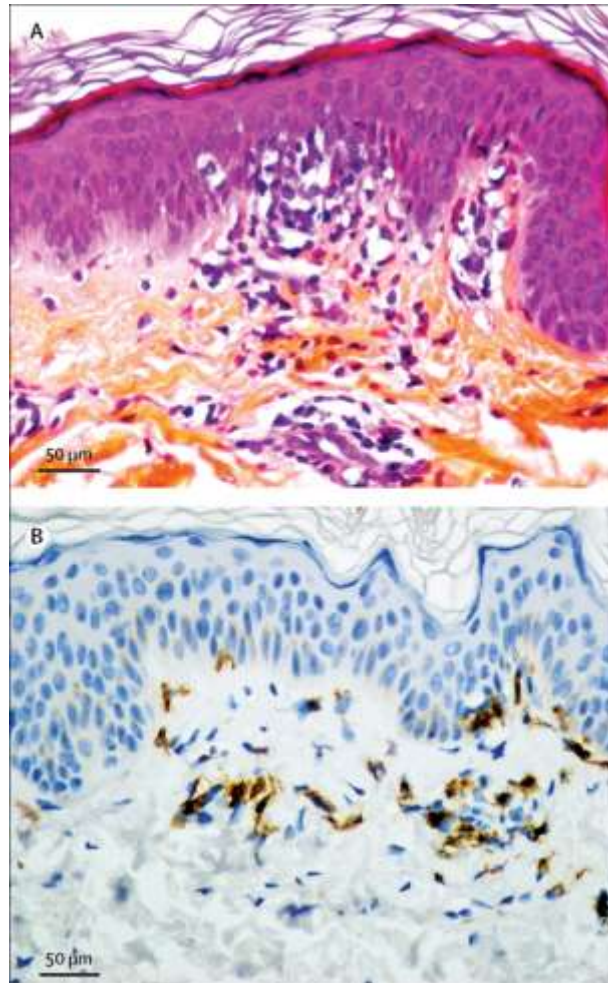


Figure 1: Histology of perilesional skin of actively spreading vitiligo (A) Dermoepidermal lymphocytic infiltrate with a lichenoid alteration pattern. Haematoxylin-eosin-saffron staining. (B) Lymphocytic cytotoxic attack with a dense CD8+ T-lymphocytic infiltrate in both the dermis and epidermis CD8 antibody immunostaining. Adapted from Ezzedine et al. 2015 (48).

3.5 Pathogenesis

The cause of vitiligo has long been debated. It is now clearly classified as an auto-immune, auto-inflammatory disease associated with multiple genetic and environmental factors leading to the detachment and destruction of melanocytes (41,58).

3.5.1 *Genetics*

It has been shown through large-scale epidemiological studies that genetic factors are very important in the development of vitiligo with a tendency to cluster in families (50,59–62). Vitiligo risk is 80% attributed to genetic factors and the rest (20%) to environmental factors (59,63). In fact, Alkhateeb et al. have shown that the frequency of vitiligo in siblings is 18 times the population frequency (50). Moreover, a number of related genes have now been identified; they are implicated in the immune response regulation, synthesis of melanin and cellular death (64–67). These genes have been as well correlated with other autoimmune disorders such as autoimmune thyroid disease, latent autoimmune diabetes in adults, rheumatoid arthritis, psoriasis, pernicious anemia, systemic lupus erythematosus, and Addison's disease (60,64,65).

3.5.2 *Oxidative stress*

Studies on the pathogenesis of vitiligo have stressed on the importance of reactive oxygen species and therefore melanocyte-intrinsic abnormalities as a possible inducer of the whole inflammatory cascade. In fact, research showed that melanocytes of vitiligo patients are more prone to oxidative stress than those of unaffected individuals (68,69). This susceptibility has been attributed to an inherited inability to manage stressors from normal cellular processes (eg, melanogenesis) or exposure to environmental factors (injury or chemicals) (48). In response to these stressors, reactive oxygen species are released from melanocytes and activate the inflammatory process and the innate immunity (5,70).

3.5.3 *Innate immunity*

Innate immunity bridges the gap between oxidative stress and adaptive immunity. The release of inflammatory signals activates the innate immune system, which represents the triggering event in vitiligo (71–74). The activation of this process includes the recruitment of natural killer cells (75) and dendritic cells (76). In addition, antigen presenting cells will migrate out of the skin to present melanocytic antigen to cytotoxic T cells (CD8+). In turn the CD8+ will be recruited to the inflammation site by cytokines and will directly destroy the melanocytes (77).

3.5.4 *Adaptive immunity*

The innate immune system stimulates the adaptive immune response by activating the dendritic cells, hence assisting autoimmune destruction of melanocytes (78). Furthermore, the presence of CD8+ T cells in lesions leads to the secretion of several cytokines, mainly IFN- γ which promotes auto-reactive CD8+ T-cell recruitment into the skin (79).

Furthermore, antibodies to melanocytic antigen have been noted in the sera of vitiligo patients and have cytolytic effect on melanocytes (80–82). However, it is not yet understood if these antibodies play a role in the development of vitiligo or they are a secondary result of the disease (83).

4 CLINICAL CLASSIFICATION

In 2011, the Vitiligo Global Issues Consensus Conference revised the classification of vitiligo. The new classification separates vitiligo into two major forms based on courses, treatment options and prognosis. Segmented vitiligo (SV) has separated from all other form

of vitiligo, while the term vitiligo was assigned to designate all non-segmented vitiligo (NSV). In addition, “mixed vitiligo”, in which SV and NSV coexist in one patient, is classified as a subgroup of NSV (Table 1) (58).

Table 1: Classification of vitiligo. Adapted from Bergqvist and Ezzedine. 2020 (42)

Type of vitiligo	Subtypes
NSV	Focal ¹ Mucosal Acrofacial Generalized Universal Rare variants of vitiligo (leukoderma punctata, hypochromic vitiligo, follicular vitiligo)
SV	Focal ¹ Unisegmental Bi- or multisegmental
Mixed (NSV + SV)	Concomitant occurrence of SV and NSV According to severity of SV
Unclassified	Focal at onset, multifocal asymmetrical nonsegmental, mucosal (one site),
¹ Can evolve into segmental (SV) or nonsegmental vitiligo (NSV).	

Non-segmental vitiligo is the most common form; it is characterized by symmetrical and bilateral white patches. Different clinical subtypes have been defined, including generalised, acrofacial, and universalis types, all have a bilateral distribution (Figure 2) (48). However, the segmental vitiligo has usually a unilateral and segmental or band-shaped distribution with early involvement of the follicular melanocyte reservoir, early age of onset, and rapid stabilization (Figure 3) (48).



Figure 2: Non-segmental vitiligo (A) Acrofacial vitiligo under ultraviolet light. Note the typical involvement of hand associated with periorificial lesions. (B) Generalised vitiligo. This patient had a few acrofacial lesions for 10 years that evolved within 6 months into a generalised form, spreading to the trunk. (C) Universal vitiligo with an affected surface area of more than 60%. Note the residual islets of pigmentation. (D) Generalised form of vitiligo with associated halo naevi. (E) Mixed vitiligo with typical segmental lesions of the trunk associated with bilateral hand lesions. Adapted from Ezzedine et al. 2015 (48)

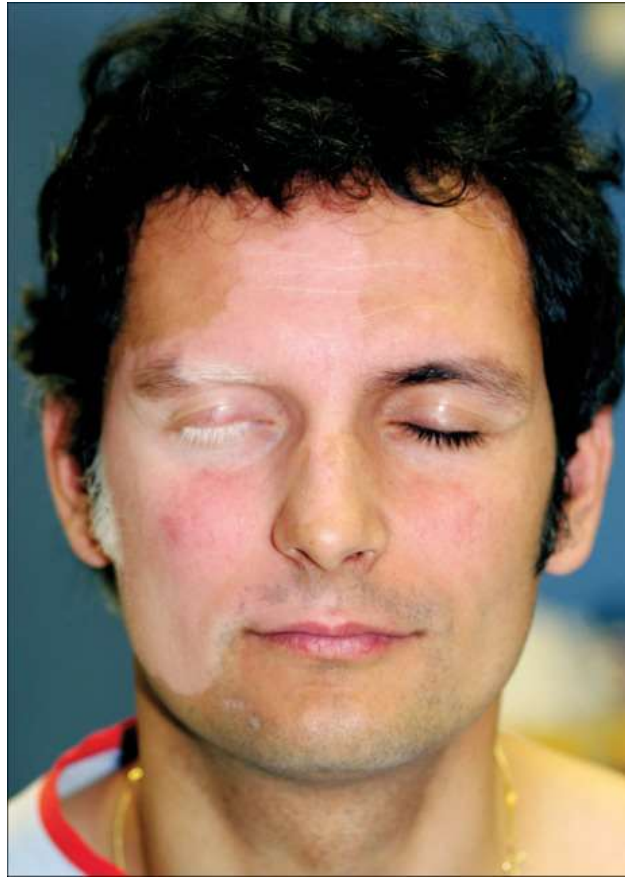


Figure 3: Typical segmental vitiligo of the face with eyelash and eyebrow whitening. Adapted from Ezzedine et al. 2015 (48)

5 DIFFERENTIAL DIAGNOSIS

The diagnosis of vitiligo is usually straightforward; however, exclusion of other conditions causing hypopigmentation and depigmentation is crucial when diagnosing vitiligo as shown in Table 2. It is mainly based on the presence of acquired, sharply demarcated, achromic, chalky-white, non-scaly macules with distinct margins in a typical distribution: periorificial, lips and tips of distal extremities, penis, segmental and areas of friction. The lesions are usually asymptomatic, however itching have been reported, especially in lesions with inflamed borders (84). The use of a narrowband Wood's lamp (using 365nm LEDs) may facilitate the diagnosis of vitiligo. Under Wood's light, vitiligo lesions emit a bright blue-white fluorescence and appear sharply demarcated, while hypopigmented skin is not

enhanced (Figure 4). The diagnosis does not usually require skin biopsies or laboratory tests (3,5,42).



Figure 4: Segmental vitiligo over the right chin of a 5-year-old boy. Adapted from Leung et al. 2021 (84)

Table 2: Differential diagnosis of vitiligo. Adapted from Bergqvist and Ezzedine. 2020 (42)

Chemically-induced leukoderma (occupational)
Phenols and other derivatives
Topical or systemic drug-induced depigmentation
<i>Genetic syndromes</i>
Hypomelanosis of Ito
Piebaldism
Tuberous sclerosis
Vogt-Koyanagi-Harada syndrome
Waardenburg syndrome
Hermanski-Pudlak syndrome
Menke's syndrome
Ziprkowski-Margolis syndrome
Griscelli's syndrome
Postinflammatory hypopigmentation
Pityriasis alba
Atopic dermatitis/allergic contact dermatitis
Psoriasis
Lichen planus
Toxic drug reactions
Posttraumatic hypopigmentation (scar)
Phototherapy- and radiotherapy-induced
Neoplasm-related hypomelanoses
Melanoma-associated leukoderma
Mycosis fungoides
Infection-related hypomelanoses
Leprosy
Pityriasis versicolor
Leishmaniasis
Onchocerciasis
Treponematoses (pinta and syphilis)
Idiopathic
Idiopathic guttate hypomelanosis
Progressive (or acquired) macular hypomelanosis
Congenital
Nevus anemicus
Nevus depigmentosus
Others
Lichen sclerosus et atrophicus
Melasma (caused by contrast between lighter and darker skin)

6 INITIAL ASSESSMENT

The evaluation of the patient with vitiligo entails a detailed history and a complete skin examination to assess disease severity and individual prognostic factors. An assessment form including personal and family history and clinical examination items was developed by the Vitiligo European Task Force (VETF) and is useful for the evaluation (Table 3) (85).

Table 3: History and examination of a patient with vitiligo

Phototype (Fitzpatrick's skin type)
Ethnic origin
Age at onset
Disease duration
Disease activity, patient's opinion (progressive, regressive, stable over the last 6 months)
Previous episodes of repigmentation, and if yes, spontaneous or not (details)
Depigmentation on scars (Koebner's phenomenon)
Stress as triggering factor (at onset of disease) or as aggravating factor (during flares). Is itch present before flares?
Thyroid disease, if yes detail, including presence of thyroid autoantibodies
Family history of premature hair graying
Family history of vitiligo (detail if needed in family tree)
Type and duration of previous treatments including opinion of patient on previous treatments (list): useful/not useful
Current treatment(s) and date of commencement
Other diseases and treatments (list)
Personal history of autoimmune diseases: if yes, which type
Family history of autoimmune diseases (detail if needed in family tree)
Halo nevus: if yes number at examination (to be put in examination sheet)
Vitiligo on genitals (to be asked and checked if necessary and accepted by patient at examination)
Global QoL assessment (10 cm analog scale) 'how does vitiligo currently (last week) affects your everyday life'
Reference of clinical photographs

Four clinical markers of active, progressive disease are of main interest and include the Koebner phenomenon, trichrome lesions, inflammatory lesions, and confetti-like depigmentation. Koebner analysis determines the appearance of new patches in previously intact skin typically in friction areas (86) . Trichrome lesions have 3 colors in close proximity—depigmented lesional skin, normally pigmented skin, and a zone of

hypopigmented skin, usually at the borders (Figure 4) (87). Inflammation is not common in vitiligo, it is characterized by erythema, scale, and pruritus within hypopigmented or depigmented lesions, particularly at the periphery of the lesions (Figure 5) (88). Confetti-like depigmentation are characterized by numerous depigmented macules (1-5 mm in diameter) clustered in groups that are frequently seen at the border of larger existing lesions (Figure 6) (89). All the previous markers are highly correlated with the severity and rapid progress of the disease and are important when assessing the patient and developing a management plan.



Figure 5: Trichrome pattern on the neck and shoulders



Figure 6: Inflammatory type of vitiligo with erythema and scale



Figure 7: Confetti-like lesions on the dorsal aspect of the foot

7 COMPLICATIONS

Vitiligo is physically disfiguring and might be stigmatizing, in addition to its devastating psychological impact leading to lower self-esteem, bullying peer-rejection, sleeping problems, depression and anxiety (90–95). Furthermore, vitiligo can lead to sexual dysfunctioning in adults where larger surface areas or genital lesions are involved (96). Moreover, vitiligo is associated with a substantial effect on the quality of life of the patients (95,97–99) and their caregivers (100).

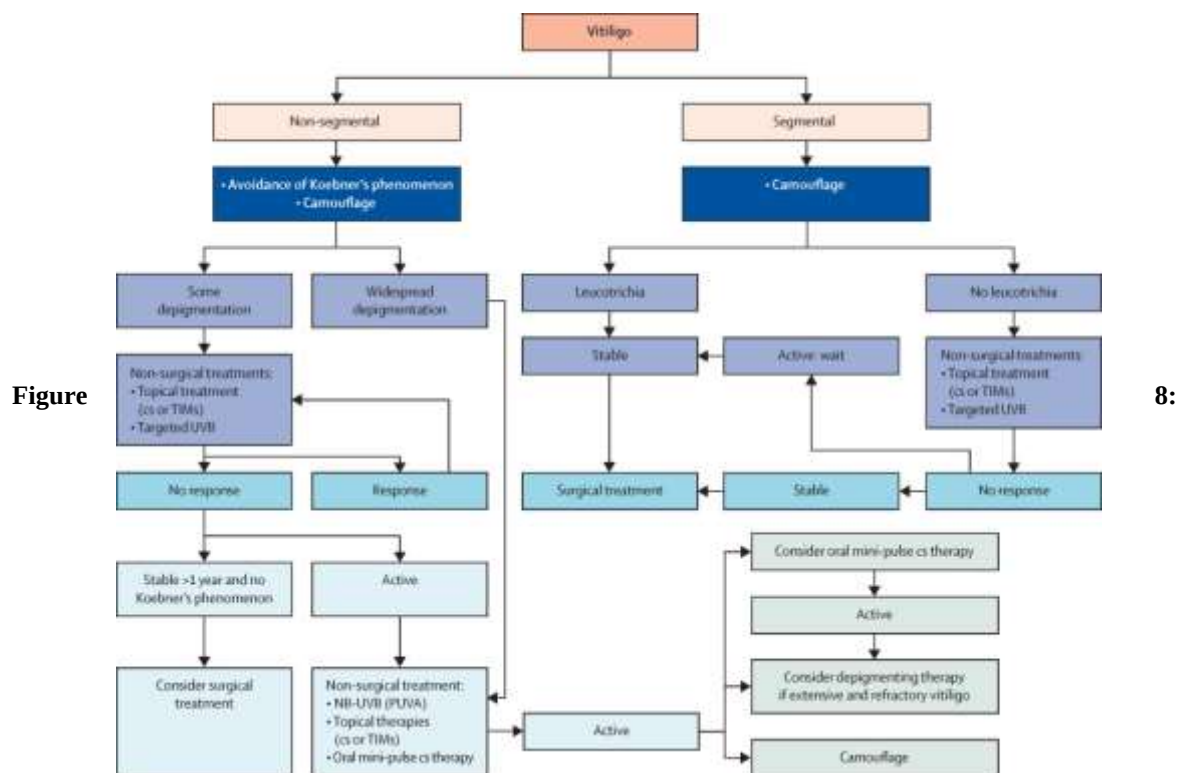
In addition to its psychological impact, multiple auto-immune diseases (50,65,101) and thyroid diseases (102,103), nail abnormalities (104,105), ocular problems (106–108) and hearing disabilities (106,109) have been associated with vitiligo.

8 MANAGEMENT OF THE DISEASE

Before any vitiligo management, the extent of the disease, personal and family history, clinical examination, in addition to psychological profile and quality of life evaluation should be assessed (48). So far, there is no cure for vitiligo, however treatments

include phototherapy, topical and systemic immunosuppressants, and surgical techniques, when used together aid in stopping the disease, stabilizing depigmented areas and stimulating repigmentation (110,111). Moreover, camouflage techniques are recommended to improve the quality of life of patients since therapeutic options are time consuming and require long-term follow-up, in addition to the poor response to treatment (48,112). Furthermore, the choice of treatment highly depends on the type, extent, distribution and activity of the disease, in addition to the patient's age, phototype and effect on quality of life.

Several guidelines were established, the latest was in 2012 by the European Dermatology Forum (113). The detailed algorithm of these guidelines is shown in Figure 8.



Therapeutic algorithm of vitiligo. cs=corticosteroids. NB=narrow band. PUVA=psoralen and UVA. TIM=topical immunomodulator. UV=ultraviolet. Adapted from Bergqvist and Ezzedine. 2020. (42)

9 ASSESSMENT TOOLS

While multiple assessment tools were developed by different researchers, there is no standardized method for assessing vitiligo in terms of extent, severity, degree of depigmentation or burden. Moreover, a core outcome set for the evaluation of vitiligo has been established which includes repigmentation, maintenance of gained repigmentation, quality of life, cosmetic acceptability, cessation of spreading, burden of treatment and harm and side effect of a treatment (10).

Below we present the different methods available in the literature and their relevance to above stated outcomes (Table 4).

Table 4: Vitiligo core outcomes and the different assessment tools

Tool	Core outcomes						
	Repigmentation	Maintenance of gained repigmentation	quality of life	cosmetic acceptability	cessation of spreading	burden of treatment	Side effect and harm
Vitiligo European Task Force (VETF)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Vitiligo Area Scoring Index (VASI)	X	X	N/A	N/A	X	N/A	N/A
Facial Vitiligo Area Scoring Index (F-VASI)	X	X	N/A	N/A	X	N/A	N/A
Vitiligo Signs of Activity Score (VSAS)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Vitiligo Disease Activity Score (VDAS) and Vitiligo Disease Improvement Score (VDIS)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Vitiligo extent score (VES) and Vitiligo extent score-plus (VES-plus)	X	X	N/A	N/A	X	N/A	N/A
Vitiligo Extent Score for a Target Area (VESTA)	X	X	N/A	N/A	X	N/A	N/A
Vitiligo Extent Tensity Index (VETI)	N/A	N/A	N/A	N/A		N/A	N/A
Patient reported measures							
Self-assessment Vitiligo Area Scoring Index (SAVASI)	X	X	N/A	N/A	X	N/A	N/A
Vitiligo Noticeability Scale (VNS)	N/A	N/A	N/A	X	N/A	N/A	N/A
Self-assessment Vitiligo Extent Score (SAVES)	X	X	N/A	N/A	X	N/A	N/A
Other							
Vitiligo Treatment Impact (VTI)	N/A	N/A	N/A	N/A	N/A	x	N/A
Vitiligo Impact Patient Scale (VIPs)	N/A	N/A	X	N/A	N/A	x	N/A
Vitiligo Impact Scale (VIS)	N/A	N/A	X	N/A	N/A	N/A	N/A
VitiQol	N/A	N/A	X	N/A	N/A	N/A	N/A

9.1 Clinician-reported outcome measures

9.1.1 Vitiligo European Task Force (VETF)

The Vitiligo European Task Force (VETF) proposed a system which combines analysis of extent, stage of disease (staging), and disease progression (spreading), in addition to the evaluation sheet that includes a full patient- and disease- related information (Table 3). In summary, extent is evaluated using the rule of 9. Staging is based on cutaneous and hair pigmentation in vitiligo patches, and the disease is staged 0–3 on the largest macule in each body region, except hands and feet, which are assessed separately and globally as one unique area. Assessment of spreading is based on Wood's lamp examination of the same largest macule in each body area. Spreading assessment is a very important evaluation since rapidly progressive vitiligo needs urgent intervention to stabilize the disease. Figure 9 Adapted from Sosa et al. 2015, summarizes the recommendation of VETF. This method is susceptible to variability due to the inter-observer variability (85).

