"A CROSS-SECTIONAL STUDY ON THE ASSOCIATION OF COMORBIDITIES IN ADULT FEMALE PATIENTS WITH VITILIGO IN TERTIARY HEALTH CARE CENTRE, KOLAR"

By

DR. SAVANA WAIKHOM, M.B.B.S.

DISSERTATION SUBMITTED TO

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IN

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Under the Guidance Of

Dr. HANUMANTHAYYA K., M.B.B.S., M.D., Professor

DEPARTMENT OF DERMATOLOGY, VENEREOLOGY AND LEPROSYSRI DEVARAJ URS MEDICAL COLLEGE, TAMAKA, KOLAR, KARNATAKA – 563101

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Date:

Place: Kolar

Signature of Guide

DR. HANUMANTHAYYA K. MD.

Professor,

Department Of Dermatology,

Venereology and Leprosy,

Sri Devaraj Urs Medical College.

Tamaka, Kolar

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Signature of HOD

DR. RAJASHEKAR. T.S

Professor & Head,

Department of Dermatology

Sri Devaraj Urs Medical College,

Tamaka, Kolar

Date:

Place: Kolar

Signature of Principal

DR. P.N.SREERAMULU

Principal,

Sri Devaraj Urs Medical College

Tamaka, Kolar

Date:

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Savana Waikhom
Signature of Student

Dr.K. Hanumanthayya
Signature of Major Advisor

Dr. K. Hanumanthayya
Professor
Dept. of Dermatology
SDUMC, Tamaka, Kolar.
KMC No. 15216

Professor & HOD
Dept. of Dermatology
R.L. Jalappa Hospital & Research Centre
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Date:

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Signature of the candidate

Dr. SAVANA WAIKHOM

LIST OF ABBREVIATIONS USED

SL NO	ABBREVIATIONS	FULL FORMS
1	DM	Diabetes mellitus
2	SLE	Systemic lupus erythematosus
3	MC1R	Melanocortin 1 receptor
4	TYR	Tyrosinase
5	MATP	Membrane-associated transport protein
6	L-DOPA	L-3,4- dihydroxyphenylalanine
7	TYRP1	Tyrosinase related protein-1
8	ACTH	Adrenocorticotropin hormone
9	α-MSH	Alpha melanocyte stimulating hormone
10	MART	Melanoma-associated antigen recognized by T cells
11	PMEL17	Premelanosome 17
12	DHI	5,6-dihydroxyindole
13	DHICA	5,6-dihydroxyindole-2-carboxylic acid
14	CD	Cysteinyl-DOPA
15	MHC	Major histocompatibility complex
16	CTLA	Cytotoxic T lymphocyte antigen
17	ACE	Angiotensin-converting enzyme

18	CAT	Catalase
19	COMT	Catechol-O-methyltransferase
20	MBL	Mannan-binding lectin
21	PTPN22	Protein tyrosine phosphatase, non-receptor type 22
22	HLA	Human leukocyte antigen
23	XBP1	X-box binding protein 1
24	FOXP1	Forkhead box P1
25	NALP1	NACHT leucine-rich repeat protein 1
26	AIS	Autoimmune susceptibility
27	SLEV	Systemic lupus erythematosus vitiligo-related gene
28	ICAM	Intercellular adhesion molecule
29	GM-CSF	Granulocyte monocyte colony-stimulating factor
30	SCF	Stem cell factor
31	SOD	Superoxide dismutase
32	MDA	Malondialdehyde
33	IFN γ	Interferon-gamma
34	FGF	Fibroblast growth factor
35	LXR α	Liver X receptor alpha
36	HMGB	High mobility group box
37	H2O2	Hydrogen peroxide
38	CRH	Corticotropin-releasing hormone

39	TNF-α	Tumor necrosis factor-alpha
40	TR	Thioredoxin reductase
41	GPx	Glutathione peroxidase

ABSTRACT

BACKGROUND:-

Vitiligo is an acquired pigmentary disorder with well-defined macules and patches, which is characterized by depigmentation due to loss of melanocytes. The worldwide prevalence varies from 0.4% to 2.0%, with a slight preponderance of females. The woman being affected two times more than males may be attributed to their health-seeking behaviour for cosmetic reasons. The cause is considered to be multifactorial-autoimmune, cytotoxic, biochemical, oxidant-antioxidant, viral, and neural mechanism in genetically predisposed people. It has shown to be associated with several autoimmune diseases both systemic and cutaneous conditions.