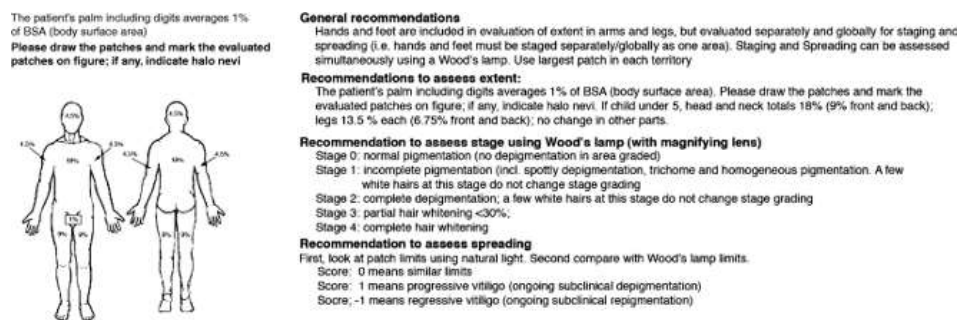


Figure 9:

Area	% Area	Staging* (0–4)	Spreading* (–1 +1)
Head and neck(0–9%)			
Trunk (0–36%)			
Arms (0–18%)			
Legs (0–36%)			
Hands and feet			
Totals (0–100%)		0–20	(–5 +5)

*largest patch in each area

Recommendations for scoring extent, stage, and spread of vitiligo; rule of 9 and scoring table

9.1.2 Vitiligo Area Scoring Index (VASI)

Vitiligo Area Scoring Index (VASI) is a quantitative tool initially developed to evaluate the response of vitiligo to treatment, specifically narrowband UV-B (NB–UV-B) phototherapy using parametric tests and is widely used to assess depigmentation in vitiligo. This method relies on the assessment of repigmentation, based on a composite estimate of the overall area of vitiligo patches at baseline and the degree of macular repigmentation within these patches over time. The patient's body is divided into five separate regions: the hands, upper extremities, trunk, lower extremities and feet. The face and neck areas are assessed separately and not included in the overall scoring. One hand unit which consists of the palm plus the volar surface of all the digits (approximately 1% of the total body surface area) (114) is and was used as a guide to estimate the baseline percentage of vitiligo involvement of each body region. For each body region, VASI is determined as the product of the vitiligo area in hand units and the extent of depigmentation within each hand-unit-measured patch (possible values of 10, 25, 50, 75, 90 or 100% as shown in Figure 10. At 100% depigmentation, no pigment is present; at 90%, specks of pigment are present; at 75%, the depigmented area exceeds the pigmented area; at 50%, the depigmented and pigmented areas are equal; at 25%, the pigmented area exceeds the depigmented area; at 10%, only specks of depigmentation are present. VASI, applied to the whole body, is calculated using the following formula, (possible range 0–100) (115).

$$\text{VASI} = \sum_{(\text{all body size})} (\text{hand units}) \times (\text{depigmentation})$$



Figure 10: Standardized assessments for estimating the degree of pigmentation to derive the Vitiligo Area Scoring Index

9.1.3 Facial Vitiligo Area Scoring Index (F-VASI)

Since facial involvement of vitiligo is an important factor in a patient's life (116), a tool for facial vitiligo assessment – F-VASI– was developed. While hand-unit has been widely used to assess affected body surfaces, patches smaller than one hand unit, especially on the face, might be challenging to assess. Therefore, F-VASI was developed using the fingertip unit (117) (FTU) (1 hand unit equals 32.1 ± 1.3 FTU), where F-VASI is the sum of all FTUs needed to measure all vitiligo lesions on the face. F-VASI can alternatively be calculated by the product of FTU multiplied by the depigmentation level of each vitiligo lesion. The depigmentation level can take a value between 0 and 1, either by a rough estimate or by selecting the most similar one from the reference image (Figure 12) (118).

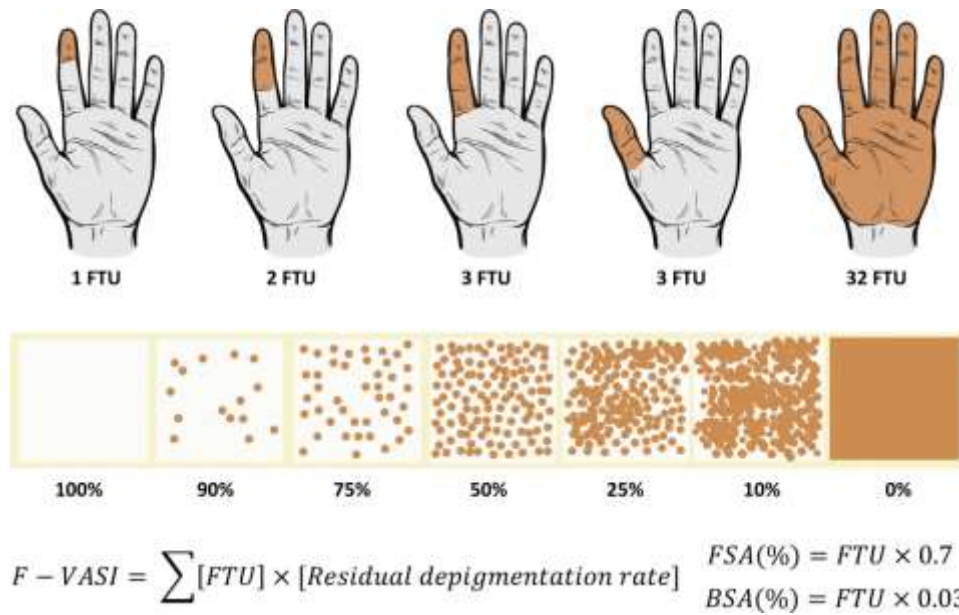


Figure 11: The fingertip unit (FTU) and F-VASI. Vitiligo lesions can be estimated by using a fingertip (1 FTU), a finger (3 FTU), a thumb (3 FTU), or a hand (32 FTU), depending on the lesion size. F-VASI is defined as the sum of all FTUs of each vitiligo lesion on the face. FTU can be converted to FSA (%) and BSA (%). BSA, Body surface area; F-VASI, Facial Vitiligo Area Scoring Index; FSA, face surface area.

9.1.4 Vitiligo Signs of Activity Score (VSAS)

Vitiligo Signs of Activity Score (VSAS) is based on the assessment of three clinical visible signs in vitiligo; confetti-like depigmentations, Koebner phenomenon and hypochromic areas/borders within 15 predefined body locations (Figure 11). The presence of at least one of the three signs in a specific area was coded 1, and 0 if none of the three signs was present, resulting in a score between 0 and 15. Each body area has the same impact on the total score. A similar score (0–15) was performed for each clinical sign separately generating subscores: confetti-like depigmentations (c-VSAS), Koebner phenomenon (k-VSAS) and hypochromic areas/borders (h-VSAS). In addition to the subscores, the intensity per area can be measured grading from 1 to 3 (Details in Figure 12) (119).

Vitiligo Signs of Activity Score (VSAS)																	
	Confetti-like depigmentation: Present: Yes ☐ No ☐ Global grade*: C1 C2 C3 Koebner type 2B: Present: Yes ☐ No ☐ Global grade*: K1 K2 K3 Hypochromic areas/borders: Present: Yes ☐ No ☐ Global grade*: H1 H2 H3																
	<table border="1"> <thead> <tr> <th></th> <th>Grade 1</th> <th>Grade 2</th> <th>Grade 3</th> </tr> </thead> <tbody> <tr> <td>Confetti-like depigmentation</td> <td>< 10</td> <td>10–50</td> <td>> 50</td> </tr> <tr> <td>Koebner phenomenon type 2B</td> <td>1</td> <td>2–5</td> <td>>5</td> </tr> <tr> <td>Hypochromic areas/borders</td> <td>1</td> <td>2–5</td> <td>> 5</td> </tr> </tbody> </table>		Grade 1	Grade 2	Grade 3	Confetti-like depigmentation	< 10	10–50	> 50	Koebner phenomenon type 2B	1	2–5	>5	Hypochromic areas/borders	1	2–5	> 5
		Grade 1	Grade 2	Grade 3													
	Confetti-like depigmentation	< 10	10–50	> 50													
Koebner phenomenon type 2B	1	2–5	>5														
Hypochromic areas/borders	1	2–5	> 5														
<table border="1"> <thead> <tr> <th>Number of locations with (at least 1) disease activity signs</th> <th>.../15</th> <th>VSAS</th> </tr> </thead> <tbody> <tr> <td>Number of locations with confetti-like depigmentation</td> <td>.../15</td> <td>c-VSAS</td> </tr> <tr> <td>Number of locations with Koebner phenomenon type 2B</td> <td>.../15</td> <td>k-VSAS</td> </tr> <tr> <td>Number of locations with hypochromic areas/borders</td> <td>.../15</td> <td>h-VSAS</td> </tr> </tbody> </table>	Number of locations with (at least 1) disease activity signs	.../15	VSAS	Number of locations with confetti-like depigmentation	.../15	c-VSAS	Number of locations with Koebner phenomenon type 2B	.../15	k-VSAS	Number of locations with hypochromic areas/borders	.../15	h-VSAS					
Number of locations with (at least 1) disease activity signs	.../15	VSAS															
Number of locations with confetti-like depigmentation	.../15	c-VSAS															
Number of locations with Koebner phenomenon type 2B	.../15	k-VSAS															
Number of locations with hypochromic areas/borders	.../15	h-VSAS															

Figure 12: Measurement instrument used to score the Vitiligo Signs of Activity Score (VSAS) and subscores (c-VSAS, k-VSAS, h-VSAS)

Vitiligo disease activity signs		Grade 1	Grade 2	Grade 3
C Confetti-like depigmentation				
K Koebner phenomenon				
H Hypochromic areas/borders				

Figure 13: Grading chart in the Vitiligo Signs of Activity Score (VSAS)

9.1.5 Vitiligo Disease Activity Score (VDAS) and Vitiligo Disease Improvement Score (VDIS)

Vitiligo Disease Activity Score (VDAS) and Vitiligo Disease Improvement Score (VDIS) are two vitiligo scores performed simultaneously to assess respectively the dynamics of vitiligo (120). A pictogram is used to assess improvement or worsening (Figure 13). All involved body areas are identified in the first figure (0–15) and in the second and third figures (follow-up figures) any activity sign will be indicated, was it activity (progression) – VDAS15 or improvement (repigmentation) – VDIS15 leading to an overall score ranging from 0 to 15. An additional option was added in each area showing the grade of difference, ranging from –4 to +4 (very much worsened or improved), resulting in a score of 0–60 (VDAS60 and VDIS60) (120).

Date: This assessment is based on an interval of months

Mark an X (for paper version) or click (for digital version) on the location(s) of involvement with vitiligo, location(s) of improvement (repigmentation) and location(s) of worsening (activity) in this patient with vitiligo. One X/lick per demarcated body area is sufficient. Palm of the hands and sole of the feet can be marked on the opposite side of the same body area (back of hand/dorsum of feet).

Indicate the AREAS INVOLVED with vitiligo in this patient

☐ There are no vitiligo lesions anymore

Is there any IMPROVEMENT (repigmentation)?

☐ Yes; mark/click below

☐ No, there has been no improvement

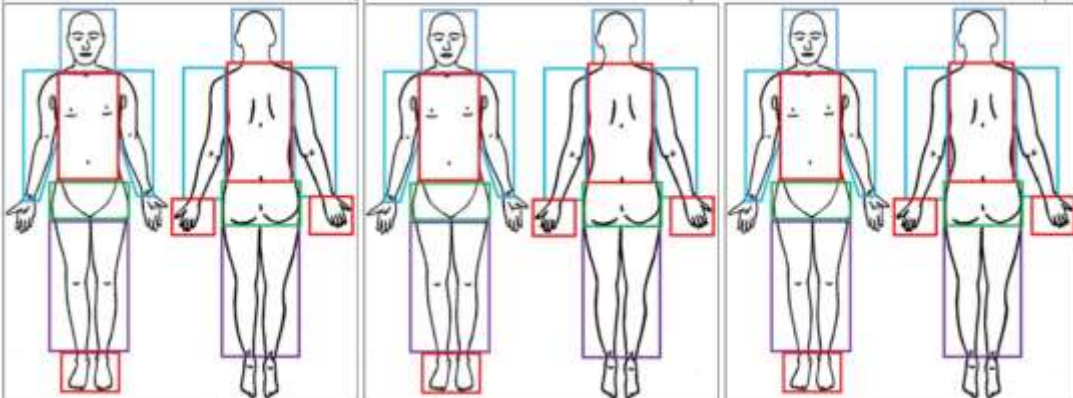
☐ I don't know

Is there any WORSENING (activity)?

☐ Yes; mark/click below

☐ No, there has been no worsening

☐ I don't know



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Optional: Add the level of 'improvement' and/or 'worsening' of the vitiligo in each area according to the following scale(s):

→

Completely improved (no vitiligo anymore) (4+)

Much improved (3+)

Moderately improved (2+)

Slightly improved (1+)

Stable (0)

Slightly worse (1-)

Moderately worse (2-)

Much worse (3-)

Very much worse (4-)

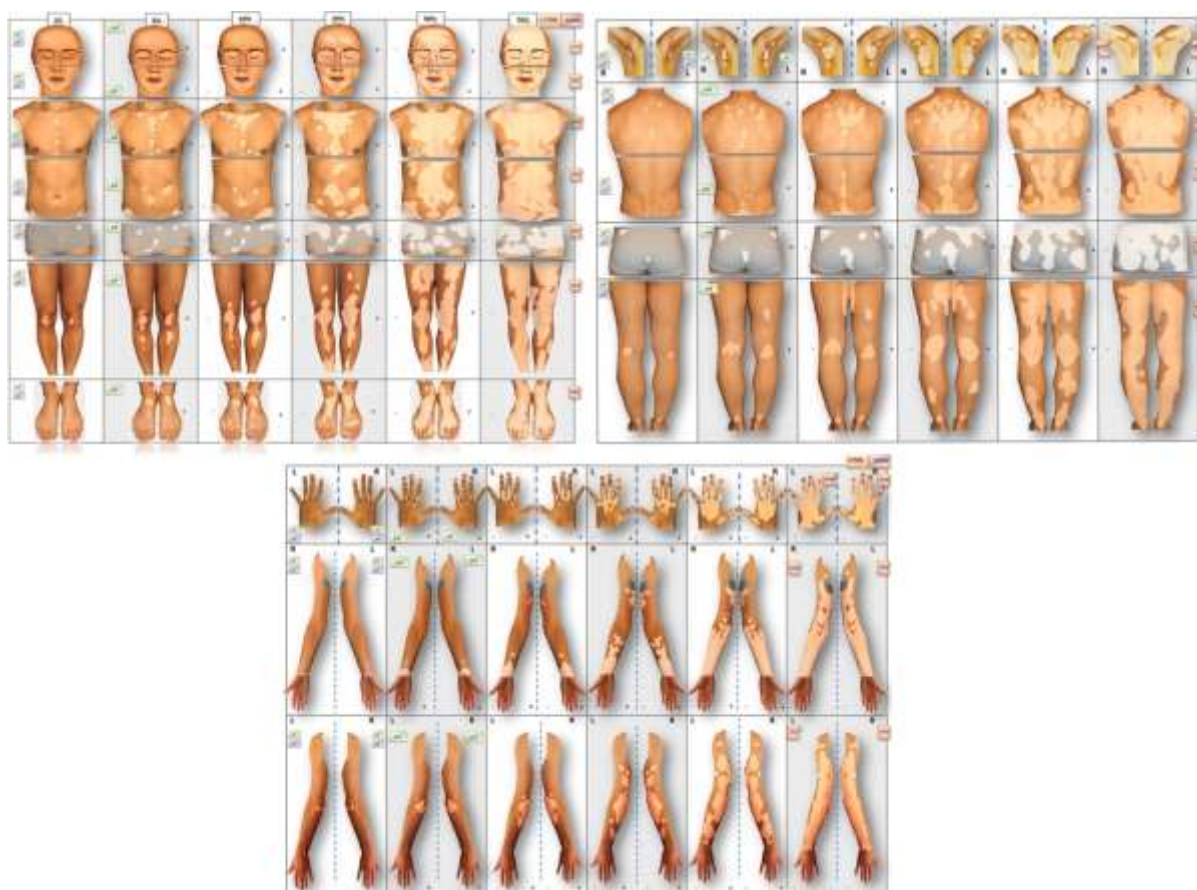
Number of locations involved with vitiligo	/15
Number of locations with improvement	/15
Number of locations with worsening	/15

Figure 14: Instrument used to score the VDAS15, VDIS15, VDAS60 and VDIS60

9.1.6 Vitiligo extent score (VES) and Vitiligo extent score-plus (VES-plus)

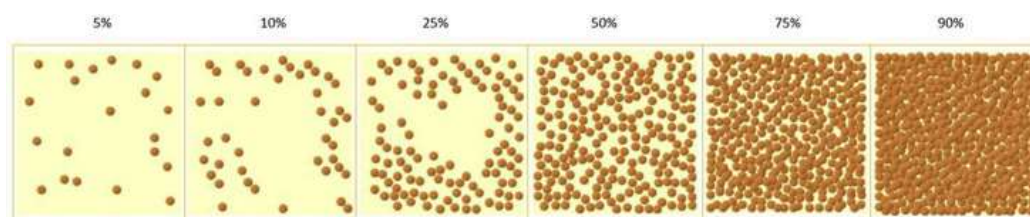
This method was developed to assess three core outcomes; repigmentation, side effects, and maintenance of gained repigmentation, that were considered essential in every clinical trial (121). The VES is a computerized severity template of vitiligo images that measures vitiligo at 19 different areas of the body, the images range from no lesion to almost 100% lesion coverage. The physician scores these 19 body areas separately by selecting the image that most resembles to the patient's status in that body area. Furthermore, options are added for a more accurate calculation such as choosing "slightly less" or "more" for extent of lesions by pressing (-) or (+) buttons or ">75%" if the involved area is more than shown in the picture, but less than 100%. Then the VES calculator converts the data into affected body surface area (BSA) score by summing up the measurements from all locations by accessing www.vitiligo-calculator.com (122).

After the release of VES, vitiligo experts' had concerns that the latter does not include an integrated perifollicular repigmentation pattern. Hence, the original instrument was modified to VESplus to optimize precision in case of treatment evaluation (Figure 15) and added perifollicular scale to the original VES (12,123,124).



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Figure 15: Scoring sheet Vitiligo Extent Score (VES).



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Figure 16: Added perifollicular repigmentation scale in the VESplus (range 5%-90%). Added perifollicular repigmentation scale in the VESplus (range 5%-90%). In each region, the VESplus score is regional VES score $\times [(100 - \text{estimated percentage of perifollicular repigmentation score})/100]$. The total VESplus score is the sum of each regional score

9.1.7 Vitiligo Extent Score for a Target Area (VESTA)

Vitiligo Extent Score for a Target Area (VESTA) is an instrument used to measure the repigmentation rate (%) in a target lesion using reference images of both marginal and perifollicular repigmentation. VESTA consists of three parts: (1) reference images of marginal repigmentation; (2) reference images of perifollicular repigmentation; and (3) a formula that can be used to calculate total repigmentation rate (%), which is the sum of the fully repigmented area (%) and the perifollicular repigmentation (%) in the remaining area (Figure 16) (125).

Figure 17: The Vitiligo Extent Area (VESTA)

9.1.8 Vitiligo extent (VETI)

Score for a Target

tensity index

The vitiligo extent tensivity index (VETI) score is a quantitative scoring system to measure the extent and severity of vitiligo. The percentage of extension involvement (p) is evaluated using the rule of nines in five body sites (head, upper limbs, trunk, lower limbs, and genitalia); the coefficient of head is 1 (9:9=1), trunk and lower limb is 4 (36:9=4), upper limb is 2 (18:9=2) and genitalia is almost 0.1 (1:9= 0.1). While the disease's tensivity is graded into

five stages depending on the depigmentation and the perifollicular pigmentation. VETI is scored based on the below formula with a maximum of 55.5 (126).

VETI score: (Percentage of head involvement $\times$ grade of intensity) + (Percentage of trunk involvement $\times$ grade of intensity) 4+ (Percentage of upper limbs involvement $\times$ grade of intensity) 2+ (Percentage of lower limbs involvement $\times$ grade of intensity) 4+ (Percentage of genitalia involvement $\times$ grade of intensity) 0.1

9.2 Patient-reported outcome measures

Since patient-oriented medicine is an emerging concept, allowing the patient's involvement in the management of chronic diseases, multiple self-assessment scores were developed to monitor the extent and severity of vitiligo.

9.2.1 Self-assessment Vitiligo Area Scoring Index (SAVASI)

The Self-assessment Vitiligo Area Scoring Index (SAVASI) (Figure 11) is an illustrated document, that uses the same basic principles as the VASI (115) adapted for patients. In the SAVASI, firstly the patient indicates in a drawing the body parts affected by vitiligo. Thereafter, the patient assesses per body part the number of hand units (to one decimal point) affected and the extent of depigmentation similarly to VASI (Refer to:

Figure 9: Recommendations for scoring extent, stage, and spread of vitiligo; rule of 9 and scoring table

Vitiligo Area Scoring Index (VASI)).

To assess depigmentation on areas that were not easily self-assessable patient could use a mirror or help from a next of kin. The SAVASI applied to the whole body is calculated alike the VASI (Refer to:

Figure 9: Recommendations for scoring extent, stage, and spread of vitiligo; rule of 9 and scoring table

Vitiligo Area Scoring Index (VASI) (127).

1. Determine for every body part how many hands (with a digit after the break) you need to cover the depigmented area on your own body.

Example: number of hands: 0.5

2. Select for every body part one the pictures below that suits the majority of the depigmented spots in that area. The percentages show the amount of depigmented skin. 100% for example means total depigmentation

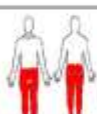
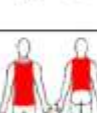
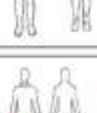
 Face and neck : number of hands:...	 Arms : number of hands:...	 Legs : number of hands:...	 Trunk : number of hands:...	 Genitals : number of hands:...	Hands: number of hands:... Feet: number of hands:...
 100% 90% 75% 50% 25% 10% 0% Green	 100% 90% 75% 50% 25% 10% 0% Green	 100% 90% 75% 50% 25% 10% 0% Green	 100% 90% 75% 50% 25% 10% 0% Green	 100% 90% 75% 50% 25% 10% 0% Green	 100% 90% 75% 50% 25% 10% 0% Green

Figure 18: SAVASI form. Patients were asked to determine for every body part how many hands (to one decimal point) were needed to cover the depigmented area. Thereafter, the patients had to select, again for every body part, the picture that suits best the majority of the depigmented spots in that area.

9.2.2 Vitiligo Noticeability Scale (VNS)

The Vitiligo Noticeability Scale (VNS) is a patient-reported outcome measure assessing how ‘noticeable’ vitiligo patches are after treatment. VNS is a single Likert-scale question “Compared with before treatment, how noticeable is the vitiligo now?” ranging from “More noticeable =1” to “no longer noticeable=5” (128); a score of ≥ 4 on the five-point VNS is proposed to represent treatment success (129).

9.2.3 Self-assessment vitiligo extent score (SAVES)

Self-assessment vitiligo extent score (SA-VES) is a simplified patient-oriented version of the Vitiligo Extent Score (VES) to measure the affected BSA of patients with vitiligo. The researchers selected the most representing pictures from the scoring sheet. In the SA-VES the number of body areas to score is reduced to 12 and no subscore options are included, as in the physicians' version (www.vitiligo-calculator.com). The patient selects the most representing pictures from the scoring sheet (Figure 18). Then a total and final SA-VES score is reported as the sum of measurements from all areas, which can be calculated by using a converting table, which is similar to the VES (130). To note that Vitiligo Extent Score (VES) has shown to be superior in terms of reliability and user-friendliness compared to Vitiligo Area Scoring Index (VASI) in which the 1% hand rule is incorporated (115,122).