OBJECTIVES: -

1) To assess association of co-morbidities in adult female patients with vitiligo.
2) To evaluate various clinical patterns in adult female vitiligo patients.

MATERIALS AND METHODS:-

A total of 53 patients with vitiligo who attended the Dermatology OPD at R.L Jalappa Hospital attached to Sri Devaraj Urs Medical College between January 2020 and July 2021 were included in the study. Data was collected after obtaining written informed consent from the patient. In every case detailed history and thorough clinical examination was carried out. Information about age of onset, site of onset, duration, history including family history, history of associated diseases, any associated symptoms use of any drugs before onset of illness, any aggravating factors, any spontaneous re-pigmentation were noted down. The data was entered in Microsoft excel sheet, a master chart was prepared

and it was analysed using IBM SPSS software version 22. P value < 0.05 was considered statistically significant.

RESULTS:-

Most of the study population (35.8 %) who came to the Dermatology OPD were 21-30 years. Age of onset varies from 8 years to 53 years of age. Majority 43.4% had duration of the disease >10 years. Positive family history was seen in 18.9% of the patients and most of them were first-degree relatives. 41.5% of the patients had vitiligo vulgaris. 43.4% of the participants had associated comorbidities among which Hypothyroidism was seen in 24.52%, Diabetes mellitus in 9.43%, Hypertension in 5.66%, Leukotrichia in 5.66%, Alopecia areata in 3.77%, Guttate Psoriasis in 1.8% and canitis in 1.8%. Koebner's phenomenon was seen in 18.9%. Legs was the most common site involved (35.8%). Spontaneous repigmentation was seen in 18.9% of the patients. 31.8% of the vitiligo vulgaris patients had associated comorbidities.

CONCLUSION:-

In this study, 43.4 % of all female adult patients with vitiligo had associated co-morbidities. Among all co-morbidities, hypothyroidism (24.52%) was the most common associated condition. These associated co-morbidities were frequently observed in vitiligo vulgaris patients than in any other clinical types of vitiligo. Early screening for those diseases is essential to start early diagnosis and prompt treatment, especially in patients with vitiligo vulgaris.

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INTRODUCTION

Vitiligo is an acquired pigmentary disorder of the skin and mucous membrane which manifests, as well-defined, depigmented macules and patches due to selective loss of melanocytes[1]. The worldwide prevalence varies from 0.4% to 2.0%, with a slight preponderance of females.[2] Its prevalence in Gujarat is 8.8%, the highest in the world.[3] There is no difference in the rate of occurrence according to race or skin type. The woman being affected two times more than males may be attributed to their health-seeking behaviour for cosmetic reasons. It is a major disease concern because of social stigma and cosmetic disfigurement leading to psychological trauma to the patients. The exact cause is not known but considered multifactorial like autoimmune, cytotoxic, biochemical, oxidant-antioxidant, viral, and neural mechanism for destruction of the melanocyte function in genetically predisposed people.[4]

Since vitiligo is an autoimmune disease, it is associated with other autoimmune diseases like thyroid disease, DM, alopecia areata, SLE, pernicious anaemia, myasthenia gravis.[5] It can also be associated with dermatological conditions like canities, atopic eczema, psoriasis, lichen planus, halo nevus, ichthyosis vulgaris.[6]

Therefore, it is paramount to spread the awareness of these comorbidities to ameliorate the disease burden and quality of life of vitiligo patients. In this study, only adult female vitiligo patients are preferred because there is less prevalence of comorbidities in children[7]; moreover, autoimmune diseases are seen more frequently in females than males.[8] Furthermore, there is a paucity of literature on the associated comorbidities in female vitiligo patients; hence this study is undertaken.

AIMS AND OBJECTIVES

The aims and objectives of the study were as follows:

1) To assess association of co morbidities in adult female patients with vitiligo.

2) To evaluate various clinical patterns in adult female vitiligo patients.