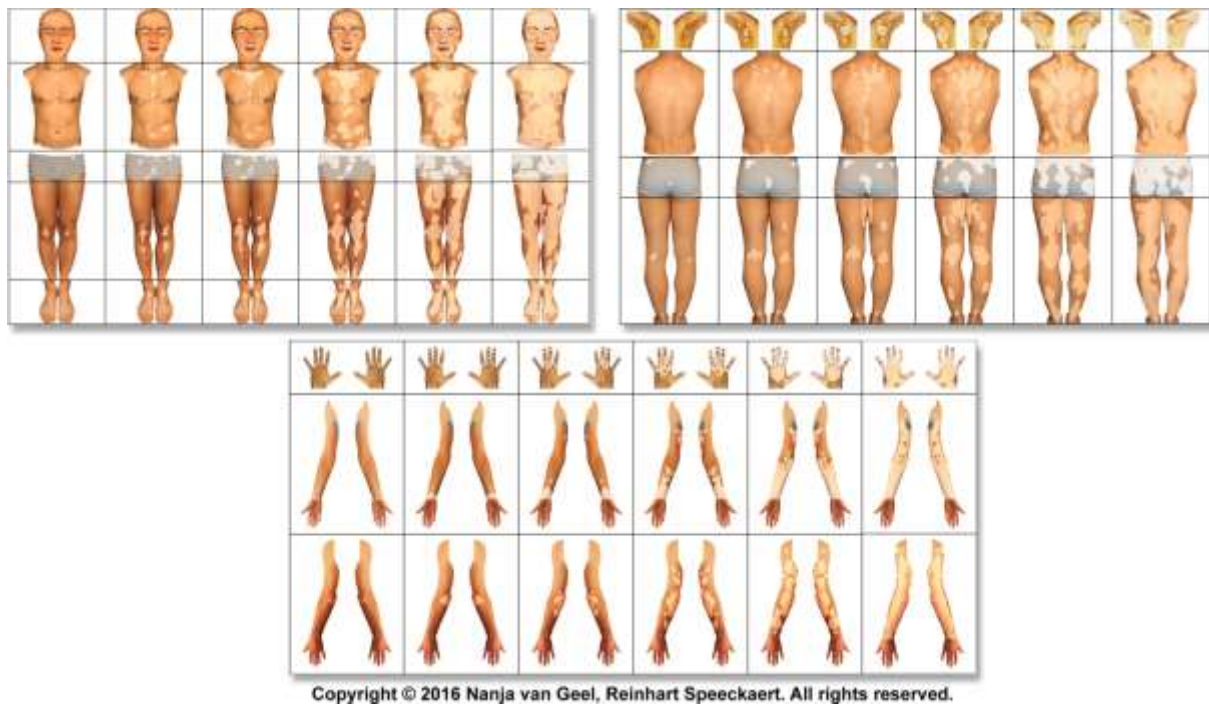


Figure 19: Scoring sheet of the Self-Assessment Vitiligo Extent Score.

9.3 Others

Since vitiligo management is challenging and requires long-term adherence of patients, tools were developed to measure the burden of the treatment in vitiligo patients (131). Furthermore, vitiligo has been associated with a decrease of quality of life due to its effect on the psychological status of the patient, hence multiple tools were developed to specifically assess the quality of life of patients with vitiligo (132–134).

CHAPTER II- MINIMAL CLINICALLY IMPORTANT DIFFERENCE

Multiple tools for the assessment of vitiligo have been developed, however, cut-offs have not yet been established to reflect the patient's improvement and the treatment's effectiveness. Furthermore, valid, reliable, and interpretable scores are essential in vitiligo research (10). In addition, proper treatment have shown to improve the overall quality of life in patients with chronic diseases (135) which is considered as an important core outcome in patients with vitiligo (10). Even though SAVES a patient-reported measure has proven to be a reliable instrument for vitiligo extent, however the minimal clinically important change of this measure has not yet been determined (130).

Patient-oriented medicine is becoming trendy in medical practice, allowing the patient's involvement in the disease management and treatment (136). Therefore, many patient-reported outcome measures (PROM), mainly self-administered questionnaires, have been developed to assess health-related quality of life, functional status, symptoms and symptom burden, health behaviors, and the patient's health care experience from a patient's point of view (137,138) and have been increasingly used as outcomes in many clinical trials (139). Furthermore, PROMs are being used in clinical informed decisions, treatment decision, comparing outcomes among health-care providers, stimulating quality improvement and evaluating practices and policies, and identifying patient preferences (138,140).

One of the main challenges that face researchers and clinicians is interpreting PROMs and to correctly identify whether a change in scores, any observed difference, is relevant or not, beyond statistical significance (136,141). Therefore, the minimal clinically important difference (MCID) has been defined by Jaeschke et al. as 'the smallest difference in score in

the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management' (142). The MCID represents a threshold value of change in PROM score considered to have a clinical significance from the patient's perspective and can be used by physicians as a criterion for effectiveness of a treatment (143) (144).

Moreover, MCID assessment has been widely used in dermatologic PROMs and in different diseases including; Acne-Specific Quality of Life Questionnaire (Acne-QoL) (145), Patient-Oriented Eczema Measure (POEM) (146), Dermatology Life Quality Index (DLQI) in inflammatory skin diseases (147), Angioedema Quality of Life Questionnaire (AE-QoL) (148), Patient-Oriented Eczema Measure (POEM) (149), Atopic Dermatitis Symptom Score (ADSS) (150), Work Productivity and Activity Impairment Questionnaire for Psoriasis (WPAI-PsO) (151), Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) in patients with chronic spontaneous urticaria (152) and numeric rating scales (NRS) for pain in atopic dermatitis (153).

The MCID in general scores and in PROMs specifically can be calculated in different ways; mainly distribution based and anchor-based methods. The distribution based methods are based on statistical significance in the change of a score while anchor-based methods actually compares between the change of PROM scores and the perceived change of the patient considered as an anchor or external criterion, giving a clear measure of the patient's improvement or deterioration (144) (154) (155) (156) (157) (158).

1.1 Distribution-based approach

Distribution-based methods use the variability of overall responses to estimate MCID without considering the patient's perspective (136) based on statistically significant changes (159). Variability is often measured by the standard error of measurement (SEM), the minimum detectable change (MDC), the standard deviation (SD), or the effect size (136,159–164). Due to the numerous calculations of MCIDs in the distribution-based methods, most researchers use a combined approach for MCIDs (163).

1.1.1 *Standard error of measurement (SEM)*

Standard Error of Measurement (SEM), is defined by $SEM = \sigma \times \sqrt{1 - Reliability}$ with σ the baseline standard deviation. The reliability can be estimated using an internal consistency estimate (Cronbach's alpha), however, authors recommend to use a test-retest reliability estimate (such as an Intra-Class Correlation coefficient) to determine SEM for calculation of MCID (164–166).

Furthermore, MCID has been proposed to be equal to $1 \times SEM$, $1.96 \times SEM$, and $1.96 \times \sqrt{2} \times SEM = 2.77 \times SEM$ (164). In fact, the $1.96 \times \sqrt{2} \times SEM$ gives a 95% confidence interval and is defined by *Minimal Detectable Change (MDC)*, considered as an estimate of the MCID of a PRO instrument (167).

1.1.2 *Standard deviation (SD)*

The standard deviation of baseline has been used in several ways to calculate a MCID. The most common and well-described distribution-based formula for calculation of

the MCID of a PROM using SD is $MCID = 0.5 * SD$ (168), however other calculation can be done, such as $0.3SD$, $1/3SD$, $0.2SD$ (163).

1.1.3 Effect size

Effect size (ES) is obtained by dividing the difference in scores from baseline to post-treatment by the standard deviation of the baseline scores; $ES = (\text{post-treatment mean score} - \text{Pre-treatment mean score}) / SD_{\text{pre-treatment}}$ (169). Cohen defined an effect size of 0.2 as small, 0.5 as moderate, and 0.8 as large (170). Hence, MCID can be calculated as $0.2 * SD_{\text{pre-treatment}}$, $1/3 * SD_{\text{pre-treatment}}$, or $0.5 * SD_{\text{pre-treatment}}$. Based on Cohen's description that "medium [effect sizes] represent an effect likely to be visible to the naked eye of a careful observer" (171), a clinically significant difference is usually considered at least a medium effect size.

1.2 Anchor-based approach

Anchor-based approach is the commonly used method for determining MCIDs in patient reported outcomes (172). This approach links an external indicator (the anchor) to the change of an outcome measure score, taking into consideration the patient's perspective and are considered as the best way to estimate MCID (136,159,173). An anchor, known also as Global Rating of Changes (GRC), is an explicit Likert scale (usually ranging from much worse, to much better) for patients to rate the change in the outcome that is measured by the PROM since baseline assessment; after a certain period or intervention (142).

Even though the external criterion method is the commonly used anchor-based approach to assess MCID, different methods were also used including within-patients score

change, between-patients score change, sensitivity- and specificity-based approach and Receiver operating characteristic (ROC) analysis (160).

1.2.1 *Within-patients score change*

This method defines MCID as the change in PROM of a group of patients selected according to their answers to a global assessment scale (142,174). The MCID is considered as the average change of the patients who exhibited small changes (142,174) or the mean change in scores of the “much improved patients” (175).

1.2.2 *Between-patients score change*

This method compares PRO scores (176) or PRO change of score of group of patients (177) with different responses to a global assessment scale. MCID is defined as the score difference between two adjacent levels on a global rating (176) or as the difference in the change score of the “better” and “unchanged” patients (177).

1.2.3 *Sensitivity- and specificity-based approach and Receiver Operating Characteristic (ROC)*

Sensitivity and specificity- based approach determines the MCID that allows for the best discrimination between groups of patients. Sensitivity is the proportion of patients who report an improvement on the anchor with a sensitivity of 1 indicating that all true positives are identified. While specificity is defined as the proportion of patients who do not report an improvement on the external criterion with a specificity of 1 indicating that all true negatives are identified, similarly to the definitions of sensitivity and specificity in diagnostic tests

(178,179). Most researchers have chosen to have equal sensitivity and specificity for their MCID value using Receiver Operating Characteristic (ROC) curves. Since a desirable MCID sensitivity and specificity has not yet been established, some researchers have chosen an MCID where sensitivity is equal to specificity, while others have chosen a compromise between sensitivity and specificity using YoudenJ index, which is the farthest point from the diagonal and closest point to the top- left of the ROC curve, as a best threshold (136). Furthermore, the area under the curve (AUC) in ROC analysis represents the probability that a score will correctly discriminate between improved and unimproved patients. This probability ranges from 0.5 to 1 with an AUC of 0.7 to 0.8 being considered as acceptable and 0.8-0.9 as excellent (180).

CHAPTER III- PSYCHOLOGICAL IMPACT OF VITILIGO

Vitiligo is not only a disfiguring disease (181); it also has a high impact on the quality of life (14,15) and psychological well-being of patients, including depression, anxiety and reduced quality of sleep (16–21,182) as seen in other cutaneous (182–187) and non-cutaneous chronic diseases (188–191). In addition, quality of life was considered as one of the core outcomes from the patients' perspective in the International e-Delphi consensus on vitiligo in 2015 (10)

A recent meta-analysis showed that included 1,799 people with vitiligo confirmed the quality of life impairment in patients with vitiligo compared with healthy controls (98) while another meta-analysis showed that patients with vitiligo were 4.96 times more likely to display depression compared with controls (192). Moreover, a recent systematic review showed the presence of psychosocial comorbidity in 32.6–90.0% of patients with vitiligo, with depression and anxiety being the most reported. Sleep disturbances ranged from 4.6% to 89%. Furthermore, the study showed that the psychosocial comorbidities were more prevalent in vitiligo compared with acne, alopecia areata, atopic dermatitis, and urticaria but less prevalent compared to psoriasis (91).

1 PREVALENCE AND CORRELATES OF DEPRESSION, ANXIETY AND SLEEP DISTURBANCE

Many studies reported high prevalence of anxiety, depression and sleep disturbances in vitiligo, while studies showed a significant difference in depression, anxiety and sleep scores between vitiligo patients and healthy controls.

1.1 Psychiatric morbidities

In 2014, Mattoo et al. reported 33.63% rate of psychiatric morbidity among vitiligo patients with no significant difference in mean General Health Questionnaire-12 (GHQ-12) score between vitiligo (6.5 ± 2.74) and psoriasis (7.12 ± 3.32) patients, same results were reported when psychiatric morbidities were assessed using the ICD-10 in a sample of 113 vitiligo patients and 103 psoriasis Indian patients (193). Conversely, a study consisting of 30 vitiligo patients and 30 psoriatic patients showed that psychiatric morbidities were significantly ($p=0.0028$) higher in psoriasis (53.3%) than vitiligo (16.22%) using the General Health Questionnaire-12 (GHQ-12) while the significance difference between vitiligo and psoriasis was not statistically tested. In a study comparing equally 37 vitiligo patients and acne patients with facial involvement to 74 healthy controls, results showed Hospital Anxiety and Depression Scale (HADS) mean scores significantly higher in vitiligo patients than controls (13.2 ± 7.5 vs. 6.3 ± 5 , respectively; $p < 0.05$), however, the study did not assess the difference in depression between vitiligo and acne patients. (194). Another study between 60 vitiligo patients and 60 controls in India using the Self-Reporting Questionnaire-24 (SRQ-24) and Skindex (a 61-item survey questionnaire) showed psychiatric morbidity in vitiligo 63.93% vs. 22.59% in control ($p < 0.0001$) (195). A recent study by Chen et al. (2020) evaluated psychiatric morbidities in 1432 vitiligo patients and 5728 controls in Taiwan using the ICD-9. Psychiatric disorders were found in 550 patients with vitiligo (38.41%) and 2028 controls (35.41%); $p=0.031$. After adjusting for sex, age, comorbidity, urbanization level of residence and facility level of care, the adjusted Hazard Ratio (HR) of psychiatric disorders for patients with vitiligo increased to 2.926 (95% CI, 2.646–3.236; $P < 0.001$) (196). A recent systematic review by Ezzedine et al. (2021) reported that psychosocial comorbidity was seen

in 32.6–90.0% of vitiligo patients, with depression (0.1-62.3%) and anxiety (1.9-67.9%) being the most common. Furthermore the study stated that factors associated with psychosocial burden factors (including psychosocial and quality of life burden) in vitiligo were being female, having lesion on visible areas (such hands and face) or genitals, being below 30 years old, having extensive area involvement, being unmarried, having longer disease duration, suffering from progressive disease, being of phototype IV-V, having lower education, being non-caucasian, with family history, being employed, higher socio-economic level. In addition, the study pointed to the association of depression with a lower overall quality of life and a prevalence of sleep disturbances ranging between 4.6% and 89% among vitiligo patients (91).

1.2 Depression

In 2012, in Singapore, Chan et al. reported 17.2% depression rate among vitiligo patients (n=145). Results showed that in vitiligo patients depression using The Center for Epidemiologic Studies Depression Scale (CES-D) was significantly associated with, being a female (OR =3.72) aged below 50 years old (OR=4.75), having more than 5 years of illness (OR=3.72), and perceiving moderate or above effect on quality of life (OR=4.8) (197). A higher prevalence was reported in India, where 30 out 53 vitiligo patients (56.6%) had major depressive disorders (198), contrary to another study reporting 10% of depression among vitiligo patients (n=30) (199). In 2015, Sangma et al. found that vitiligo patients (n=100) were significantly more depressed than controls (n=50) with Hamilton Depression Rating Scale (HAMD) mean score of 8.45 ± 3.44 and 3.20 ± 2.43 , respectively and a prevalence rate of 59% depression. Furthermore, results showed significant high mean depression scores in

females, married patients, vitiligo vulgaris, in those with skin lesions on exposed parts of the body, and in unstable vitiligo (200). In 2016, Lai et al. showed that the pooled odds ratio of depression among patients with vitiligo was 5.64 (95% CI 1.98–16.03; $p = 0.001$) compared to controls (16). Similarly, another meta-analysis on studies published from 2001 to 2016 reported that patients with vitiligo (pooled prevalence: 56%, 95% CI 0.5-0.62) were 4.96 times more likely to display depression compared with controls and that the prevalence of depression in Asian and female patients with vitiligo was significantly higher than that in Caucasian and male ones (192). One study from Egypt in 2017 ($n=108$) reported 39.25% prevalence of depression using the DSM-V (18). Moreover, a study in India, reported a significantly higher prevalence of depression in vitiligo patients (62.29%) compared to controls (6.65%) using the Skindex (195). Another study in India in 2019, included 150 vitiligo patients showed that 44% were depressed using the Quick Inventory of Depressive Symptomatology (QIDS-SR-16) questionnaire, the mean QIDS-SR-16 score was significantly higher in the 18–30-year age group ($p= 0.02$), among which 51.7% ($n=41$) were depressed (14). Moreover, Sawant et al. (2019) reported a prevalence of depression equal to 52% in a sample of 100 vitiligo patients using the Beck's Depression Inventory (BDI). Results from the study showed that females had significantly higher depression scores than males (mean= 28.04 ± 20.5 vs 17.3 ± 17.1 , respectively; $p=0.008$) (201). Furthermore, Alharbi et al. (2020) reported in a study on 308 vitiligo patients from Saudi Arabia that 52.4% of the patients had mild depression while 14.3% suffered from severe depression using the Modified Beck Depression Inventory Scale. The prevalence of depression was significantly associated with marital status ($p<0.001$) and educational level ($p=0.001$), being highest among single patients (61.2%) and those with lower than high school education (64.9%). Additionally, depression was higher among patients with shorter duration of the disease

compared with longer disease duration (66.7% versus 40.0%, $p < 0.001$) and the use of phototherapy ($p = 0.064$). However, depression was not significantly associated with gender of the patient ($p = 0.932$) or the affected body part ($p = 0.837$) (202). A recent study by Chen et al. (2020) evaluated 1432 vitiligo patients and 5728 controls in Taiwan using the ICD-9, results showed that 3.49% of vitiligo patients suffered from major depressive disorders compared to 2.53% controls ($p = 0.051$). In addition, the study showed an increased risk for major depressive disorders by an adjusted HR of 3.721 compared to controls ($p < 0.001$) (196). Also, a 28% ($n = 100$) depression's prevalence was reported in Iran, where depression was correlated with age ($r = -0.255$; $p = 0.010$). Furthermore, the study results showed no significant difference of depression between vitiligo patients and controls ($n = 100$), however single patients with vitiligo were more depressed than single control subjects (16.7% vs. 7.7%; $p = 0.033$) (203). Similarly to previous findings, Öztekin et al. (2020) reported significantly higher mean of BDI score in vitiligo than in controls ($p < 0.001$) in a sample of 67 vitiligo patients and 69 controls (204). One of the largest case-control studies included equally 3962 vitiligo and controls showed using a non-validated questionnaire that a feeling of depressed mood among vitiligo patients aged 10 years and above was three times more common than that among controls, while depression with psychosocial impact was 2.09 times higher in vitiligo patients. Furthermore, females had 1.49 times more depressed mood than males (205). Moreover, a study in Thailand, showed that among 104 patients with vitiligo, 13.5% were depressed as per PHQ-9, while being depressed was significantly associated with being employed and having new lesions (OR=4.12, 95%CI: 1.20–14.16; $p = 0.025$) (206). Finally, the latest studies on depression among vitiligo patients compared to controls showed a mean Hamilton Rating scale of Depression (HAM-D) score of 8.20 ± 3.99 among vitiligo patients, significantly ($p < 0.0001$) higher than in the control group (3.26 ± 1.91) (99) and that the mean

of Hospital Anxiety and Depression Scale (HAD) score was lower in control (11.3 ± 3.4) compared to vitiligo (15 ± 7) (207). Contrary to the mentioned studies, Karelson et al. reported the analysis of the Emotional State Questionnaire (ES-Q) item scale did not reveal any statistically significant differences in the mean scores for depression in vitiligo compared to healthy controls. In addition, results showed that subjects with higher depression scored higher on the DLQI than non-depressed subjects with vitiligo (7.18 vs. 4.19; $p < 0.05$) and developed vitiligo earlier (mean age: 18.1 years vs. 27.1 years). Furthermore, subjects with psoriasis showed statistically higher scores on the ES-Q item scale in depression compared with vitiligo patients and healthy controls (20).

1.3 Anxiety

A study from Egypt in 2017 ($n=108$) reported 34.36% prevalence of anxiety using the DSM-V (18). Furthermore, a recent study in 2020 comparing 1432 vitiligo patients and 5728 controls in Taiwan using the ICD-9, reported that 12.22% of vitiligo patients suffered from anxiety compared to 8.57% controls, respectively ($p < 0.001$). Patients with vitiligo had an increased risk of developing anxiety with an adjusted HR of 3.845 ($P < 0.001$) compared to controls (196). An additional study compared anxiety in 100 vitiligo patients and 100 controls using Beck Anxiety Inventory (BAI), and General Health Questionnaire (GHQ 28) showed that females were more anxious than males. Adding that women whose hands were affected, and married patients with facial, arm, and hand involvement were significantly more anxious (203). A recent meta-analysis (2020) on anxiety reported that anxiety rates among vitiligo patients was significantly higher in females than males (47.32% vs. 42.4%, respectively; $p=0.03$). Furthermore, the pooled odds ratio (OR) of anxiety among patients with vitiligo was

1.13 [95% CI 0.75, 1.70] vs. controls, however the difference was not statistically significant when vitiligo was compared to acne, psoriasis and eczema (208). Similarly, a case-control study on 30 vitiligo patients and 30 psoriatic patients showed an equal anxiety rate of 3.3% among both group (199). Finally, in a recent meta-analysis Liu et al. reported a pooled OR; 6.14 (95% CI: 3.35–11.24; $P < 0.001$), for the prevalence of anxiety in vitiligo patients compared to healthy controls and a higher risk of anxiety in females than males (pooled OR = 2.24; 95% CI: 1.31–3.84; $p = 0.003$) (209).

Contrary to the mentioned studies, Karelson et al. reported the analysis of the Emotional State Questionnaire (ES-Q) item scale did not reveal any statistically significant differences in the mean scores for general or social anxiety in vitiligo compared to healthy controls. However, subjects with psoriasis showed statistically higher scores on the ES-Q item scale in general anxiety compared with vitiligo patients and healthy controls (20).

1.4 Sleep disturbances

Papadopoulos et al. showed that major changes in sleeping habits occurred significantly more among vitiligo patients (31%) than in healthy controls (6.8%) (210). A study in 2008 reported that vitiligo patients suffered from multiple sleep disturbances (sleepwalking, nocturnal enuresis, night illusions, sleep terrors and nightmares) significantly more than the control group, while patients suffering from other dermatological diseases only reported significantly more often nightmares and nocturnal enuresis compared to the control group (19). In 2015, Sangma et al. reported that 89% of vitiligo patients ($n=100$) had difficulty in initiation of sleep compared to 38% of controls ($n=50$) (200). A study from Egypt in 2017 ($n=108$) reported 18.62% prevalence of sleep disorders using the DSM-V (18).

Furthermore, a study consisting on 30 vitiligo patients and 30 psoriatic patients showed that sleep disturbance was the most common complaint and was present in 56.6% of psoriasis patients and 20% of the vitiligo patients ($p=0.0034$) (199). Similarly to previous findings, Öztekin et al. (2020) reported significantly higher mean of Pittsburgh Sleep Quality Sleep (PSQI) score in vitiligo than in controls ($p<0.001$) in a sample of 67 vitiligo patients and 69 controls (204). Furthermore, a recent study using a 45-item sleep-related instrument showed that about 49.9% of patients with vitiligo (204 out of 409) experienced insomnia, while development, aggravation, or recurrence of vitiligo was considered as the first reasons for primary insomnia in 71.1% of the sample (81 out of 114). After adjusting for gender, age and comorbidity, the multivariate logistic regression revealed that vitiligo in face and neck ($OR=2.62$; 95% CI:2.03–3.17; $p=0.032$), progression in vitiligo ($OR=2.50$; 95% CI:1.62–3.31; $p=0.002$), and oral corticosteroids ($OR=2.71$; 95% CI:2.11–3.19; $p=0.021$) are risk factors for insomnia patients in vitiligo (211). Conversely, no statistically significant differences in the mean scores for insomnia in vitiligo compared to healthy controls was found in a study using the Emotional State Questionnaire (ES-Q) item scale, while subjects with psoriasis showed statistically higher scores on the ES-Q item scale in insomnia compared with vitiligo patients and healthy controls, while 30% of vitiligo patients had sleep disturbances (20).

1.5 Vitiligo on exposed body areas

The involvement of patches on visible areas such as hands and face has not only been found to be correlated with increased psychiatric morbidity, but also to decreased quality of

life compared of vitiligo patients to healthy controls and to vitiligo patients with unexposed lesions (91,212).

Ramakrishna et al. (2014) reported 79.2% psychiatric morbidity in a sample of 53 vitiligo patients and 56.6% rate of major depressive disorder significantly correlated with having patches on exposed areas (198). In 2015, Sangma et al. results showed a significant high mean depression scores in patients with skin lesions on exposed parts of the body (n=100) (200). Furthermore, a case-control study on patients with lesions on exposed body parts showed prevalences of depression and anxiety among vitiligo patients equal to 27% and 21%, respectively. In addition, the number of depressed (PHQ-9 $\geq$ 10) vitiligo patients (n=26) was significantly higher (p=0.04) than those with melasma (n=11) or acquired dermal macular hyperpigmentation (n=22) with no significant difference in anxiety. Furthermore, the results showed that students, those who studied up to high school, had vitiligo vulgaris and had higher VIDA score had higher probability of suffering from depression requiring treatment. No significant correlation was detected with anxiety (213). Contrary, A recent study published in 2020 in Thailand, showed that among 104 patients with vitiligo there was no statistical association between depression and involved lesions locations (206).

In 2005, Ongenae et al. showed in two studies that the involvement of the face/head/neck significantly impaired the quality of life, independently of the reported disease severity (n=78) (214). In addition, vitiligo at least moderately affecting head, face or neck areas, trunk, and correlated significantly with the overall DLQI score (n=102) (215). Furthermore, a study in Germany on 1023 vitiligo patients showed that patients with visible lesions experienced a lower quality of life on DLQI and EuroQol-5D (ED-5D) (216). Results

from two studies in Italy by Ingordo et al. in 2012 and 2014 on 47 and 161 vitiligo patients, respectively, showed that the localization on the hands and on the face influenced significantly quality of life using the DLQI (217,218). Moreover, on sample of 54 Estonian vitiligo patients and 57 controls, results showed that the total DLQI was associated with depigmentation of the hands ($p = 0.008$) (20). In addition, Silverberg et al. found that quality of life (DLQI) was associated with an affected body surface area (BSA) of more than 25% (Adjusted OR, 2.17 [95% CI, 1.71-2.75; $p < .001$]) and that the number of body parts affected negatively impacted the quality of life, while only lesions on the face, arms, hands, legs, and feet were significantly associated with being self-conscious about vitiligo (219). A study assessing quality of life using the vitiligo quality of life score (VitQol) among 184 vitiligo patients in the US, reported that QOL patients with exposed lesions (hands, neck, face) had a worse quality of life than those having non-exposed lesions; median VitQol: 39 [0-94] vs. 31 [0-93]; $p = .01$) (116). Similarly, a study in Brasil, showed that mean DLQI in patients with exposed lesions was significantly higher (7.9 ± 6.3) than in those with invisible lesions (1.1 ± 1.4), $p < 0.001$ (220). Likewise, Bassiouny et al. reported that DLQI was worse (higher) in patients with visible vitiliginous lesions vs. unapparent lesions (mean DLQI score: 20.3 ± 2.1 and 13.1 ± 2.3 , respectively) (112). Conversely, a study on 889 vitiligo patients using camouflage showed an association between reduced quality of life and involvement of any part of the body except for face and upper arms (221).

Finally, in a recently published study reporting workshops with patients with vitiligo, repigmentation of face, hands or neck was considered as the most suitable outcome for vitiligo patients (12,13,141). Furthermore, the perception of vitiligo severity was significantly correlated with the presence of patches on the face, which ranked first amongst 15 body areas

in a sample of 50 vitiligo patients (222). Not surprisingly, most of the ongoing clinical trials have a primary outcome assessing the effect of interventions on improving facial vitiligo underlining the importance of assessment tools specifically targeting the face (223) (224) (225) (226) (227) (228) (229) (230) (118).

2 RATIONALE

Affection of visible areas in vitiligo has been associated with higher impact on the psychological health of the patient, as a result repigmentation of facial, hands and neck in vitiligo was considered as the most suitable outcome for patients as shown in many recent clinical trials and in the workshops with vitiligo patients on repigmentation (13). Furthermore, appropriate disease management has shown to reduce these psychological comorbidities and improve the overall quality of life of patients. Hence, determining an MCID for a vitiligo PROM is important to help clinicians in assessing improvement or deterioration from their patients' perspectives and to adjust the treatment accordingly.

Many studies have assessed the prevalence and correlates of depression, anxiety and sleep disturbances in vitiligo patients in multiple countries; however, results on correlates are controversial and involved a small sample size.

Moreover, studies have been published comparing psychological comorbidities, specifically depression, anxiety and sleep disturbance within dermatological diseases such as vitiligo, psoriasis and acne. However, the impact of these parameters are underestimated in chronic skin diseases such as vitiligo compared to other non-cutaneous chronic diseases as the majority of skin diseases do not affect life expectancy and literature lacks research

comparing psychological disorders in chronic cutaneous diseases and non-cutaneous chronic diseases.

3 AIMS AND OBJECTIVES

The objectives of this study are to:

- To establish an MCID for the SAVES, a patient-reported outcome for vitiligo severity, and to evaluate whether the face is a good proxy for disease severity.
- To determine prevalence and correlates of depression, anxiety and sleep disturbances among vitiligo patients in French population.
- To compare quality of life parameters (anxiety, depression and sleep disorders) between patients with vitiligo and those with diabetes and hypertension.

CHAPTER IV- METHODOLOGY

This study was in the context of the Community of Patients for Research (ComPaRe; www.compare.aphp.fr) e-cohort (231). As of year 2017 and still ongoing, adult patients with chronic diseases (cutaneous and non-cutaneous) for at least six months were invited to participate and fill in an online questionnaire including socio-demographic characteristics, anthropometric and lifestyle data, in addition to questionnaires related to quality of life, burden of treatment, quality of sleep, physical activity and mental health. Furthermore, each patient is asked to fill in specific questionnaires related to his/her medical condition(s). The data is updated on a yearly basis or every other year (232).

1 STUDY DESIGN

This is a cross-sectional study in the context of the ComPaRe e-cohort. Vitiligo patients as well as patients with diabetes or hypertension were invited to participate through the researchers involved in the cohort, media platforms, posters in hospitals and clinics, patients associations, and snowball method.

Patients with comorbid vitiligo, diabetes or hypertension were excluded from the study. Among invited patients who were eligible for inclusion, 540 vitiligo, 633 diabetic, and 1153 hypertensive patients filled in electronically the initial questionnaire. Among which 1903 and 1922 patients filled in the mental health and the quality of sleep questionnaires, respectively. In fact these numbers are adequate as per EpiInfo, where the minimal sample size required for a 95% confidence interval, 50% frequency and a margin of error of 5% is 384 patients per disease.

2 DATA COLLECTION

2.1 Initial questionnaire

The initial questionnaire assessed socio-demographic characteristics (age, gender, height, weight, education, marital status, working status, number of comorbidities, residence, date of first diagnosis, etc...), lifestyle habits (smoking status, alcohol consumption, etc...) and quality of life (ED-5Q questionnaire).

Anthropometric measures (height and weight) were self-reported, body mass index (BMI) was determined as weight in kilograms and divided by height in meters squared, then categorized into underweight ($\text{BMI} < 18.5 \text{ kg/m}^2$), normal weight ($18.5 \leq \text{BMI} < 24.9 \text{ kg/m}^2$), overweight ($25.0 \leq \text{BMI} \leq 29.9 \text{ kg/m}^2$) and obese ($\text{BMI} \geq 30 \text{ kg/m}^2$). For smoking status, patients were asked whether they are regular or occasional smokers, if they quit smoking or never smoked. As for alcohol consumption, participants were asked about the frequency of alcohol intake per week. Regarding work status, patients were asked to choose if they are currently working, if they were unemployed, studying, on retreat or in disability. The categories were then merged into working, not working, studying. Same for educational level, patients were asked to specify the level of their college education, non-university diploma or certificate, or university degree, and then the categories were merged into university degree and no-university degree.

2.2 Self-Assessment Vitiligo Extent Score (SAVES)

The Self-Assessment Vitiligo Extent Score (SAVES) is a validated patient reported outcome in which patients self-report their disease extent derived from the Vitiligo Extent

Score. To be able to report the score, the patient is asked to look at a figure where multiple pictures with different patches patterns on different body parts are shown, the total SAVES score is then calculated by adding up measurements from all body areas as explained previously ([CHAPTER I- 9.2.3 Self-assessment vitiligo extent score \(SAVES\)\)](#) (130).

Vitiligo patients registered in ComPaRE were trained face-to-face by the members of the vitiligo scientific committee of ComPaRE on how to fill in the SAVES, afterwards the questionnaire was electronically submitted. The SAVES was collected during the initial registration to SAVES and a second collection was performed one year after with the global assessment scale used as an anchor. The global assessment scale is a 5-point Likert question for extent “since the last year, do you think that the extent (affected area) of your vitiligo...?”, with potential answers “Much more important”/”Slightly more important”/”Equal”/”Slightly less important”/”Much less important”.

2.3 General Anxiety Disorder (GAD-7) Anxiety

Many self-assessment tools were used to assess anxiety among vitiligo patients. The commonly used scales are the Hospital Anxiety and Depression scale (HADS), General Health Questionnaires (GHQ-12 or GHQ-28), Emotional state Questionnaire (ES-Q) and General Anxiety Disorder (GAD-7) as reported by different systematic reviews and meta-analysis (91,92,208,209). GAD-7 is a 7-items, self-administered questionnaire based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (233). Furthermore, the scale was validated in different settings including primary care centers, hospitals and community samples (234) (235) (236) and in different languages including

French (237). The internal consistency of the GAD-7 and the test-retest reliability are good (Cronbach's $\alpha = .92$, and intra-class correlation = 0.83).

The score is calculate by assigning values 0, 1, 2, and 3 to the 4-points Likert responses “Not at all”, “Several days”, “More than half of the days”, and “Nearly every day”, respectively (Figure 20). The total score ranges between 0 and 21, computed by summing up the values of the 7-items. Cut points of 5, 10, and 15 are interpreted as representing mild, moderate, and severe levels of anxiety, while a score greater than 10 suggests that the patient suffers from general anxiety disorders with an optimized sensitivity (89%) and specificity (82%) (233).

GAD-7				
Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

Total Score	=	Add Columns	—	+	—	+	—
-------------	---	-------------	---	---	---	---	---

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Figure 20: The generalized anxiety disorder 7-item (GAD-7) scale

2.4 Patient Health Questionnaire (PHQ-9)

Depression was also evaluated through different self-administered questionnaire, similarly to anxiety. Tools included General Health Questionnaire (GHQ-12 and GHQ-28), HADS, Beck's Depression Inventory (BDI), Center for Epidemiologic Studies Depression Scale (CES-D), and Hamilton Depression Rating Scales (HDRS) as reported in many systematic reviews and meta-analysis (16,91,92,192).

For the aim of this study, we used the Patient Health Questionnaire (PHQ-9). PHQ-9 is a self-administered version of the Primary Care Evaluation of Mental Disorders (PRIME-MD) that have shown an excellent internal and test-retest reliability. The PHQ-9 is a depression scale that scores each of the 9 DSM-IV criteria as "0" (Not at all) to "3" (Nearly every day) (Figure 21). The total score is calculated by summing up all the items and ranges from 0 to 27. PHQ-9 scores of 5, 10, 15, and 20 represent mild, moderate, moderately severe, and severe depression, while a score above or equal to 10 indicating major depression with equal sensitivity and specificity of 88% (238).

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

NAME: _____ DATE: _____

Over the last 2 weeks, how often have you been bothered by any of the following problems?
(use "✓" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3

add columns + +

TOTAL:

(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card).

10. If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?	Not difficult at all	_____
	Somewhat difficult	_____
	Very difficult	_____
	Extremely difficult	_____

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Figure 21: Patient health questionnaire 9-item (PHQ-9) scale

2.5 Pittsburgh Sleep Quality Index (PSQI)

The Pittsburgh Sleep Quality Index (PSQI) was developed to assess sleep quality over a 1-month time interval. PSQI is a 19-items self-reported questionnaire, generating 7 components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction (Figure 22). The seven component scores are added to generate one global score, with a range of 0 to 21,

where “0” indicates no difficulty and “21” indicating severe difficulties. A cut point above 5 was set to distinguish good and bad sleepers with a sensitivity of 89.6% and specificity of 86.5% ($\kappa = 0.75$, $p \leq 0.001$) (239) (240).

The scoring of PSQI is shown below.

Component 1: Subjective sleep quality—question 9

<u>Response to Q9</u>	<u>Component 1 score</u>
Very good	0
Fairly good	1
Fairly bad	2
Very bad	3

Component 1 score:_____

Component 2: Sleep latency—questions 2 and 5a

<u>Response to Q2</u>	<u>Component 2/Q2 subscore</u>
< 15 minutes	0
16-30 minutes	1
31-60 minutes	2
> 60 minutes	3

<u>Response to Q5a</u>	<u>Component 2/Q5a subscore</u>
Not during past month	0
Less than once a week	1
Once or twice a week	2
Three or more times a week	3

<u>Sum of Q2 and Q5a subscores</u>	<u>Component 2 score</u>
0	0
1-2	1
3-4	2
5-6	3

Component 2 score:_____

Component 3: Sleep duration—question 4

<u>Response to Q4</u>	<u>Component 3 score</u>
> 7 hours	0
6-7 hours	1
5-6 hours	2
< 5 hours	3

Component 3 score:_____

Component 4: Sleep efficiency—questions 1, 3, and 4

Sleep efficiency = (# hours slept/# hours in bed) X 100%

hours slept—question 4

hours in bed—calculated from responses to questions 1 and 3

<u>Sleep efficiency</u>	<u>Component 4 score</u>
> 85%	0
75-84%	1
65-74%	2
< 65%	3

Component 4 score:_____

Component 5: Sleep disturbance—questions 5b-5j

Questions 5b to 5j should be scored as follows:

Not during past month 0

Less than once a week 1

Once or twice a week 2

Three or more times a week 3

<u>Sum of 5b to 5j scores</u>	<u>Component 5 score</u>
0	0
1-9	1
10-18	2
19-27	3

Component 5 score:_____

Component 6: Use of sleep medication—question 6

Response to Q6 Component 6 score

Not during past month 0

Less than once a week 1

Once or twice a week 2

Three or more times a week 3

Component 6 score:_____

Component 7: Daytime dysfunction—questions 7 and 8

Response to Q7 Component 7/Q7 subscore

Not during past month 0

Less than once a week 1

Once or twice a week 2

Three or more times a week 3

Response to Q8	Component 7/Q8 subscore
No problem at all	0
Only a very slight problem	1
Somewhat of a problem	2
A very big problem	3

Sum of Q7 and Q8 subscores	Component 7 score
0	0
1-2	1
3-4	2
5-6	3

Component 7 score:_____

Global PSQI Score: Sum of seven component scores:_____

Name_____ Date_____

Sleep Quality Assessment (PSQI)

What is PSQI, and what is it measuring?

The Pittsburgh Sleep Quality Index (PSQI) is an effective instrument used to measure the quality and patterns of sleep in adults. It differentiates "poor" from "good" sleep quality by measuring seven areas (components): subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month.

INSTRUCTIONS:

The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

During the past month,

- When have you usually gone to bed? _____
- How long (in minutes) has it taken you to fall asleep each night? _____
- What time have you usually gotten up in the morning? _____
- How many hours of actual sleep did you get at night? _____
 - How many hours were you in bed? _____

5. During the past month, how often have you had trouble sleeping because you	Not during the past month (0)	Less than once a week (1)	Once or twice a week (2)	Three or more times a week (3)
A. Cannot get to sleep within 30 minutes				
B. Wake up in the middle of the night or early morning				
C. Have to get up to use the bathroom				
D. Cannot breathe comfortably				
E. Cough or snore loudly				
F. Feel too cold				
G. Feel too hot				
H. Have bad dreams				
I. Have pain				
J. Other reason (s), please describe, including how often you have had trouble sleeping because of this reason (s):				
6. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
8. During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?				
9. During the past month, how would you rate your sleep quality overall?	Very good (0)	Fairly good (1)	Fairly bad (2)	Very bad (3)

Figure 22: Pittsburg sleep quality index (PSQI)

2.6 EuroQol-5D (ED-5D)

EuroQol is a standardized non-disease specific questionnaire developed by EuroQol Group for assessing health-related quality of life (241). The EQ-5D is a five dimensions questionnaire including mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has five levels (no problems, slight problems, moderate problems, severe problems, unable to/extreme problems). The respondent is asked to indicate his/her health state by checking the box next to the most appropriate response level for each of the five dimensions. Responses are coded as single-digit numbers expressing the severity level selected in each dimension. The digits for the five dimensions can be combined in a 5-digit code that describes the respondent's health state, representing the five severity levels of a dimension; however these digits have no arithmetic properties and cannot be summed to generate one value. Furthermore, The EQ visual analog scale (EQ VAS) records the respondent's overall current health on a vertical visual analogue scale, where the endpoints are labeled 'The best health you can imagine' and 'The worst health you can imagine' (Figure 23). The EQ VAS provides a quantitative measure of the patient's perception of their overall health (242).

Making any EQ-5D (sample) version available on a publicly accessible webpage is **permitted**. For reproduction/ displaying any EQ-5D sample version, please submit a request for permission by using the EQ-5D registration form.

Figure 1/ UK (English) EQ-5D-5L Paper Self-Complete (sample version)

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about ☐
- I have slight problems in walking about ☐
- I have moderate problems in walking about ☐
- I have severe problems in walking about ☐
- I am unable to walk about ☐

SELF-CARE

- I have no problems washing or dressing myself ☐
- I have slight problems washing or dressing myself ☐
- I have moderate problems washing or dressing myself ☐
- I have severe problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities ☐
- I have slight problems doing my usual activities ☐
- I have moderate problems doing my usual activities ☐
- I have severe problems doing my usual activities ☐
- I am unable to do my usual activities ☐

PAIN / DISCOMFORT

- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

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Figure 23: ED-5Q-5L

EQ-5D-5L health states can also be represented by a single summary number (index value), which reflects how good or bad a health state is according to the preferences of the general population of a country/ region. Figure 24 shows the latest value sets for France. In order to calculate the index value, each level in a dimension is replaced by the determined value set, and the whole is subtracted from 1 (considered as full health state) (243).

From: A French Value Set for the EQ-5D-5L

	MO	SC	UA	PD	AD
<i>Unweighted model</i>					
Level 2	0.0338811	0.0374599	0.0110561	0.0231809	0.0192951
Level 3	0.0433628	0.0494521	0.0367977	0.0467445	0.0464464
Level 4	0.1779412	0.1715431	0.1158802	0.2662137	0.2027724
Level 5	0.318512	0.2580982	0.2380036	0.4455017	0.287614
<i>Weighted model</i>					
Level 2	0.03739	0.03836	0.01373	0.02198	0.02948
Level 3	0.04774	0.05078	0.03979	0.04704	0.04683
Level 4	0.17949	0.17225	0.11589	0.26374	0.20985
Level 5	0.32509	0.25833	0.24005	0.44399	0.25803

PD pain and discomfort, MO mobility, AD anxiety/depression, SC self-care, UA usual activities

Figure 24: ED-5D-5L value set for France (2020)

3 STATISTICAL ANALYSIS

The data was retrieved on .csv files. Patients with concomitant vitiligo/ diabetes/ hypertension were excluded from the study. Data cleaning and statistical analysis were performed using R software (244) and the MCID was calculated by cutpointr package (245). The significance level was set at p-value <0.05.

3.1 MCID

3.1.1 Assessment of the MCID of the SAVES using a distribution-based approach

In this study, we focused on two common approaches for distribution based calculations of the MCID for the SAVES: 1) through the use of the baseline standard deviation (SD); where $MCID = 0.5 * SD$; and 2) by calculating the minimal detectable change (MDC) as the lowest change beyond random errors through the standard error of measurement (SEM), defined as $MDC = 1.96 * \sqrt{2} * SEM$; where $SEM = SD * \sqrt{(1 - reliability)}$ and reliability estimated through the Intra-Class Correlation coefficient.

3.1.2 Assessment of the MCID of the SAVES using an anchor-based approach

Before assessing the MCID for the SAVES with an anchor-based approach, we assessed the quality of our anchor question by calculating the correlation between the anchor and the change in SAVES (score at t1 – score at t0) using Spearman’s rank-order correlation coefficient. Furthermore, we estimated the Area Under the Curve (AUC) to evaluate whether the change of SAVES in a one-year interval correctly discriminated between the classification of the anchor.

Since the degree of variation depends on the direction of the change (37), data from the anchor question were used to divide the sample into two subgroups; improved and worsened participants, hence two anchors were created as follows. For worsened patients, individuals who scored “slightly more important” or “much more important” were given a score of 1 and those who were “equivalent” were given a score of 0. Improved patients are those who answered “slightly less important” or “much less important” were recoded as 1 while those who answered “equivalent” were given a score of 0

The MCID was determined using the J Youden index (246), defined as $J = \max(\text{Sensitivity} + \text{Specificity} - 1)$ which produces a balanced index of sensitivity and specificity (247). 95% confidence interval of the cut-off point values was estimated using a 1000 bootstrap method.