REVIEW OF LITERATURE

Vitiligo is an acquired pigmentary disorder with well-defined macules and patches, which is characterized by depigmentation due to loss of melanocytes.[9]. It was also earlier known by the term 'Sufaid Dagh', 'Phulbahari', 'Bars', 'Bahak', 'Kilas', 'Palita', 'Kodha', 'Sweta Kushta', 'Dhawal Kustha'.[10] It is typified by its well demarcated chalky white macules and patches. Skin discoloration greatly affects the patients' quality of life primarily, young women. The worldwide prevalence varies from 0.4% to 2.0%, with a slight preponderance of females .[11]

The word was originated from 'vitelius', which is a Latin word meaning vale, denoting pale pink flesh of calf that looks like white lesions of vitiligo.[12] Some say that it is derived from a Latin word 'vitium' meaning defect.[13]

Classification of vitiligo[14,15]

Vitiligo is classified into segmental vitiligo, that does not traverse the midline, non-segmental vitiligo, and mixed vitiligo of both segmental and non-segmental vitiligo. Based on extent and distribution, it is also classified into the following:

Localized:

1. Focal: one or more macules in one area, but not clearly in a segmental distribution.
2. Unilateral/segmental: one or more segments of the body lesions involving only one side of the body and stop abruptly at the midline.
3. Mucosal: mucous membrane only

Generalized:

1. Vulgaris: widely distributed depigmented lesions
2. Acrofacial: distal extremities and face
3. Mixed: combination of segmental and generalized (acrofacial and/or vulgaris) types
4. Universal:
    a. Complete or nearly complete depigmentation
5. Special forms
    a. Trichrome vitiligo
    b. Quadrichrome vitiligo
    c. Inflammatory vitiligo

Synthesis of melanin:

1. Melanocytes are those cells that produce a pigment called melanin, present in hair follicles, the skin, inner ear cochlea, choroids, ciliary body, and iris. They derive from the neural crest cells of the neural tube. Progenitor melanoblasts get to final destinations by traversing dorsolaterally between the mesodermal and ectodermal layers. A maximum number of melanocytes are seen in skin and hair follicles. Cutaneous melanocytes are located in the basal layer and the proximal hair bulb during the anagen phase. In the interfollicular epidermis, one melanocyte is surrounded by 36 keratinocytes.[16,17] Factors affecting the skin colour of a person are determined by the activity of melanocytes, the concentration of melanosomes, and the rate of transfer of melanosomes to the keratinocytes.

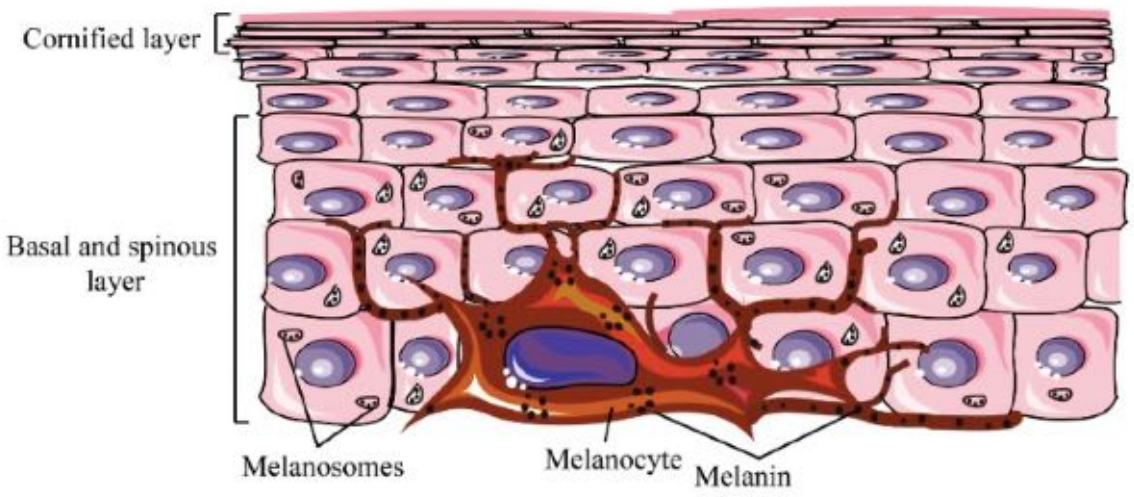


Figure 1: Demonstrating Epidermal-melanin unit

Melanosomes are membrane-bound organelle where melanin is synthesized with the help of various enzymes present in melanocytes. Melanosomes can be eumelanosomes or pheomelanosomes. Eumelanosomes are large and elliptical in shape and synthesize eumelanin which is black in colour, whereas pheomelanosomes are smaller, spherical in shape, and synthesize pheomelanin which is yellowish to brownish in colour.[16] It requires important enzymes and protein to produce melanin pigment.