3.1.3 Association between the involvement of the face and hands and patients' perceived change in the extent of their vitiligo

Finally, two ordinal logistic regression were performed to estimate the association between patients' perceived change in the extent of their vitiligo, assessed using the anchor question and the change in the involvement of the face or hands between the two SAVES measures at t=0 and t=1.

3.2 Descriptive statistics

Quantitative and qualitative measurements were summarized as mean $\pm$ standard deviation (SD) and n (%), respectively.

3.3 Bivariate analysis

The bivariate analysis was performed using the dependent variables GAD-7 (no anxiety vs. anxiety using a cut-off ≥ 10) and PHQ-9 (no depression vs. depression with a cut-off ≥ 10) as dichotomous and PSQI as continuous and gender, age, marital status, educational level, working status, body mass index (BMI), alcohol consumption, smoking status, number of comorbidities, occurrence of vitiligo or diabetes or hypertension, and quality of life (ED-5D) as independent variables.

To estimate the association between GAD or PHQ and categorical variables Chi-square was used, while t-test was used for continuous variables. For PSQI, the correlation was tested using Pearson or Spearman correlation coefficients and independent t-test or ANOVA or Kruskal-Wallis were used to assess the association with dichotomous/categorical variables.

3.4 Multivariate analysis

In order to determine the correlates of the psychological morbidities in vitiligo, three multiple linear regressions were performed between the dependent variables (PHQ-9, GAD-7 and PSQI as continuous variables) and the different confounders (age, gender, marital status, employment status, education level, number of diseases, BMI, smoking status, frequency of alcohol consumption, number of alcohol glasses, physical activity, value index, evaluation of health, phototype, age at onset, affected area and SAVES). The model was performed using linear regressions since the assumptions for the logistic regression were not met.

Furthermore, logistic and multivariable regressions were performed in order to assess depression, anxiety and quality of sleep among vitiligo patients compared to diabetics or hypertensive participants. Outcome variables PHQ-9 and GAD-7 were used as dichotomous and PSQI as a continuous variable. All independent variables were included as confounders in the regressions in addition to the type of disease; age, gender, marital status, employment status, education level, number of diseases, BMI, smoking status, frequency of alcohol consumption, number of alcohol glasses, physical activity, value index and evaluation of health.

Concerning the assumptions for logistic regressions using PHQ-9 or GAD-7 as independent variables, independence of observation and linear relationship between the continuous independent variables and the logit transformation of the dependent variable.

For multiple linear regressions, assessed and met assumptions were the continuous type of the dependent variable, independence of residuals, linear relationship between the

dependent variable and each of the independent variables, homoscedasticity, no multicollinearity, normality of residuals.

4 ETHICAL CONSIDERATION

The ComPaRe cohort was approved by the Institutional Review Board (IRB) of Hôtel-Dieu Hospital, Paris, (IRB: 0008367). The web site and the data of ComPaRe are hosted in France at the *Assistance Publique–Hôpitaux de Paris* (AP-HP), and are protected by physical and logical security measures. Only ComPaRE committee members have access to the data and can grant access for specific researchers upon submission of a detailed proposal. All participants are asked to sign a consent form stating that the collected data is completely confidential and anonymous and will only be used for research purposes. Furthermore, at any time of the collection process, the participant is eligible to access his/her data and has the right to stop his/her registration.

CHAPTER V- RESULTS

1 MCID

Our sample consisted of 244 vitiligo patients with a mean age of 51.14 ± 12.59 and 181 females (74.2%). The majority (71.55%) of the participants were fair skinned (Fitzpatrick skin phototype I to III) (Table 5). The means of the total SAVES at inclusion and 1 year after were 11.42 ± 15.87 and 12.19 ± 16.64 , respectively.

Table 5: Participants' characteristics (n=244)

Variable		Mean/Frequency	SD/%
Age		51.14	12.59
Gender	Male	63	25.8
	Female	181	74.2
Fitzpatrick skin Phototype	I	4	1.72
	II	31	13.36
	III	131	56.47
	IV	60	25.86
	V	5	2.16
	VI	1	0.43

1.1 Assessment of the MCID of the SAVES using a distribution-based approach

Using the distribution-based method; the MCID and the MDC of the SAVES were respectively equal to 7.935% and 7.864% BSA (Table 6).

Table 6: MCID using distribution-based methods

Standard deviation at baseline (SD)	15.87
Interclass correlation (95%CI)	0.968 (0.959-0.975)
Minimal detectable change (MDC) ^a	7.864
Minimal clinically important difference (MCID) ^b	7.935
95%CI: 95% confidence interval ^a MDC = 2.77 *SEM; SEM = SD *√1-r ^b MCID=0.5 SD	

1.2 Assessment of the MCID of the SAVES using an anchor-based approach

Approximately half of the sample (47.5%) declared worsening of the extent of their vitiligo as compared to the previous year, while only 8.2% perceived improvement in their vitiligo (Table 7).

Table 7: Self-Assessment Vitiligo Extent Score (SAVES) description (n=244)

		At time =0 mean ± SD	At time=1 mean ± SD or % frequency
Total SAVES		11.42±15.87	12.19±16.64
Vitiligo extent compared to last year	Much less important		2.0 (5)
	Slightly less important		6.1 (15)
	Equivalent		44.3 (108)
	Slightly more important		41.8 (102)
	Much more important		5.7 (14)
SAVES: Self-Assessment Vitiligo Extent Score; SD: Standard deviation			

A significant moderate correlation ($r = -0.339$; $p=0.017$) was detected between the anchor question, assessing patients' perceived change in their vitiligo extent and the change in patients' SAVES score between t0 and t1. As for the receiver operating characteristic (ROC) analysis, the results showed a significant AUC equal to 64.0% and 58.1% in worsened (Figure 25) and improved patients (Figure 26), respectively.

Using anchor-based methods, the MCID for worsened patients was equal to a 0.247% BSA (95% CI: [0.009, 0.333]) increase of the facial SAVES with 71.3% sensitivity and 53.4% specificity. For improved participants the MCID was equal to a decrease of the total SAVES by 0.217% (95% CI: [-0.223, 0.399]) with sensitivity and specificity equal to 55% and 66.7%, respectively (Figures 25 & 26).

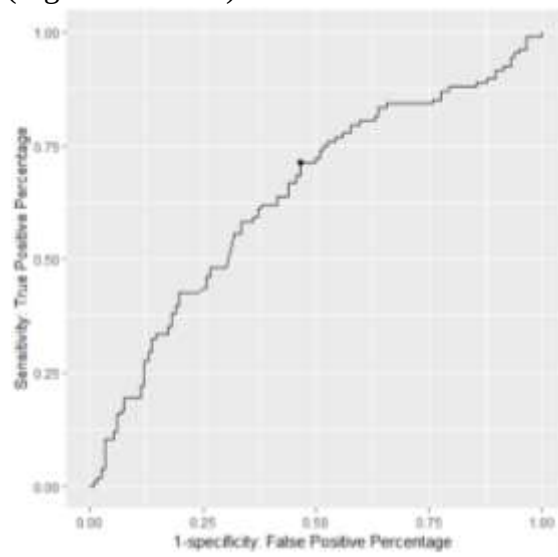


Figure 25: ROC curve in aggravated vitiligo patients

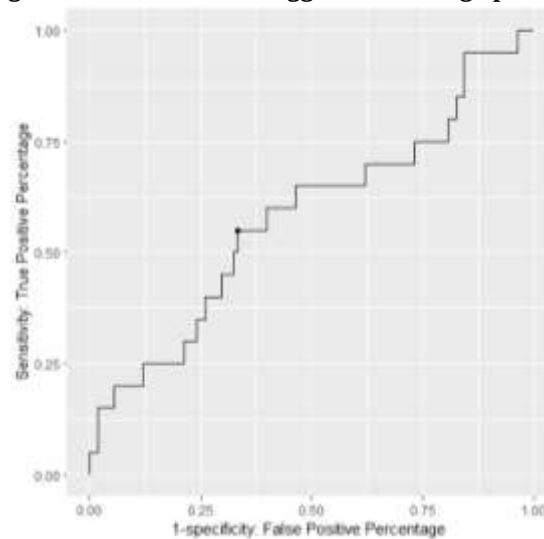


Figure 26: ROC curve in ameliorated vitiligo patients

1.3 Association between the involvement of the face and hands and patients' perceived change in the extent of their vitiligo

Involvement of hands was not significantly associated with perceived change, while an increase in facial severity was significantly correlated with the patient's perception of deterioration (OR= 7.428; 95%CI: 1.206, 45.761; p=0.031) (Table 8).

Table 8: Regression analysis for SAVES

Ordinal regression for facial SAVES with the global assessment scale ^b				
Parameter	Odds ratio	95% Confidence Interval		p-value
		Lower	Upper	
Ordinal regression for facial SAVES with the global assessment scale ^b				
Difference ^a of facial SAVES	7.428	1.206	45.761	.031
Difference of total SAVES (except face)	.016	.000	1.753	.084
SAVES: Self-Assessment Vitiligo Extent Score				
Significance was set at p<0.05				
^a Difference= SAVES at t ₀ – SAVES at t ₁				
^b “Since the last year, do you think that the extent (affected area) of your vitiligo?” much more important/slightly more important / Equivalent/slightly less important /much less important.				
^c Ameliorated patients are those who answered “slightly less important” or “much less important” to the global assessment scale and were recoded as 1 while those who answered “equivalent” were given a score of 0.				
^d Aggravated patients are individuals who answered “slightly more important” or “much more important” to the global assessment scale and were given a score of 1 and those who answered “equivalent” were given a score of 0.				

2 DEPRESSION, ANXIETY AND SLEEP DISTURBANCES

2.1 Descriptive analysis

2.1.1 Socio-demographic characteristics

A total of 2326 subjects (37.62 % men and 62.38 % women) with a mean age of 55.32±13.69 years participated in the study. Among the participants, 540 had vitiligo, 633 were diabetic and 1153 suffered from hypertension. In addition, 69.9% of vitiligo participants, 62.9% of diabetic and 68.7% of the hypertensive were married or living in

couple. Approximately half of the patients work (53.2%), with the highest percentage among vitiligo patients (70.5%). In addition, approximately half of the participants have a university degree across all studied diseases. Characteristics of study population are summarized in Table 9.

Table 9: Socio-demographic characteristics

Variable		Total (n=2326)		Vitiligo (n= 540)		Diabetes (n=633)		Hypertension (n=1153)	
		N or mean	% or SD	N or mean	% or SD	N or mean	% or SD	N or mean	% or SD
Age		55.32	13.69	49.75	13.08	54.16	14.58	62.21	10.98
Gender	Male	875	37.6	132	24.4	271	42.8	472	40.9
	Female	1451	62.4	408	75.6	362	57.2	681	59.1
Marital status	Single	757	32.6	162	30.1	234	37.1	361	31.3
	In couple/Married	1566	67.4	377	69.9	397	62.9	792	68.7
Employment status	I don't work	1088	46.8	159	29.4	312	49.4	617	53.5
	I work	1237	53.2	381	70.6	320	50.6	536	46.5
Education level	University degree	1129	48.6	285	52.8	284	44.9	560	48.6
	No university degree	1196	51.4	255	47.2	348	55.1	593	51.4
N= frequency; SD= standard deviation									

2.1.2 Medical and lifestyle characteristics

Participants reported a mean of number of diseases of 3.26 ± 2.95 , with the highest mean of 3.9 ± 3.33 among hypertensive patients. Moreover, 63.3% of vitiligo patients were of normal weight, while the percentage of body mass index (BMI) was approximately the same among normal, overweight and obese in diabetic and hypertensive patients (34.4% and 33.0%, 31.1% and 37.0%, 33.0% and 28.5%, respectively). Between 7.3 and 12.6% of the participants reported smoking regularly, while most of the participants stated never smoking or quitting smoking. Furthermore, the mean consumption of alcohol was 1.62 ± 1.92 glasses with the lowest mean among diabetic patients (1.52 ± 1.22), while 21.5% of the participants did not drink alcohol, and drinking more than 4 times per week was the highest among hypertensive patients (14.5%). The highest proportion of participants reported performing

intense activity (60.8%), with the lowest percentage among vitiligo patients (54.9%) (Table 10).

Table 10: Medical and lifestyle characteristics

		Total (n=2326)		Vitiligo (n= 540)		Diabetes (n=633)		Hypertension (n=1153)	
Variable		N or mean	% or SD	N or mean	% or SD	N or mean	% or SD	N or mean	% or SD
Number of diseases		3.26	2.95	1.92	1.22	2.85	2.74	3.9	3.33
BMI	Underweight	49	2.1	23	4.3	9	1.4	17	1.5
	Normal	940	40.4	342	63.3	218	34.4	380	33.0
	Overweight	754	32.4	130	24.1	197	31.1	427	37.0
	Obese	583	25.1	45	8.3	209	33.0	329	28.5
Smoking status	I don't smoke	1021	43.9	262	48.5	262	41.4	497	43.1
	I quit smoking	990	42.6	193	35.7	260	41.1	537	46.6
	I smoke occasionally	107	4.6	42	7.8	31	4.9	34	3.0
	I smoke regularly	207	8.9	43	8.0	80	12.6	84	7.3
Frequency of alcohol consumption	I don't drink alcohol	470	21.5	93	17.6	152	26.5	225	20.6
	once per month	439	20.0	99	18.8	118	20.6	222	20.3
	2 to 4 times per month	652	29.8	198	37.6	161	28.1	293	26.9
	2 to 3 times per week	382	17.4	102	19.4	87	15.2	193	17.7
	4 or more times per week	248	11.3	35	6.6	55	9.6	158	14.5
Number of alcohol glasses		1.62	1.92	1.61	1.06	1.52	1.22	1.62	1.24
Physical activity levels	Low activity	34	4.2	8	4.1	10	4.9	16	3.9
	Moderate activity	283	35.0	80	41.0	55	27.1	148	36.1
	Intense activity	492	60.8	107	54.9	139	68.0	246	60.0
N= frequency; SD= standard deviation; BMI= body mass index									

2.1.3 Quality of life parameters

The five dimensions of the ED-5D showed that 58.6% of the participants have no problem at the mobility level, 85.9% have no problem for taking care of themselves, 58.2% have no problem performing their usual activities, 25.3% don't suffer from pain and discomfort, and 34.8% reported no depression or anxiety. The highest frequencies on the deterioration of quality of life were reported in 0.8% and 0.3% of diabetic patients at the level of mobility and self-care, respectively. In addition, inability to perform usual activities and

extreme pain and discomfort was seen in 0.9% and 2.2% of hypertensive patients. Among vitiligo patients, 8.5% reported severe anxiety and depression. From another hand, the mean of self-evaluation of health scale was 68.15 ± 20.00 , with a lowest mean of 67.59 ± 18.57 among diabetic patients, in consistence with a decreased mean value index of 0.86 ± 0.17 in diabetes as well (Table 11).

Among 1903 participants who filled in the GAD-7 and PHQ-9, 6.2% showed severe depression, with a highest proportion among 399 vitiligo patients (5.3%), while depression was shown in 30.8% of 502 diabetic participants. As for anxiety, 9% of the participants exhibited severe anxiety, among which vitiligo patients had percentages of severe anxiety and clinical anxiety equal to 10.5% and 21.3%, respectively (Table 11).

A total of 1285 patients replied to the PSQI which showed a mean score of 10.01 ± 3.62 . Hypertensive patients reported difficulties in sleep with a mean PSQI score of 8.08 ± 4.32 , whereas 58.2% of vitiligo patients were bad sleepers (Table 11).

Table 11: Quality of life parameters

		Total n=2326		Vitiligo n= 540		Diabetes (n=633)		Hypertension (n=1153)	
Variable		N or mean	% or SD	N or mean	% or SD	N or mean	% or SD	N or mean	% or SD
Quality of life	Mobility								
	No problem	1280	58.6	398	81.6	330	55.2	552	50.3
	Slight problems	391	17.9	48	9.8	110	18.4	233	21.2
	Moderate problems	344	15.8	34	7.0	91	15.2	219	20.0
	Severe problems	159	7.3	8	1.6	62	10.4	89	81.0
	Unable to/extreme problems	9	0.4	0	0.0	5	0.8	4	0.4
	Self-care								
	No problem	1874	85.9	468	95.9	497	83.1	909	82.9
	Slight problems	199	9.1	12	2.5	68	11.4	119	10.8
	Moderate problems	93	4.3	6	1.2	29	4.8	58	5.3
	Severe problems	13	0.6	1	0.2	2	0.3	10	0.9
	Unable to/extreme problems	4	0.2	1	0.2	2	0.3	1	0.1

Usual activities								
No problem	1270	58.2	379	77.8	303	50.6	588	53.6
Slight problems	453	20.7	60	12.3	148	24.7	245	22.3
Moderate problems	319	14.6	32	6.6	100	16.7	187	17.0
Severe problems	125	5.7	14	29.0	43	7.2	68	6.2
Unable to/extreme problems	17	0.8	2	0.4	5	0.8	10	0.9
Pain/Discomfort								
No problem	552	25.3	207	42.4	137	22.9	208	18.9
Slight problems	711	32.5	160	32.8	192	32.1	359	32.7
Moderate problems	620	28.4	92	18.9	164	27.4	364	33.2
Severe problems	265	12.1	26	5.3	96	16.0	143	13.0
Unable to/extreme problems	37	1.7	3	0.6	10	1.7	24	2.2
Depression/Anxiety								
No problem	741	34.8	146	30.9	198	33.9	397	37.1
Slight problems	744	35.0	190	40.2	202	34.6	352	32.9
Moderate problems	482	22.7	97	20.5	139	23.8	246	23.0
Severe problems	161	7.6	40	8.5	45	7.7	76	7.1
Unable to/extreme problems	0	0.0	0	0.0	0	0.0	0	0.0
Value Index	0.85	0.19	0.93	0.10	0.86	0.17	0.86	0.19
Evaluation of health	68.15	20.00	77.61	15.28	67.59	18.57	70.42	19.72
PHQ-9	7.63	6.11	6.43	5.03	6.22	5.67	5.77	5.43
Depression levels	Minimal depression	703	36.9	140	35.1	178	35.4	385
	Mild depression	637	33.5	147	36.8	170	33.8	320
	Moderate depression	277	14.6	64	16.0	66	13.1	147
	Moderately severe depression	169	8.9	27	6.8	69	13.7	105
	Severe depression	117	6.2	21	5.3	20	4.0	44
Depression	No	1340	70.4	287	71.9	348	69.2	705
	Yes	563	29.6	112	28.1	155	30.8	296
GAD-7	5.82	5.07	4.85	3.75	5.16	5.01	4.56	4.85
Anxiety levels	Minimal anxiety	845	46.0	151	37.8	247	49.2	477
	Mild anxiety	650	34.2	163	40.9	158	31.5	329
	Moderate anxiety	206	10.8	43	10.8	54	10.8	109
	Severe anxiety	171	9.0	42	10.5	43	8.6	86
Anxiety	No	1525	80.2	314	78.7	405	80.7	806
	Yes	377	19.8	85	21.3	97	19.3	195
PSQI	10.01	3.62	6.95	3.77	6.86	4.49	8.08	4.32
PSQI levels	Good sleeper	123	9.5	100	41.8	148	41.1	204
	Bad sleeper	1176	90.5	139	58.2	212	58.9	482

N=frequency; SD=standard deviation, PHQ-9=Patient Health Questionnaire-9; GAD-7=General Anxiety Disorder-7; PSQI= Pittsburgh Sleep Quality Index

2.1.4 Vitiligo parameters

In addition to the above variables, some parameters specific for vitiligo were assessed are shown in table 8. The majority of the participants (69.8%) were fair skinned and the mean age at onset was 26.21 ± 13.30 . Face, hands and foot were mainly affected in 34.2% of the patients and the mean SAVES score was 10.91 ± 15.59 (Table 12).

Table 12: Specific vitiligo parameters

		Vitiligo n= 489	
		N or mean	% or SD
Phototype	Fair (I,II,III)	340	69.8
	Dark (IV,V,VI)	147	30.2
Age at onset		26.21	13.30
Affected areas	One side of the body	22	4.5
	from both sides, all over the body	300	61.3
	Mainly at the level of the face, hands and foot	167	34.2
Total SAVES		10.91	15.59
N=frequency; SD=standard deviation; SAVES= Self-Assessment Vitiligo Extent Score			

2.2 Correlates of depression, anxiety and sleep disturbances among vitiligo patients

2.2.1 Depression

Among 1903 participants who replied to the depression score, 29.6% were found depressed. Moreover, the prevalence of depression in vitiligo (28.1%), diabetes (30.8%) and hypertension (29.6%) was not statistically different ($p=0.669$).

Among vitiligo patients ($n=399$), depression was not significantly associated with age (48.61 ± 12.76 vs. 48.54 ± 12.78 , $p=0.963$), however, females were significantly more depressed than males with proportions of 32.1% vs. 15.5% ($p<0.001$). Moreover, married/in

couple participants were less depressed compared to single ones (35.6% vs. 25.0%, $p=0.032$). There was no significant difference among students versus working and non-working participants. Furthermore, higher prevalence of depression was seen among patients without a university degree compared to university degrees holders (33.5% and 23.2%, $p=0.022$) (Table 13).

A higher mean of number of comorbidities was found significantly associated with depression (3.00 and 2.03, $p<0.001$). In addition, higher percentage of obese vitiligo patients (50%) were found depressed compared to normal weight patients (23.2%). Among depressed patients, the highest prevalence was within those who smoked regularly (56.3%) compared to other categories and who never drank alcohol compared to those who consumed alcohol 2 to 4 times per week (42.2% vs. 21.9%, $p=0.008$), however, the mean amount of consumed alcohol and level of activity were not significantly associated with depression (Table 13).

The value index and self-evaluation of health showed significantly lower means among depressed individuals (0.94 ± 0.10 vs. 0.84 ± 0.18 and 79.87 ± 12.97 vs. 62.68 ± 20.23). Furthermore, the mean PSQI scores were higher revealing a deteriorated quality of sleep as seen in the categorical PSQI, where the majority of depressed participants were bad sleepers (Table 13).

2.2.2 Anxiety

A total of 1902 participants answered the GAD-7 questionnaire. The proportions of anxious vitiligo, diabetic and hypertensive patients were not statistically different (21.3%, 19.3% and 19.5%, $p=0.704$). Age and marital status were not significantly correlated with

anxiety, while being a female was positively associated (23.8% vs. 13.4%, $p=0.029$) (Table 13).

Mean number of diseases and BMI were not associated with anxiety. Similarly to depression, anxiety was correlated to regular smokers compared to non-smokers (43.8% vs. 16.8%, $p=0.007$) (Table 13).

Concerning quality of life parameters, the value index and evaluation of health means were significantly lower among anxious patients in vitiligo (0.93 ± 0.11 vs. 0.84 ± 0.19 , $p=0.002$ and 78.32 ± 13.88 vs. 61.76 ± 22.20 , $p<0.001$). Moreover, sleep quality was significantly lower among anxious patients with PSQI mean of 10.15 ± 4.78 , in concordance with the prevalence of bad sleepers among anxious patients (Table 13).

2.2.3 Sleep disturbance

A total of 1285 patients replied to the PSQI questionnaire. A significant difference in the mean PSQI was observed between vitiligo patients (7.21 ± 4.05) and hypertensive patients (8.45 ± 4.33) and between diabetic and hypertensives (7.56 ± 4.32 vs. 8.45 ± 4.33 , respectively) with the highest mean among patients with hypertension. Younger age was weakly correlated with lower quality of sleep ($r=-0.135$, $p<0.001$). Moreover, PSQI means were significantly higher in vitiligo females compared to males and those who did not acquire a university degree compared to those who do (7.89 ± 2.87 vs. 5.51 ± 2.87 , 8.21 ± 4.30 vs. 6.67 ± 4.21 , and 9.54 ± 4.39 vs. 6.97 ± 3.79 , respectively) (Table 13).

The number of diseases was weakly but significantly correlated with sleep disturbances among all diseases. Furthermore, the mean PSQI was significantly higher

among obese patients compared to patients with normal BMI in vitiligo (9.64 ± 4.39 vs. 6.92 ± 3.88 , $p=0.032$). In addition, vitiligo patients who never smoked showed significantly lower PSQI means than those who smoked regularly (8.26 ± 4.25 vs. 10.23 ± 4.42 , $p<0.001$). (Table 13).

Finally, a negative moderate correlation was found between value index and evaluation of health from a hand and PSQI scores from another hand among participants with vitiligo ($r=-0.437$ and $r=-0.435$) (Table 13).

Phototype, age at onset, affected area and total and facial SAVES were not significantly associated with anxiety, depression or quality of sleep among vitiligo patients (Table 13).

Table 13: Correlates of depression, anxiety and quality of sleep in vitiligo

Variables		PHQ-9		p-value	GAD-7			PSQI				
		No depression PHQ<10	Depression PHQ>=10		No anxiety GAD-7 <10	Anxiety GAD-7>=10	p-value	PSQI (7.21±4.05)		p-value		
		287 (71.9%)	112(28.1%)		314(78.4%)	85(21.3%)		mean(SD)	Correlation (r)			
		N (%) or mean (SD)	N (%) or mean (SD)		N (%) or mean (SD)	N (%) or mean (SD)						
Socio-demographic variables												
Age		48.61(12.76)	48.54(12.78)	0.963	48.85(12.88)	47.64(12.26)	0.436		0.106	0.103		
Gender	Male	82(84.5)	15(15.5)	0.001	84(86.6)	13(13.4)	0.032	5.51(2.87)		<0.001		
	Female	205(67.9)	97(32.1)			230(76.2)		72(23.8)			7.89(2.87)	
Marital status	Single	76(64.4)	42(35.6)	0.032	90(76.3)	28(23.7)	0.267	7.19(4.22)		0.909		
	Married	210(75.0)	70(25.0)			223(79.6)		57(20.4)			7.25(3.99)	
Employment status	I don't work	78 (65.5)	41(34.5)	0.064	89(74.8)	30(25.2)	0.214	7.82		0.227		
	I work	209(74.6)	71(25.4)			225(80.4)		55(19.6)			7.01	
Education level	University degree	162(76.8)	49(23.2)	0.022	172(81.5)	39(18.5)	0.145	7.86(4.01)		0.021		
	No university degree	125(66.5)	63(33.5)			142(75.5)		46(24.5)			6.65(4.02)	
Medical and lifestyle parameters												
Number of diseases		2.03(1.52)	3.00(2.70)	<0.001	2.21(1.85)	2.67(2.36)	0.096		0.243	<0.001		
BMI	Underweight	12(66.7)	6(33.3)	0.005	13(72.2)	5(27.8)	0.401	7.25(3.55)		0.032		
	Normal	199(76.8)	60(23.2)			209(80.7)		50(19.3)			6.92(3.88)a	
	Overweight	58(67.4)	28(32.6)			67(77.9)		19(22.1)			7.06(4.28)	
	Obese	18(50.0)	18(50.0)			25(69.4)		11(30.6)			9.64(4.39)a	
Smoking status	I don't smoke	152(77.6)	44(22.4)	0.001	163(83.2)	33(16.8)	0.007	6.58(4.00)		<0.001		
	I quit smoking	97(69.8)	42(30.2)			108(77.7)		31(22.3)			7.45(3.63)	
	I smoke occasionally	24(75.0)	8(25.0)			25(78.1)		7(21.9)			6.86(3.72)	
	I smoke regularly	14(43.8)	18(56.3)			18(56.3)		14(43.8)			10.79(4.64)a	

Frequency of alcohol consumption	I don't drink alcohol	37(57.8)	27(42.2)	0.008	48(75.0)	16(25.0)	0.113	7.77(4.34)		0.36
	once per month	49(63.6)	28(36.4)		54(70.1)	23(29.9)		7.89(3.94)		
	2 to 4 times per month	114(78.1)	32(21.9)		119(81.5)	27(18.5)		6.58(3.87)		
	2 to 3 times per week	59(79.7)	15(20.3)		64(86.5)	10(13.5)		6.98(3.94)		
	4 or more times per week	20(71.4)	8(28.6)		21(75.0)	7(25.0)		7.34(3.84)		
Number of alcohol glasses		1.68(1.13)	1.45(1.23)	0.074	1.63(1.15)	1.56(1.22)	0.607		-0.079	0.222
Physical activity levels	Low activity	5(3.9)	1(2.8)	0.943	4(66.7)	2(33.3)	0.365	N/A		0.325
	Moderate activity	55(42.6)	16(44.4)		62(87.3)	9(12.7)		6.63(3.33)		
	Intense activity	69(53.5)	19(52.8)		73(83.0)	15(17.0)		7.38(4.55)		
Quality of life										
Value Index		0.94(0.10)	0.84(0.18)	<0.001	0.93(0.11)	0.84(0.19)	0.002		-0.437	<0.001
Evaluation of health		79.87(12.97)	62.68(20.23)	<0.001	78.32(13.88)	61.76(22.20)	<0.001		-0.435	<0.001
PSQI		6.17(3.36)	10.36(4.37)	<0.001	6.52(3.53)	10.15(4.78)	<0.001	N/A		
PSQI levels	Good sleeper	88(51.2)	10(16.4)	<0.001	88(89.8)	10(10.2)	0.001			
	Bad sleeper	84(48.8)	51(83.6)		97(71.9)	38(28.1)				
Parameters specific to vitiligo										
Phototype	Fair (I, II, III)	185(72.3)	71(27.7)	0.982	200(78.1)	56(21.9)	0.421	7.32(3.91)		0.382
	Dark (IV, V, VI)	76(72.4)	29(27.6)		86(819)	19(18.1)		6.79(4.29)		
Age at onset		27.71(14.81)	24.63(13.60)	0.072	27.08(14.55)	26.40(14.53)	0.584		0.067	0.314
Affected areas	One side of the body	10(66.7)	5(33.3)	0.662	13(86.7)	2(13.3)	0.726	8.00(4.50)		0.736
	from both sides, all over the body	154(71.3)	62(28.7)		172(79.6)	44(20.3)		7.00(3.92)		
	Mainly at the level of the face, hands and foot	99(75.0)	33(25.0)		103(78.0)	29(22.0)		7.24(4.17)		
Total Saves		10.56(15.74)	13.77(18.04)	0.098	11.60(16.88)	10.87(14.77)	0.733		-0.4	0.544
Total visage		0.77(0.99)	0.77(0.97)	0.986	0.81(1.02)	0.61(0.83)	0.08		-0.046	0.494
PHQ-9=Patient Health Questionnaire-9; GAD=General Anxiety Disorder; PSQI=Pittsburgh Sleep Quality Index; N=frequency, SD=standard deviation, BMI=Body Mass Index.; BMI=Body Mass Index, SAVES=self-assessment vitiligo extent score. Significance level set at p-value<0.05.										

2.3 Comparison of depression, anxiety and sleep quality between patients with vitiligo vs. diabetes or hypertension

The prevalence of depression, in our study, was 28.1% in vitiligo, 30.8% in diabetes and 29.6% in hypertension with no significant differences across diseases, while that of anxiety was 21.3% in vitiligo, 19.3% in diabetes and 19.5% in hypertension with significantly higher GAD means among vitiligo patients (6.46 ± 5.07 , 5.63 ± 5.06 and 5.65 ± 5.07 , respectively in vitiligo, diabetes and hypertension). The mean score of PSQI was significantly higher (reduced quality of sleep) among hypertensive individuals compared to patients with diabetes or vitiligo (6.95 ± 3.77 , 6.86 ± 4.49 and 8.08 ± 4.32 , respectively in vitiligo, diabetes and hypertension).

In addition to the correlates of depression, anxiety and sleep quality among vitiligo, diabetes and hypertension, we compared the different variables between vitiligo from a hand and diabetes and hypertension from another hand in patients with depression, anxiety and sleep disturbances. The analysis is shown below.

2.3.1 Depression

a. Vitiligo vs. diabetes

Across genders among depressed participants, the proportion of females was significantly higher in vitiligo than in diabetes (86.6% vs. 67.1%, $p < 0.001$). Furthermore, a vitiligo working patients were significantly higher than diabetic ones (63.4% vs. 47.7%, $p = 0.011$). The mean number of comorbidities was higher among diabetic than vitiligo patients (4.30 ± 4.06 vs. 3.00 ± 2.67 , $p = 0.002$). Concerning BMI, the proportion of obese

diabetic patients (42.6%) was significantly ($p<0.001$) higher than that of vitiligo (16.1%), while the proportion of vitiligo patients with normal BMI was higher than diabetes (53.6% vs. 30.3%, $p<0.001$). The quality of life of vitiligo was significantly better than diabetic with means of value index equal to 0.84 ± 1.18 and 0.70 ± 0.24 , respectively and means evaluation of health equal to 62.68 ± 20.23 vs. 52.67 ± 20.27 (Table 14).

Table 14: Comparison between vitiligo and diabetes among depressed patients

		Depression PHQ>=10		
		Vitiligo 112(41.9%)	Diabetes 155(58.1%)	p-value
Variables		N (%) or mean (SD)	N (%) or mean (SD)	
Socio-demographic variables				
Age		48.65(12.78)	49.84(13.93)	0.439
Gender	Male	15(13.4)	51(32.9)	<0.001
	Female	97(86.6)	104(67.1)	
Marital status	Single	42(37.5)	65(41.9)	0.465
	Married	70(62.5)	90(58.1)	
Employment status	I don't work	41(36.6)	81(52.3)	0.011
	I work	71(63.4)	74(47.7)	
Education level	University degree	49(43.8)	72(46.5)	0.662
	No university degree	63(56.3)	83(53.5)	
Medical and lifestyle parameters				
Number of diseases		3.00(2.67)	4.30(4.06)	0.002
BMI	Underweight	6(5.4)	2(1.3)	<0.001
	Normal	60(53.6)	47(30.3)	
	Overweight	28(25.0)	40(75.0)	
	Obese	18(16.1)	66(42.6)	
Smoking status	I don't smoke	44(39.3)	73(47.1)	0.59
	I quit smoking	42(37.5)	54(34.8)	
	I smoke occasionally	8(5.2)	8(7.1)	
	I smoke regularly	18(16.1)	20(12.9)	
Frequency of alcohol consumption	I don't drink alcohol	27(24.5)	51(35.9)	0.338
	once per month	28(25.5)	26(18.3)	
	2 to 4 times per month	32(24.6)	35(29.1)	
	2 to 3 times per week	15(13.6)	20(14.1)	
	4 or more times per week	8(7.3)	10(7.0)	

Number of glasses		1.45(1.23)	1.32(1.34)	0.428
Physical activity levels	Low activity	1(2.8)	3(7.5)	0.106
	Moderate activity	16(44.4)	9(22.5)	
	Intense activity	19(52.8)	28(70.0)	
Quality of life				
Value Index		0.84(0.18)	0.70(0.24)	<0.001
Evaluation of health		62.68(20.23)	52.67(20.27)	<0.001
PSQI		10.36(4.37)	10.19(4.32)	0.801
PSQI levels	Good sleeper	10(16.4)	17(15.7)	0.911
	Bad sleeper	51(83.6)	91(84.3)	
PHQ= Patient Health Questionnaire, N=frequency, SD=standard deviation, BMI=Body Mass Index, PSQI=Pittsburgh Sleep Quality Index				
Identical letters denote a significant difference between categories				
Significance level set a p<0.05				

b. Vitiligo vs. hypertension

Depressed vitiligo patients had lower mean age than hypertensive patients (48.65 ± 12.78 and 55.67 ± 11.62 , $p < 0.001$). Moreover, a significant difference was detected across genders, with higher proportions of vitiligo females (86.6% vs. 75.7%, $p = 0.016$). Among people who work the highest proportion was seen in vitiligo (63.4% and 44.9%, $p < 0.001$). Depressed working hypertensive patients (40.2%) were significantly higher than vitiligo (28.0%), while vitiligo with normal BMI were more depressed (53.6% vs. 28.0%). In addition, the quality of life of hypertensive was worse than vitiligo with means value index of 0.68 ± 0.26 vs. 0.84 ± 0.18 and means of evaluation of health of 52.34 ± 19.64 and 62.68 ± 20.23 . Finally, the quality of sleep among depressed hypertensive patients was less than those depressed with vitiligo (mean PSQI = 11.85 ± 4.02 and 10.36 ± 4.37 , $p = 0.013$) (Table 15).

Table 15: Comparison between vitiligo and hypertension among depressed patients

Variables		Depression PHQ>=10		
		Vitiligo 112(27.5%)	Hypertension 296(72.5%)	p-value
		N (%) or mean (SD)	N (%) or mean (SD)	
Socio-demographic variables				
Age		48.65(12.78)	55.67(11.62)	<0.001
Gender	Male	15(13.4)	72(24.3)	0.016
	Female	97(86.6)	224(75.7)	
Marital status	Single	42(37.5)	107(36.1)	0.8
	Married	70(62.5)	189(63.9)	
Employment status	I don't work	41(36.6)	163(55.1)	<0.001
	I work	71(63.4)	133(44.9)	
Education level	University degree	49(43.8)	119(40.2)	0.516
	No university degree	63(56.3)	177(59.8)	
Medical and lifestyle parameters				
Number of diseases		3.00(2.67)	5.30(3.70)	<0.001
BMI	Underweight	6(5.4)	4(1.4)	<0.001
	Normal	60(53.6)	83(28.0)	
	Overweight	28(25.0)	90(30.4)	
	Obese	18(16.1)	119(40.2)	
Smoking status	I don't smoke	44(39.3)	120(40.5)	0.267
	I quit smoking	42(37.5)	125(42.2)	
	I smoke occasionally	8(7.1)	9(3.0)	
	I smoke regularly	18(16.1)	42(14.2)	
Frequency of alcohol consumption	I don't drink alcohol	27(24.5)	87(31.3)	0.416
	once per month	28(25.5)	61(21.9)	
	2 to 4 times per month	32(29.1)	59(24.8)	
	2 to 3 times per week	15(13.6)	30(10.8)	
	4 or more times per week	8(7.3)	31(11.2)	
Number of glasses		1.45(1.23)	1.60(2.78)	0.576
Physical activity level	Low activity	1(2.8)	6(7.8)	0.439
	Moderate activity	16(44.4)	27(35.1)	
	Intense activity	19(52.8)	44(57.1)	
Quality of life				
Value Index		0.84(0.18)	0.68(0.25)	<0.001
Evaluation of health		62.68(20.23)	52.34(19.64)	<0.001
PSQI		10.36(4.37)	11.85(4.02)	0.013
PSQI level	Good sleeper	10(16.4)	12(5.9)	0.009
	Bad sleeper	51(83.6)	192(94.1)	
PHQ= Patient Health Questionnaire, N=frequency, SD=standard deviation, BMI=Body Mass Index, PSQI=Pittsburgh Sleep Quality Index				
Identical letters denote a significant difference between categories				
Significance level set a p<0.05				

2.3.2 Anxiety

a. Vitiligo vs. diabetes

The proportion of anxious vitiligo females was higher than diabetic ones (84.7% vs. 62.9%, $p=0.001$). The proportions of vitiligo and diabetes also differed according to work status, where the rate of working patients was significantly higher among vitiligo (64.7%) compared to 47.4% working diabetic patients. similarly to depressed patients, a higher proportion was determined in diabetic obese patients (38.1% vs. 12.9%), while 58.8% of vitiligo patients with normal BMI were depressed compared to 33% among diabetic ones. The mean number of diseases was higher among diabetic (4.11 ± 3.50) compared to vitiligo (2.67 ± 2.36), $p=0.001$. The means of value health and evaluation of health were higher in vitiligo (0.84 ± 0.20 and 51.76 ± 22.20) than diabetes (0.72 ± 0.24 and 50.78 ± 19.55) (Table 16).

Table 16: Comparison between vitiligo and diabetes among anxious patients

Variables		Anxiety GAD>=10		
		Vitiligo 85(46.7%)	Diabetes 97(53.3%)	p-value
		N (%) or mean (SD)	N (%) or mean (SD)	
Socio-demographic variables				
Age		47.64(12.26)	50.31(12.21)	0.143
Gender	Male	13(15.3)	36(37.1)	0.001
	Female	72(84.7)	61(62.9)	
Marital status	Single	28(32.9)	37(38.1)	0.465
	Married	57(67.1)	60(61.9)	
Employment status	I don't work	30(35.3)	51(52.6)	0.019
	I work	55(64.7)	46(47.4)	
Education level	University degree	39(45.9)	45(46.4)	0.945
	No university degree	46(54.1)	52(53.6)	
Medical and lifestyle parameters				
Number of diseases		2.67(2.36)	4.11(3.50)	0.001

BMI	Underweight	5(5.9)	2(2.1)	<0.001
	Normal	50(58.8)	32(33.0)	
	Overweight	19(22.4)	26(26.8)	
	Obese	11(12.9)	37(38.1)	
Smoking status	I don't smoke	33(38.8)	42(43.3)	0.825
	I quit smoking	31(36.5)	35(36.1)	
	I smoke occasionally	7(8.2)	5(5.2)	
	I smoke regularly	14(16.5)	15(15.5)	
Frequency of alcohol consumption	I don't drink alcohol	16(19.3)	28(32.6)	0.207
	once per month	23(27.7)	16(18.6)	
	2 to 4 times per month	27(32.5)	21(24.4)	
	2 to 3 times per week	10(12.0)	14(16.3)	
	4 or more times per week	7(8.4)	7(8.1)	
Number of glasses		1.56(1.22)	1.48(1.39)	0.689
Physical activity level	Low activity	2(7.7)	3(9.7)	0.428
	Moderate activity	9(34.6)	6(19.4)	
	Intense activity	15(57.7)	22(71.0)	
Quality of life				
Value Index		0.84(0.20)	0.72(0.24)	0.002
Evaluation of health		61.76(22.20)	50.78(19.55)	0.001
PSQI		10.15(4.78)	10.91(4.33)	0.379
PSQI levels	Good sleeper	10(20.8)	8(12.3)	0.221
	Bad sleeper	38(79.2)	57(87.7)	
GAD=General Anxiety Disorder, N=frequency, SD=standard deviation, BMI=Body Mass Index, PSQI=Pittsburgh Sleep Quality Index				
Identical letters denote a significant difference between categories				
Significance level set a p<0.05				

b. Vitiligo vs. hypertension

Anxious participants with hypertension were significantly older than vitiligo patients (55.51 ± 12.19 vs. 47.63 ± 12.26 , $p < 0.001$), while the proportion of females among vitiligo patients was significantly higher than those with hypertension (84.7% vs. 72.8%, $p = 0.031$). Moreover, the rates in employment status were significantly with a higher proportion among vitiligo working patients (64.7% vs. 41.0%, $p < 0.001$). In addition, the mean number of

diseases was significantly lower in vitiligo (2.67 ± 2.36 vs. 5.49 ± 3.87 , $p < 0.001$). Similarly to depression, anxious patients with normal BMI were significantly higher in vitiligo (58.8%) than diabetes (27.2%), while obese ones were fewer among vitiligo (12.9% vs. 41.5%). Concerning quality of life, the difference of means of value index and evaluation of health was significant with higher means among vitiligo patients (0.84 ± 0.20 and 61.75 ± 22.20 vs. 0.65 ± 0.26 and 50.82 ± 20.01 , respectively). Moreover, the quality of sleep was lower among hypertensive patients (12.09 ± 4.27 vs. 10.15 ± 4.78 , $p = 0.010$) (Table 17).

Table 17: Comparison between vitiligo and hypertension among anxious patients

Variables		Anxiety GAD>=10		
		Vitiligo 85(30.4%)	Hypertension 195(69.6%)	p-value
		N (%) or mean (SD)	N (%) or mean (SD)	
Socio-demographic variables				
Age		47.63(12.26)	55.51(12.19)	<0.001
Gender	Male	13(15.3)	53(27.2)	0.031
	Female	72(84.7)	142(72.8)	
Marital status	Single	28(32.9)	72(36.9)	0.523
	Married	57(67.1)	123(63.1)	
Employment status	I don't work	30(35.3)	115(59.0)	<0.001
	I work	55(64.7)	80(41.0)	
Education level	University degree	39(32.0)	83(68.0)	0.607
	No university degree	46(29.1)	112(70.9)	
Medical and lifestyle parameters				
Number of diseases		2.67(2.36)	5.49(3.87)	<0.001
BMI	Underweight	5(5.9)	6(3.1)	<0.001
	Normal	50(58.8)	53(27.2)	
	Overweight	19(22.4)	55(28.2)	
	Obese	11(12.9)	81(41.5)	
Smoking status	I don't smoke	33(38.8)	72(36.9)	0.552
	I quit smoking	31(36.5)	86(44.1)	
	I smoke occasionally	7(8.2)	10(5.1)	
	I smoke regularly	14(16.5)	27(13.8)	

Frequency of alcohol consumption	I don't drink alcohol	16(19.3)	55(29.6)	0.362
	once per month	23(27.7)	49(26.3)	
	2 to 4 times per month	27(32.5)	43(23.1)	
	2 to 3 times per week	10(12.0)	24(12.9)	
	4 or more times per week	7(8.4)	15(8.1)	
Number of glasses		1.56(1.22)	1.85(3.28)	0.434
Physical activity level	Low activity	2(7.7)	6(11.3)	0.507
	Moderate activity	9(34.6)	12(22.6)	
	Intense activity	15(57.7)	35(66.0)	
Quality of life				
Value Index		0.84(0.20)	0.65(0.26)	<0.001
Evaluation of health		61.75(22.20)	50.82(20.01)	<0.001
PSQI		10.15(4.78)	12.09(4.27)	0.01
PSQI level	Good sleeper	10(20.8)	9(6.9)	0.007
	Bad sleeper	38(79.2)	122(93.1)	
GAD=General Anxiety Disorder, N=frequency, SD=standard deviation, BMI=Body Mass Index, PSQI=Pittsburgh Sleep Quality Index				
Identical letters denote a significant difference between categories				
Significance level set a p<0.05				

2.3.3 Sleep disturbance

c. Vitiligo vs. diabetes

While assessing quality of sleep among gender between vitiligo and diabetes, the mean PSQI in diabetic males (6.66 ± 4.21) was significantly ($p=0.019$) higher than in vitiligo males (5.51 ± 2.87). In addition, the mean PSQI among vitiligo patients who smoked regularly was significantly higher than diabetic who smoked regularly (10.49 ± 4.65 vs. 7.66 ± 4.52 , $p=0.014$) (Table 18). The correlation with age, number of diseases, value index and evaluation of health was similar in vitiligo and diabetes.