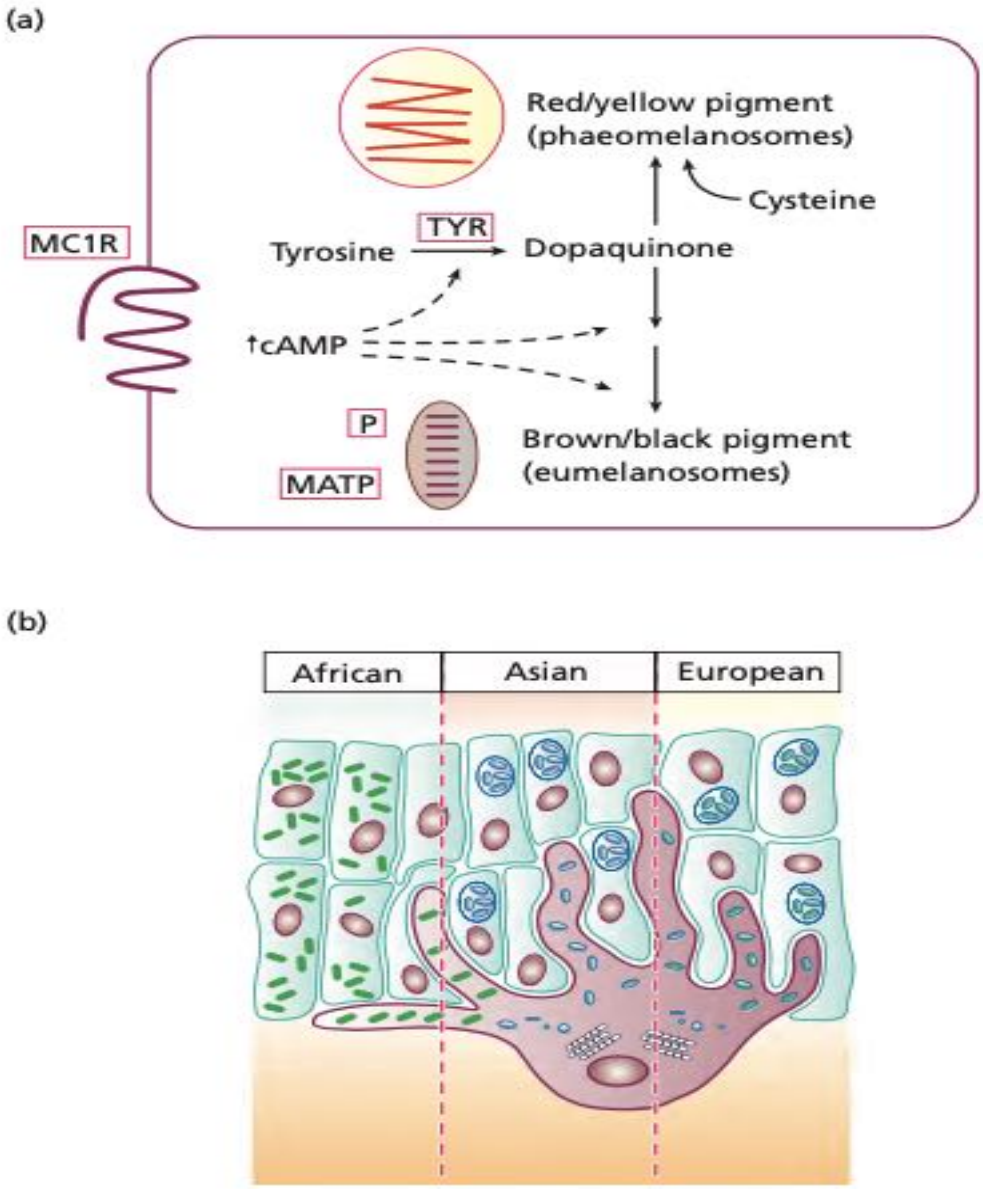


Figure 2: (a) Activation of the melanocortin 1 receptor (MC1R) promotes the synthesis of eumelanin at the expense of phaeomelanin. Oxidation of tyrosine by tyrosinase (TYR), however, is required for synthesis of both pigment types. Melanosomal membrane components, including the membrane-associated transport protein (MATP) and the pink-eyed dilution protein (P), play a role in determining the amount of pigment synthesis within melanosomes. (b) In African, Asian and European skin there is a gradient of melanosome size and number; in addition, melanosomes in African skin are more widely dispersed.