Table 18: Comparison of sleep disturbance between vitiligo and diabetes patients

PSQI		Vitiligo 7.21±4.05	Diabetes 7.56±4.32	p-value
Variable		mean(SD) or r		
Socio-demographic variables				
Age		0.106	-0.002	
Gender	Male	5.51(2.87)	6.66(4.21)	0.019
	Female	7.89(8.21)	8.21(4.30)	0.466
Marital status	Single	7.19(4.22)	7.94(4.54)	0.233
	Married	7.25(3.99)	7.31(4.17)	0.889
Employment status	I don't work	8.24(4.86)	8.10(4.48)	0.848
	I work	7.01(3.84)	7.15(4.17)	0.752
Education level	University degree	6.65(4.02)	6.90(4.21)	0.609
	No university degree	7.86(4.01)	8.11(4.35)	0.619
Medical and lifestyle parameters				
Number of diseases		0.24	0.31	
BMI	Underweight	7.25(3.55)	5.25(5.06)	0.392
	Normal	6.92(3.88)	6.73(4.05)	0.693
	Overweight	7.06(4.28)	6.89(4.04)	0.809
	Obese	9.64(4.39)	9.36(4.41)	0.787
Smoking status	I don't smoke	6.58(7.06)	7.60(4.62)	0.051
	I quit smoking	7.45(3.63)	7.51(4.05)	0.910
	I smoke occasionally	6.86(3.72)	7.27(3.59)	0.743
	I smoke regularly	10.49(4.64)	7.66(4.52)	0.014
Frequency of alcohol consumption	I don't drink alcohol	7.77(4.34)	9.08(4.17)	0.111
	once per month	7.89(3.94)	7.78(4.84)	0.902
	2 to 4 times per month	6.58(3.87)	7.19(4.15)	0.313
	2 to 3 times per week	6.98(3.94)	7.05(4.17)	0.926
	4 or more times per week	7.36(3.84)	6.10(4.03)	0.337
Number of glasses		-0.08	-0.21	
Physical activity level	Low activity	N/A		
	Moderate activity	6.63(3.33)	7.68(4.42)	0.195
	Intense activity	7.38(4.55)	6.60(4.36)	0.322
Quality of life				
Value Index		-0.44	-0.46	
Evaluation of health		-0.44	-0.42	
SD=standard deviation, r= Pearson's or Spearman's correlation, PSQI=Pittsburgh Sleep Quality Index, BMI=Body Mass Index Significance set at p<0.05				

d. Vitiligo and hypertension

PSQI means in both genders were lower among vitiligo patients than in hypertensive ones (male: 5.51±2.87 vs. 6.97±3.79, female: 7.89±8.21 vs. 9.54±4.38). Moreover single and

married vitiligo patients had a better quality of sleep compared to patients with hypertension (PSQI mean $\pm$ SD: 7.19 $\pm$ 4.22 vs. 8.94 $\pm$ 4.43, and 7.25 $\pm$ 3.99 vs. 8.23 $\pm$ 4.27, respectively). Vitiligo patients with university degree had significantly a lower mean PSQI score (6.65 $\pm$ 4.02 vs. 8.23 $\pm$ 4.22, $p < 0.001$). In addition, patients with hypertension having a normal weight had a lower quality of sleep compared to the same BMI category in vitiligo patients, similarly to hypertensive patients who don't smoke, don't drink and performing a moderate physical activity compared to the same variables categories in vitiligo patients. Finally, the correlation with age, number of diseases, value index and evaluation of health was the same in vitiligo and hypertensive participants (Table 19).

Table 19: Comparison of quality of sleep between vitiligo and hypertensive patients

		Vitiligo 7.21 $\pm$ 4.05 mean(SD) or r	Hypertension 8.45 $\pm$ 4.32 mean(SD) or r	p-value
Socio-demographic variables				
Age		0.110	-0.135	
Gender	Male	5.51(2.87)	6.97(3.79)	0.001
	Female	7.89(8.21)	9.54(4.38)	<0.001
Marital status	Single	7.19(4.22)	8.94(4.43)	0.003
	Married	7.25(3.99)	8.23(4.27)	0.011
Employment status	I don't work	8.24(4.86)	8.71(4.44)	0.492
	I work	7.01(3.84)	7.15(4.17)	0.752
Education level	University degree	6.65(4.02)	8.23(4.22)	<0.001
	No university degree	7.86(4.01)	8.68(4.43)	0.084
Medical and lifestyle parameters				
Number of diseases		0.240	0.284	
BMI	Underweight	7.25(3.55)	9.00(4.00)	0.302
	Normal	6.92(3.88)	8.16(4.39)	0.004
	Overweight	7.06(4.28)	8.02(4.11)	0.131
	Obese	9.64(4.39)	9.39(4.45)	0.808
Smoking status	I don't smoke	6.58(7.06)	8.26(4.25)	<0.001
	I quit smoking	7.45(3.63)	8.35(4.35)	0.064
	I smoke occasionally	6.86(3.72)	8.21(4.44)	0.335
	I smoke regularly	10.49(4.64)	10.23(4.42)	0.639
Frequency of alcohol consumption	I don't drink alcohol	7.77(4.34)	9.96(4.85)	0.012
	once per month	7.89(3.94)	8.75(4.11)	0.219
	2 to 4 times per month	6.58(3.87)	8.18(4.12)	0.003
	2 to 3 times per week	6.98(3.94)	7.90(4.44)	0.209
	4 or more times per week	7.36(3.84)	7.27(3.82)	0.936
Number of glasses		-0.080	-0.158	

Physical activity level	Low activity	N/A		
	Moderate activity	6.63(3.33)	8.29(4.38)	0.010
	Intense activity	7.38(4.55)	7.93(4.49)	0.439
Quality of life				
Value Index		-0.440	-0.433	
Evaluation of health		-0.440	-0.419	
SD=standard deviation, r= Pearson's or Spearman's correlation, PSQI=Pittsburgh Sleep Quality Index, BMI=Body Mass Index Significance set at p<0.05				

2.4 Regressions for vitiligo patients

Regressions were performed to assess the correlates of depression, anxiety and sleep disturbances among vitiligo patients including age, gender, marital status, employment status, education level, number of diseases, BMI, smoking status, frequency of alcohol consumption, number of alcohol glasses, physical activity, value index, evaluation of health, phototype, total SAVES, affected body area and age at onset. However, the assumptions for logistic regressions were not met, therefore, PHQ-9 and GAD-7 were used as continuous variables and a multiple linear regression was performed, in addition to the PSQI.

The PHQ regression showed that married patients were less depressed than single ones (Unstandardized β = -2.209, 95%CI: -3.764; -0.655, p=0.005). However, individuals with university degrees and those who smoked regularly were more depressed than those who did not acquire a university degree and did not smoke (Unstandardized β =1.608, 95%CI: 0.283; 2.932, p=0.017 and Unstandardized β =5.628, 95%CI: 1.849; 9.406, p=0.004, respectively). Contradictory results were seen in the association of depression with the quality of life parameters, where the self-evaluation of health showed a better quality of life with lower PHQ scores, while an increase in the value index was associated with a higher PHQ score (Unstandardized β = -0.075, 95%CI: -0.133; -0.017, p=0.011 and Unstandardized β =11.718, 95%CI: 2.037; 21.399, p=0.018, respectively). Furthermore, lower quality of sleep was

correlated with higher PHQ scores (Unstandardized $\beta=0.781$, 95%CI: 0.569; 0.994, $p<0.001$). Among the specific parameters for vitiligo, patients with darker skin were more depressed than those with fair skin (Unstandardized $\beta=1.618$, 95%CI: 0.018; 3.218, $p=0.047$), while those who had patches everywhere on both sides of their body were less depressed than those with patches from one side (Unstandardized $\beta=-5.016$, 95%CI: -10.041; 0.010, $p=0.050$) (Table 20).

Among all variables controlled for, only PSQI was associated with anxiety, where a worse quality of sleep was associated with higher anxiety scores (Unstandardized $\beta=0.304$, 95%CI: 0.082; 0.527, $p=0.007$) (Table 21).

Furthermore, higher age was associated with lower quality of sleep (Unstandardized $\beta=0.085$, 95%CI: 0.015; 0.155, $p=0.017$), while being a male, earning a university degree, smoking occasionally and higher value index were associated with a better quality of sleep (lower PSQI scores). However, higher SAVES and late age at onset was significantly correlated with lower PSQI score (Unstandardized $\beta=-0.052$, 95%CI: -0.097; -0.008, $p=0.021$ and Unstandardized $\beta=-0.065$, 95%CI: -0.125; -0.004, $p=0.036$, respectively) (Table 22).

Table 20: Depression regression among vitiligo patients

Parameter	PHQ-9 score			
	Unstandardized β	95% Confidence Interval		p-value
		Lower	Upper	
Age	.035	-.039	.109	.356
Gender (Female)				
Male	-1.324	-2.956	.307	.112
Marital status (Single)				
Married/couple	-2.209	-3.764	-.655	.005
Working status (I don't work)				
I currently work	-1.446	-3.540	.648	.176
Education level (no university degree)				
University degree	1.608	.283	2.932	.017

Phototype (Fair skin)				
Dark	1.618	.018	3.218	.047
Affected body area (One side of the body)				
Mainly face, hands and feet	-4.318	-9.498	.861	.102
Everywhere on both sides	-5.016	-10.042	.010	.050
Total SAVES	.027	-.019	.073	.248
Age at onset	-.022	-.084	.040	.483
Number of diseases	-.268	-.917	.381	.419
BMI (Underweight)				
Obese	-1.167	-5.577	3.243	.604
Overweight	-2.292	-5.904	1.321	.214
Normal	-2.546	-5.938	.845	.141
Smoking status (No, I don't smoke)				
Yes, I smoke regularly	5.628	1.849	9.406	.004
Yes, I smoke occasionally	-1.033	-3.700	1.633	.448
I quit smoking	.808	-.677	2.293	.286
Frequency of alcohol consumption (Never)				
4 times or more per week	-2.626	-5.801	.550	.105
2 to 3 times per week	-.563	-3.165	2.039	.672
2 to 4 times per month	-1.425	-4.146	1.296	.305
Once per month	.319	-2.597	3.236	.830
Number of alcohol glasses	.118	-.040	.277	.143
Physical activity (Moderate activity)				
Intense activity	-.740	-2.139	.658	.300
Value index	11.718	2.037	21.399	.018
Evaluation of health	-.075	-.133	-.017	.011
PSQI	.781	.569	.994	.000
PHQ-9: Patient Health Questionnaire 9, SAVES : Self-Assessment Vitiligo Extent Score, BMI : Body Mass Index, PSQI: Pittsburgh Sleep Quality Index Significance set at p<0.05.				

Table 21: Anxiety regression among vitiligo patients

Parameter	GAD-7 score			
	Unstandardized B	95% Confidence Interval		p-value
		Lower	Upper	
Age	-.021	-.099	.057	.591
Gender (Female)				
Male	-.999	-2.711	.713	.253
Marital status (Single)				
Married/couple	-.584	-2.214	1.047	.483
Working status (I don't work)				
I currently work	-1.709	-3.906	.487	.127
Education level (no university degree)				
University degree	.932	-.457	2.322	.189

Phototype (Fair skin)				
Dark	.304	-1.374	1.983	.722
Affected body area (One side of the body)				
Mainly face, hands and feet	-1.427	-6.861	4.007	.607
Everywhere on both sides	-2.383	-7.657	2.890	.376
Total SAVES	-.003	-.051	.045	.890
Age at onset	-.002	-.068	.063	.946
Number of diseases	-.341	-1.023	.340	.326
BMI (Underweight)				
Obese	-1.230	-4.177	1.718	.414
Overweight	-.441	-2.156	1.274	.614
Normal	.344	-3.214	3.902	.850
Smoking status (No, I don't smoke)				
Yes, I smoke regularly	2.860	-1.104	6.824	.157
Yes, I smoke occasionally	.616	-2.182	3.414	.666
I quit smoking	-.024	-1.582	1.534	.976
Frequency of alcohol consumption (Never)				
4 times or more per week	-.628	-3.960	2.703	.712
2 to 3 times per week	1.174	-1.556	3.904	.399
2 to 4 times per month	-.904	-3.759	1.950	.535
Once per month	.037	-3.023	3.097	.981
Number of alcohol glasses	.123	-.043	.289	.147
Physical activity (Moderate activity)				
Intense activity	-1.109	-2.577	.358	.138
Value index	-.983	-11.139	9.173	.850
Evaluation of health	-.035	-.095	.026	.264
PSQI	.304	.082	.527	.007
GAD-7: General Anxiety Disorder 7, SAVES : Self-Assessment Vitiligo Extent Score, BMI : Body Mass Index, PSQI: Pittsburgh Sleep Quality Index Significance set at p<0.05.				

Table 22: Quality of sleep regression among vitiligo patients

Parameter	PSQI score			
	Unstandardized B	95% Confidence Interval		p-value
		Lower	Upper	
Age	.085	.015	.155	.017
Gender (Female)				
Male	-1.917	-3.447	-.387	.014
Marital status (Single)				
Married/couple	-.472	-1.945	1.002	.530
Working status (I don't work)				
I currently work	1.762	-.200	3.725	.078
Education level (no university degree)				
University degree	-1.264	-2.530	.001	.050

Phototype (Fair skin)				
Dark	-.149	-1.734	1.437	.854
Affected body area (One side of the body)				
Mainly face, hands and feet	2.716	-1.447	6.879	.201
Everywhere on both sides	1.686	-2.402	5.774	.419
Total SAVES	-.052	-.097	-.008	.021
Age at onset	-.065	-.125	-.004	.036
Number of diseases	.536	-.092	1.164	.094
BMI (Underweight)				
Obese	-.053	-2.829	2.723	.970
Overweight	-.201	-1.809	1.408	.807
Normal	-.736	-4.089	2.617	.667
Smoking status (No, I don't smoke)				
Yes, I smoke regularly	-2.288	-6.022	1.446	.230
Yes, I smoke occasionally	-2.491	-4.920	-.061	.044
I quit smoking	-.007	-1.472	1.458	.993
Frequency of alcohol consumption (Never)				
4 times or more per week	-1.705	-4.846	1.437	.288
2 to 3 times per week	-.586	-3.171	1.999	.657
2 to 4 times per month	-2.270	-4.913	.372	.092
Once per month	-1.396	-4.263	1.470	.340
Number of alcohol glasses	.059	-.097	.215	.458
Physical activity (Moderate activity)				
Intense activity	.121	-1.233	1.476	.861
Value index	-11.266	-20.652	-1.881	.019
Evaluation of health	-.039	-.095	.018	.179
PSQI: Pittsburgh Sleep Quality Index, SAVES: Self-Assessment Vitiligo Extent Score, BMI : Body Mass Index. Significance set at p<0.05.				

2.5 Regression analysis between diseases

Six different regressions were performed in order to assess depression, anxiety and quality of sleep among vitiligo patients compared to diabetics or hypertensive participants. All variables from the bivariate analysis were adjusted for in the regression, including age, gender, marital status, employment status, education level, number of diseases, BMI, smoking status, frequency of alcohol consumption, number of alcohol glasses, physical activity, value index, evaluation of health and quality of sleep (only for depression and anxiety).

2.5.1 Depression

Two logistic regressions were performed to assess the association between depression and type of disease after controlling for the above stated variables. Tables 23 and 24 summarize the regressions results.

Patients with vitiligo have a significantly higher risk of depression than diabetic patients (OR=1.769, 95% CI: 1.002-3.122, $p=0.049$), however no significance was found with hypertensive patients (OR=1.798, 95% CI: 7.06-4.575, $p=0.218$). Moreover, among vitiligo and diabetic participants, employed patients were at lower risk of depression (OR=0.269, 95% CI: 0.079-0.912, $p=0.035$) and those with higher BMI were twice more at risk for depression (OR=2.719, 95% CI: 1.392-5.311, $p=0.003$). In addition, the increase of the perception of health decreased the likelihood of depression, while patient with a higher PSQI (worse quality of sleep) were 1.4 times more likely to be depressed when comparing vitiligo to diabetes or to hypertension (Tables 23 and 24).

Table 23: Logistic regression for vitiligo and diabetes with depression after controlling for confounders

Variable	PHQ-9			
	Odds ratio	95% Confidence interval		p-value
		Lower	Upper	
Disease (diabetes)	1.769	1.002	3.122	.049
Age	.958	.910	1.009	.102
Gender (female)	.878	.249	3.105	.841
Marital status (single)	1.159	.387	3.468	.792
Employment status (unemployed)	0.269	0.079	0.912	.035
Education level (university degree)	2.197	.791	6.100	.131
Number of diseases	.892	.700	1.137	.356
BMI (underweight)	2.719	1.392	5.311	.003
Smoking status (I don't smoke)	1.290	.731	2.276	.380
Frequency of alcohol consumption (I don't drink)	1.017	.633	1.634	.944
Number of alcohol glasses	.667	.382	1.164	.154
Physical activity (low)	.803	.287	2.244	.676

Value Index	7.964	.079	799.927	.378
Evaluation of health	.952	.917	.987	.009
PSQI	1.422	1.224	1.653	<0.001
PHQ-9: Patients Health Questionnaire, BMI:Body Mass Index, PSQI: Pittsburgh Sleep Quality Index. The model explained 48.5% (Nagelkerke R^2) of the variance in depression and correctly classified 85.5% of cases. Significance level set at $p<0.05$				

Table 24: Logistic regression for vitiligo and hypertension with depression after controlling for confounders

Variable	PHQ-9			
	Odds ratio	95% Confidence interval		p-value
		Lower	Upper	
Disease (hypertension)	1.798	.706	4.575	.218
Age	.976	.939	1.014	.214
Gender (female)	1.004	.439	2.298	.992
Marital status (single)	.653	.296	1.444	.293
Employment status (unemployed)	1.062	0.448	2.521	.891
Education level (university degree)	.732	.353	1.519	.402
Number of diseases	1.010	.881	1.159	.882
BMI (underweight)	1.106	.675	1.811	.689
Smoking status (I don't smoke)	1.434	.925	2.222	.107
Frequency of alcohol consumption (I don't drink)	1.276	.908	1.795	.161
Number of alcohol glasses	.853	.592	1.228	.392
Physical activity (low)	.877	.452	1.700	.697
Value Index	.183	.011	3.177	.243
Evaluation of health	.971	.948	.994	.013
PSQI	1.383	1.245	1.536	.000
PHQ-9: Patients Health Questionnaire, BMI:Body Mass Index, PSQI: Pittsburgh Sleep Quality Index. The model explained 49.8% (Nagelkerke R^2) of the variance in depression and correctly classified 87.2% of cases. Significance level set at $p<0.05$				

2.5.2 Anxiety

Similarly to depression, two logistic regressions were performed to assess the association between anxiety and type of disease after controlling for all collected variables. Tables 25 and 26 summarize the regressions results.

Having vitiligo or diabetes or hypertension was not significantly associated with anxiety. However, an increase of 1 year in age was associated with a lower risk of anxiety in the vitiligo/diabetes participants (OR=0.946, 95% CI: 0.900-0.996, $p=0.033$) and in the

vitiligo/hypertension groups (OR=0.934, 95% CI: 0.892-0.977, p=0.003). Furthermore, being married decreased the likelihood of being anxious (OR=0.382, 95% CI: 0.153-0.955, p=0.040) among the vitiligo and hypertensive patients. In addition, non-worker participants with vitiligo or diabetes have 4 times more risk of anxiety (OR=4.636, 95% CI: 1.153-18.640, p=0.031). The value index significantly reduced the risk of anxiety among patients with vitiligo or hypertension, while an increase of 1 unit in the PSQI score increased the risk of depression by 1.187 (OR=1.187, 95% CI: 1.061-1.329, p=0.003) (Tables 25 and 26).

Table 25: Logistic regression for vitiligo and diabetes with anxiety after controlling for confounders

Variable	GAD-7			
	Odds ratio	95% Confidence interval		p-value
		Lower	Upper	
Disease (diabetes)	.972	.551	1.715	.922
Age	.946	.900	.996	.033
Gender (female)	.683	.166	2.813	.598
Marital status (single)	.703	.232	2.134	.534
Employment status (unemployed)	0.260	0.076	0.897	.033
Education level (university degree)	1.764	.592	5.256	.308
Number of diseases	.931	.729	1.188	.565
BMI (underweight)	1.922	.924	3.998	.080
Smoking status (I don't smoke)	.738	.391	1.393	.349
Frequency of alcohol consumption (I don't drink)	1.312	.781	2.204	.305
Number of alcohol glasses	.872	.516	1.474	.609
Physical activity (low)	.574	.209	1.575	.281
Value Index	.217	.003	18.021	.498
Evaluation of health	.983	.946	1.021	.370
PSQI	1.119	.982	1.275	.093
GAD-7: General Anxiety Disorder 7, BMI:Body Mass Index, PSQI: Pittsburgh Sleep Quality Index. The model explained 30.6% (Nagelkerke R^2) of the variance in anxiety and correctly classified 88.1% of cases. Significance level set at p<0.05				

Table 26: Logistic regression for vitiligo and hypertension with anxiety after controlling for confounders

Variable	GAD-7			
	Odds ratio	95% Confidence interval		p-value
		Lower	Upper	
Disease (hypertension)	.677	.197	2.327	.536
Age	.934	.892	.977	.003
Gender (female)	2.092	.767	5.700	.149
Marital status (single)	.382	.153	.955	.040

Employment status (unemployed)	0.566	0.223	1.435	.566
Education level (university degree)	.539	.222	1.309	.172
Number of diseases	.981	.853	1.130	.793
BMI (underweight)	1.003	.575	1.749	.991
Smoking status (I don't smoke)	1.104	.665	1.832	.702
Frequency of alcohol consumption (I don't drink)	.927	.625	1.373	.704
Number of alcohol glasses	1.223	.876	1.707	.238
Physical activity (low)	1.148	.533	2.473	.725
Value Index	.042	.002	.744	.031
Evaluation of health	.979	.952	1.007	.136
PSQI	1.187	1.061	1.329	.003
GAD-7: General Anxiety Disorder 7, BMI:Body Mass Index, PSQI: Pittsburgh Sleep Quality Index. The model explained 41.7% (Nagelkerke R^2) of the variance in anxiety and correctly classified 91.7% of cases. Significance level set at $p<0.05$				

2.5.3 Sleep disturbance

Two multiple linear regressions were performed to assess the association between PSQI and vitiligo/diabetes, after controlling for different confounders. The regression analysis showed no significant association with the type of disease ($p=0.260$).

When comparing vitiligo to diabetes, working patients had significantly higher PSQI by 1.537 compared to non-workers (Unstandardized $\beta= 1.225$, 95% CI: 0.147-2.075, $p=0.039$), while having a university degree decreased the PSQI by 1.083 (Unstandardized $\beta= -1.083$, 95% CI: -2.048 – -0.117, $p=0.028$). In addition, having quit smoking decreased the quality of sleep by 2.444 compared to smoking regularly (Unstandardized $\beta=2.444$, 95% CI: 0.422-4.467, $p=0.018$). The increase of 1 unit in the value index score decreased the PSQI by 11.063 (Unstandardized $\beta=-11.063$, 95% CI= -15.861 – -6.266, $p<0.001$), however, depressed patients had significantly higher PSQI (Unstandardized $\beta= 4.048$, 95% CI: 2.626 – 5.470, $p<0.001$) (Table 27).

While comparing vitiligo to hypertension, the results showed that females have a lower quality of sleep compared to males (Unstandardized $\beta= -1.451$, 95% CI: -2.325 – -

0.577, $p=0.001$) and that an increased number of diseases reduced the quality of life (Unstandardized $\beta= 0.177$, 95% CI: 0.010 – 0.344, $p=0.038$). Moreover, being overweight increased the PSQI score by 0.911 (Unstandardized $\beta=0.911$, 95% CI: 0.011 – 1.811), $p=0.047$), similarly, a positive significant associated was detected between depression and PSQI (Unstandardized $\beta= 3.777$, 95% CI: 2.615 – 4.939, $p<0.001$) (Table 28).

Table 27: Multiple linear regression for vitiligo and diabetes with quality of sleep after controlling for confounders

Variable	Unstandardized β	PSQI		
		95% Confidence interval		p-value
		Lower	Upper	
Disease (diabetes)	.307	-.229	.843	.260
Age	.049	-.001	.099	.055
Gender (male)	-.940	-2.036	.156	.092
Marital Status (single)	-.757	-1.853	.338	.174
Employment (unemployed)	1.225	.060	2.389	.039
Education level (no university degree)	-1.083	-2.048	-.117	.028
Number of diseases	.255	-.006	.516	.055
BMI (normal)				
Underweight	.966	-2.134	4.066	.539
Overweight	-.386	-1.582	.810	.525
Obese	-.685	-2.264	.895	.393
Smoking status (yes, I smoke regularly)				
Non, I don't smoke	1.991	-.053	4.035	.056
I quit smoking	2.444	.422	4.467	.018
Yes, I smoke occasionally	.215	-2.403	2.834	.871
Frequency of alcohol consumption (I don't drink alcohol)				
Once per month	-.522	-2.397	1.353	.583
2 to 4 times per month	.196	-1.560	1.952	.826
2 to 3 times per week	.066	-1.726	1.859	.942
4 or more times per week	.356	-1.866	2.578	.752
Number of alcohol glasses	-.095	-.610	.420	.717
Physical activity (moderate activity)				
Low activity	.972	-3.960	5.904	.698
Intense activity	-.374	-1.412	.664	.478
Value Index	-11.063	-15.861	-6.266	<0.001
Evaluation of health	.007	-.032	.046	.718
GAD-7	-.067	-1.755	1.620	.937
PHQ-9	4.048	2.626	5.470	<0.001
PSQI: Pittsburgh Sleep Quality Index, BMI:Body Mass Index, GAD-7:General Anxiety Disorder 7, PHQ-9: Patient Health Questionnaire 9. Significance set at $p<0.05$.				

Table 28: Multiple linear regression for vitiligo and hypertension with quality of sleep after controlling for confounders

Variable	PSQI			
	Unstandardized β	95% Confidence interval		p-value
		Lower	Upper	
Disease (hypertension)	.052	-.972	1.076	.921
Age	.025	-.018	.068	.251
Gender (male)	-1.451	-2.325	-.577	.001
Marital Status (single)	-.522	-1.414	.370	.251
Employment (unemployed)	-0.123	-1.047	0.801	.794
Education level (no university degree)	.078	-.695	.851	.843
Number of diseases	.177	.010	.344	.038
BMI (normal)				.794
Underweight	-.215	-2.906	2.476	.875
Overweight	.911	.011	1.811	.047
Obese	.525	-.743	1.793	.416
Smoking status (yes, I smoke regularly)				
Non, I don't smoke	-1.635	-3.490	.221	.084
I quit smoking	.072	-.770	.914	.866
Yes, I smoke occasionally	-1.473	-3.518	.572	.157
Frequency of alcohol consumption (I don't drink alcohol)				
Once per month	-.773	-2.237	.691	.299
2 to 4 times per month	-.026	-1.460	1.408	.972
2 to 3 times per week	-.097	-1.590	1.396	.898
4 or more times per week	-.734	-2.346	.877	.371
Number of alcohol glasses	.070	-.305	.445	.714
Physical activity (moderate activity)				
Low activity	.821	-1.495	3.138	.486
Intense activity	.179	-.658	1.016	.675
Value Index	-2.855	-6.425	.714	.117
Evaluation of health	-.011	-.039	.017	.421
GAD-7	.434	-1.020	1.888	.557
PHQ-9	3.777	2.615	4.939	<0.001
PSQI: Pittsburgh Sleep Quality Index, BMI:Body Mass Index, GAD-7:General Anxiety Disorder 7, PHQ-9: Patient Health Questionnaire 9. Significance set at $p < 0.05$.				

CHAPTER VI- DISCUSSION

Vitiligo is the most common disfiguring skin disorder having a substantial impact on quality of life and psychological status of affected individuals including depression, anxiety and reduced quality of sleep. Despite the multiple assessment tools for vitiligo extent, no cut-offs were established to reflect the patient's improvement and for the treatment's effectiveness. Furthermore, multiple comparative studies have evaluated depression, anxiety and quality of sleep among vitiligo patients compared to other skin diseases, however, none of them compared the psychological impact with non-cutaneous chronic diseases.

1 MCID

For the moment, most of the clinical trials evaluating the severity of vitiligo are choosing facial involvement as a primary outcome whether this main outcome is a physician assessment or a patient assessment. However, until today, no study has showed clearly that the involvement of face can be used as a global impression of severity.

In this study, we evaluated the perception of global severity using a global assessment score of severity at a 1 year interval and a validated patient reported outcome measure, the SAVES. Our results showed that changes in facial SAVES deeply affect the perception of global severity of vitiligo from patients' perspective. This is in line with previously published research, suggesting that patients are deeply affected psychologically by vitiligo involving the face amongst other visible areas (248). The major finding in this study is the determination of the MCID based on SAVES, as an increasing number of clinical trials for vitiligo are evaluating the severity of the face as a primary outcome using a PROM. Since it is crucial to

evaluate how patients perceive the effects of interventions (249), current research is suggesting reporting in clinical trials not only the difference between the intervention and control groups, but also the difference in PROM among patients who exhibited a small, moderate or large improvement or deterioration (250). In fact with the exception of the VNS there is no fully validated PROM addressing repigmentation. However, one should keep in mind that the VNS mainly assesses cosmetic acceptability of repigmentation, which is a subjective evaluation that has limitations. One of these limitations is that the VNS was validated with photographs from patients with mainly dark skin which is not reflective of real world data and limits generalizability of the results. Hence there is a need for objective PROs tools that assess the meaningful change which is the case of the SA-VES.

Furthermore, we determined the MCID of total SAVES among worsened and improved patients, separately. The anchor was moderately correlated with the difference of total SAVES, in line with the literature's recommendation (136,251). In addition, the ROC analysis and AUC showed an acceptable discrimination capacity (approximately 64%) between patients who worsened and those who were stable (252).

In line with our findings, MCIDs for both worsened and improved patients were similar to what was reported by Uitentuis et al in a study involving 135 patients in 2021, where the MIC for SAVES was found to be 0.2% BSA (253). However, in the latter study, the authors did not report different values of MCID for worsening and improvement (254). From another hand, in our study, the MDC was found to be higher than the MCID, generated by the anchor-based method in both worsened and improved patients which means that the change cannot be differentiated from measurement errors at 95% confidence interval; this is mainly related to the small sample size (160,255).

Even though vitiligo is not affected by gender, 74% of the participants were female, consistently with results from the COMPARE e-cohort where 76.1% of the vitiligo participants were females (256). In fact, many researches have shown that females are more responsive than males to online surveys (257). Unfortunately stratification by gender could not be conducted due to the small samples size

In this project, performed in the context with ComPaRe e-cohort, we determined the correlates of depression, anxiety and quality of sleep among vitiligo patients, in addition we compared these psychological parameters between vitiligo and diabetes from a hand and vitiligo and hypertension from another hand. Furthermore, we confirmed that changes in facial patches are reflective of the global severity perception of vitiligo and we determined a cut-off for the SAVES, a self-assessment tool for vitiligo extent, in ameliorated and aggravated patients.

2 CORRELATES OF DEPRESSION, ANXIETY AND QUALITY OF SLEEP IN VITILIGO PATIENTS

In the current study, we are not going to debate the results of diabetes and hypertension separately, which is beyond our scope, however, the comparative results between vitiligo from a hand and diabetes or hypertension from another hand will be discussed in the next paragraph.

In our study the prevalences of depression and anxiety among vitiligo patients were 28.1% and 21.3%, respectively and the mean PSQI score was 6.95. The prevalence of depression and anxiety varies among diagnostic criteria (91). In this study the prevalence of depression was similar to what was reported by Dabas et al. (27%) using the PHQ-9 and in

concordance with the pooled prevalence reported in two meta-analysis in 2017 and 2018 (29% in both studies) (92,192) . In contrast to our results, Silpa-archa et al. (206) and Kosaraju et al. (258) reported lower prevalence of depression, 13.55% and 0%, respectively. In both studies the sample size is relatively low (104 and 6 vitiligo patients, respectively). Similarly to our results, anxiety prevalence in vitiligo using GAD-7 was 21% in Dabas et al. (213). However, a lower rate of 12.22% was reported in Taiwan using the ICD-9 as diagnostic tool (196). While higher rates were found in Egypt, where 34.36% of vitiligo patients were anxious using the DSM-V (18), and in meta-analysis studies (33%) (92) and 35.8% (208). To note that only one published study used the GAD-7 as a tool to assess anxiety in vitiligo. Even though PHQ-9 and GAD-7 have high sensitivity, however, the positive predictive values of these tools is low (238,259). Therefore a clinical psychological assessment is recommended. The PSQI mean score among vitiligo patients was 6.95 ± 3.77 , similarly to what was reported by Oztekin et al. (2021) where the PSQI mean score was equal to 6 (4 – 9.5). Furthermore, our results showed a prevalence of bad sleepers among vitiligo patients equal to 58.2%, differently from other studies which reported higher (89%) (200) or lower (30% and 18.62%) (18,20) prevalences of sleep disturbance. This discrepancy is mainly due to the different tools used in the literature.

Similarly to other studies, our results showed that females were more depressed than males (32.1% vs. 15.5%, $p=0.001$) (91,192,197,201,203,205,209). Furthermore, patients with no university degree were more depressed than those who have earned a university degree, as has been shown in Dabas et al. using the PHQ-9 as an assessment tool for depression (213), in Alharbi et al. and Sarma et al. (202,205), and in a recent systematic review (91), where lower education was significantly correlated with depression. In addition, our results showed

that depression was associated with an impaired quality of life and quality of sleep similarly to what was reported in previous studies (14,20,91,194,211,260). This result was inverted in the regression analysis, which might be due to the use of the PHQ-7 as a continuous variable. In line with the systematic review by Ezzedine et al. (91), this research showed a higher depression scores among vitiligo patients with darker skin (phototype IV and V). Moreover, the regression did not show any association of depression with age and working status similarly to what was reported in studies using the PHQ-9 as a depression score (206,213). As for the severity and extent of vitiligo, this study showed no association between depression and SAVES or affected area, similarly to the results reported by Silpa-Archa et al. using the same scales (PHQ-9 and VES) (206). However, Dabas et al. reported an association between depression and vitiligo extent using the VIDA that have been demonstrated to be an unreliable instrument (261). Similarly to our results in the bivariate and multivariate analysis, many studies showed that single patients were more depressed than married ones (91,202,203).

Furthermore, in the current study, we could not demonstrate a relationship between depression and affected area, the reason could be related to the formulation of the question and options; “one side of the body”, “from both sides, all over the body”, and “mainly at the level of the face, hands and feet”, which might have caused a confusion in patients having simultaneously patches on one side or both sides in addition to patches on the face, hands and feet. A controversial finding is that depression was not associated with the disease severity (using SAVES), especially that the visibility of lesions may impair self-esteem resulting in psychological disturbances. This might be due to the fact that, in our sample, the SAVES mean was 10.68 ± 0.70 (median= 4.42), which is relatively low. Even though, no significance

was reported between depression and age at onset, however, the analysis showed that depression is associated with duration of the disease above > 5 years (results not reported), similarly to what was reported in multiple studies (112,197,203,216,262).

Our results showed an association between the number of comorbidities and higher depression scores. In fact, poor health outcomes have been correlated with multiple chronic illnesses and current evidence relate some shared biological mechanism between depression and chronic diseases (263). Furthermore, depression was associated with a higher risk of developing chronic conditions (264). Since our study is cross-sectional, we could not assess whether the depression occurred before or after the accumulation of different comorbidities. Moreover, similarly to our results, an increase in depression score was correlated to regular smoking status, however, the direction of association between depression and smoking cannot be assessed and still debatable within the literature. Some studies propose that depressed individuals turn to smoking to reduce their depressive symptoms, while other studies suggest that smoking leads to depression through the stimulation of the hypothalamic–pituitary–adrenal system, hence dysregulation of the neurotransmitter system due to nicotine exposure (265). Finally, the bivariate analysis showed a relationship between depression and alcohol intake, however, the association was not significant in the regression analysis knowing that previous research suggest that increased alcohol intake increases the risk of depression (266). This discrepancy in our result might be due to the low number of vitiligo participants who consumed alcohol frequently (more than 4 times per week) and that the mean number of consumed alcohol glasses among vitiligo patients is relatively low in our study, in addition to the type of the PHQ-9 used as continuous in the multivariate aalysis.

Few studies assessed the correlates of anxiety among vitiligo patients, our results showed an association in the bivariate analysis between anxiety and being female, smoking regularly, lower quality of life indices and disturbed quality of sleep. These results are in line with multiple meta-analytical studies where females have shown to be more anxious than males (208,209) while Dabas et al. did not find any correlation with anxiety using the GAD-7 in a small sample of 20 anxious vitiligo patients (213). Moreover, similarly to our results, compromised quality of life has been reported among patients with anxiety disorders (267,268). Finally, anxiety has been associated with a reduced quality of sleep, in fact, Individuals with anxiety often suffer from disturbed sleep, and, conversely, inadequate sleep can initiate or worsen anxiety due to common physiological mechanisms (269).

Quality of sleep was correlated to age, gender, educational level, number of disease, BMI, smoking status were associated to sleep disturbances. However, after controlling for confounders, age, gender, educational level remained risk factors for sleep disorders, in addition to Total SAVES, age at onset and quality of life. In line with our study, being a female and older age was correlated with lower quality of sleep in the only study by Liu et al. that assessed correlates of insomnia among vitiligo patients (211), the correlation between sleep and being a female is explained by a multiple biologic and psychosocial factors (270), while insomnia is considered as a normal aging occurring in older adults mainly due to the increase in chronic conditions (270). However, the latter study did not report an association with education, disease extent and age at onset or duration of vitiligo, and quality of life. While lower sleep quality was associated with lower educational level in our study and different studies assessing quality of sleep among adults (270–272), the association was not significant in Liu et al, maybe due to the different categorization used for educational levels.

Furthermore, our study showed an association with the higher age at onset and the severity of the disease, differently from what was reported by Liu et al. using the VASI that has shown to be inferior in terms of reliability and user-friendliness compared VES (from which the SAVES was derived) (122).

3 DEPRESSION, ANXIETY AND QUALITY OF SLEEP AMONG VITILIGO VS. DIABETES OR HYPERTENSION PATIENTS

Further, in our study we compared the correlates of depression, anxiety and quality of sleep between vitiligo from a hand and diabetes/hypertension from another hand.

The prevalence of depression, in our study, was 28.1% in vitiligo, 30.8% in diabetes and 29.6% in hypertension with no significant differences across diseases, while that of anxiety was 21.3% in vitiligo, 19.3% in diabetes and 19.5% in hypertension with significantly higher GAD means among vitiligo patients (6.46 ± 5.07 , 5.63 ± 5.06 and 5.65 ± 5.07 , respectively in vitiligo, diabetes and hypertension). The mean score of PSQI was significantly higher among hypertensive individuals compared to those with vitiligo or diabetes (6.95 ± 3.77 , 6.86 ± 4.49 and 8.08 ± 4.32 , respectively in vitiligo, diabetes and hypertension). The result of the multivariate analysis showed that vitiligo patients were more depressed than diabetic ones, with no significant difference with hypertensive patients.

Furthermore, our results showed that depressed or anxious vitiligo patients were females and younger than depressed or anxious hypertensive patients, mainly due to the higher age of onset of hypertension (273) compared to vitiligo (274). Females across the three diseases were significantly more depressed or anxious than males, which is a common finding in the majority of studies assessing gender differences in depression and anxiety

(275,276). The reason behind this higher rate is that women are more sensitive to interpersonal relationships, in addition to the hormonal changes in women throughout their lives (277). Moreover, females with vitiligo were more depressed or anxious than females with diabetes or hypertension, which is mainly related to the disfiguring effects of vitiligo associated with a lower self-esteem and distorted body image. In addition, the prevalence of employed depressed or anxious vitiligo patients was significantly higher than diabetic and hypertensive patients; which correlates with the stigmatization, lowest self-esteem and social avoidance among vitiligo patients (201,214,278–280). Moreover, depressed or anxious vitiligo patients experience significantly a higher quality of life and have less comorbidities compared to diabetes and hypertension, the decrease in quality of life in the latter diseases is mainly due to the higher number of comorbidities, amount of medication and higher risk of health complications among diabetic and hypertensive patients (281–283). Moreover, depressed and anxious patients with vitiligo had a better quality of sleep than hypertensive, but not diabetic patients, this difference is mainly due to the bidirectional relation between hypertension and sleep (284,285). Finally, BMI was significantly different across diseases where depressed or anxious diabetic or hypertensive patients were more obese than patients with vitiligo. These results among diabetic patients are due to common physiological processes and substrates between diabetes, depression and obesity including inflammatory proteins and hormonal pathways, in addition, obesity can worsen blood pressure by activating the renin angiotensin aldosterone system (286,287).

Quality of sleep was also compared among patients with vitiligo and those with diabetes or hypertension. Our results showed increased sleep disturbances among diabetic and hypertensive males and females compared to vitiligo. In fact, diabetes has been

associated with sleep apnea and snoring which leads to sleep restriction and fragmentation (288), further, the frequent urination caused by diabetes may lead to frequent use of the bathroom and hence a decreases quality of sleep. While the impact of quality of sleep among hypertensive patients might be due to the dual direction of correlation between hypertension and sleep (284,285). Moreover, the quality of sleep was worse among hypertensive patients with a university degree compared to vitiligo, in fact, study, examination and related stress were found to significantly increase blood pressure and hence reduce the quality of sleep (289). Further, vitiligo patients who performed moderate physical activity had a better quality of sleep than hypertensive patients. It has been shown that sleep and exercise exert a mutual positive effect (290). Actually, moderate activity is a potential therapy for treating and preventing vitiligo progression by acting on the inflammatory process (291). While physical activity has shown to be a non-pharmacological treatment for hypertension (292), early morning exercise (which could not be evaluated in our study) is recommended for a better control of nocturnal blood pressure and hence, better quality of sleep (293). The results in the current study reported that normal weight hypertensive individuals have a decreased quality of sleep compared to vitiligo patients with normal BMI, whereas those who don't smoke experienced more disrupted sleep, similarly to hypertensive patients who did not drink alcohol. These findings seem controversial; however the overall mean score of PSQI is significantly higher in hypertension than in vitiligo, furthermore, the differences of mean PSQI score within the categories of each disease are in line with the literature. Moreover, vitiligo regular smokers have a poorer quality of sleep compared to diabetes.

4 STRENGTHS AND LIMITATIONS

This study presents much strength as it encompasses few limitations. This is the first study to assess the MCID of total SAVES among worsened and improved patient. Even though the MCID was lower than the MCD, our results will help clinicians in assessing the effectiveness of the prescribed treatment as well as the deterioration perceived by their patient. While we could not determine the MCID for facial SAVES due to its exponential nature and the inability to compute a change in BSA, however we were able to show that facial SAVES can give a global impression of the course of the vitiligo. The small number of participants is a first limitation in this study, as discussed previously; the AUC, sensitivity and specificity are highly dependent of the sample size. A second limitation is the recall bias on the global assessment question; some people may not be able to really estimate if they were better or worse one year ago. Moreover, this is the first study to compare psychological morbidities in vitiligo and non-cutaneous chronic diseases. Despite the larger number of patients with hypertension compared to vitiligo, we could determine a higher prevalence rate of anxiety among vitiligo patients compared to hypertension and to prove that psychological comorbidities in skin diseases are as important as those in non-cutaneous chronic diseases. However, we could not correlate the disease severity to the psychological comorbidities due to the different severity scales used in vitiligo, diabetes and hypertension.

5 RESEARCH PROSPECTS

Our results open new research opportunities for developing a new quantitative PROM to assess improvement or deterioration of the face among vitiligo patients since the noticeability or any significant change of patches should be determined from the patient's perspective. Moreover, a severity measurement scale might be validated for cutaneous and non-cutaneous chronic diseases in order to assess the impact of disease severity on the psychological morbidities and on quality of life.

CHAPTER VII- CONCLUSION

As it is crucial for clinicians to appropriately manage the treatment, and for patients to perceive changes, we suggest a difference of 0.217% to 0.247% BSA of total SAVES as a sign of improvement or deterioration. Although these changes show significant clinical amelioration or deterioration, further evaluation on a larger sample size is needed to be able to detect smaller differences. Furthermore, developing a new scale for assessing repigmentation of the face is of high interest as patients' perception of their facial patches is of most importance compared to other body parts. Ultimately, this global impression of severity could correlate with an improved quality of life. Lastly, dermatologists are encouraged to consider these data because the findings of PRO instruments are critical to assisting clinicians and patients to make informed decisions regarding any intervention.

Our findings highlight the impact of psychological comorbidities on the life of patients with vitiligo, as shown a higher anxiety rate was detected among patients with vitiligo compared to hypertensive patients, and depression rates comparable to diabetes and hypertension, whereas vitiligo patients experience a better quality of sleep than hypertensive, however, similar to diabetics.

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