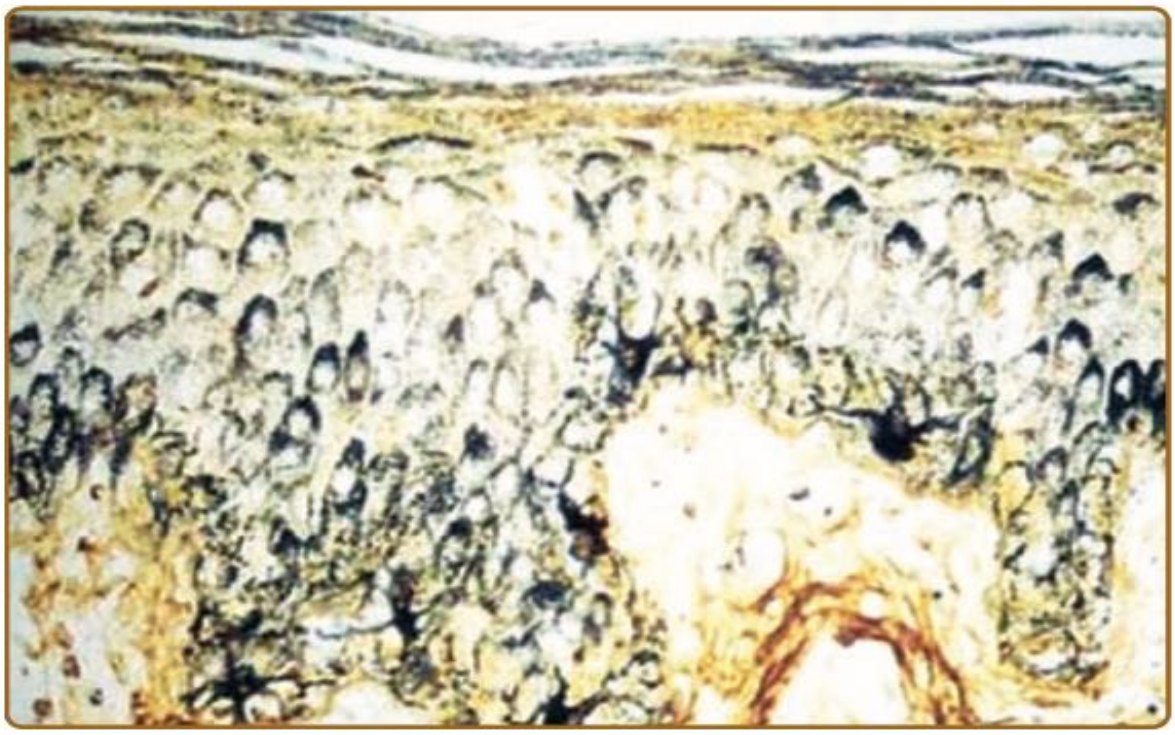


Figure 3: Melanosomes are organized into supranuclear “caps” within keratinocytes (Fontana-Masson stain).

The enzymatic machinery and important structural components of melanosomes are [18,19,20]:

1. Tyrosinase – Tyrosinase synthesis starts in the endoplasmic reticulum, and further glycosylation takes place in the Golgi apparatus. It catalyzed tyrosine to form L-DOPA (L-3,4- dihydroxyphenylalanine) and further L-DOPAquinone by oxidation.
2. Tyrosinase related protein-1 (TYRP1) – there are two types of Tyrosinase related protein - TYRP1 and TYRP-2. Both have catalytic activity and take part in melanogenesis.
3. SLC24A5 – also known as MATP, OCA4

4. MART-1/Melan A – present in stage 1 and 2 melanosomes, and helps in regulation of PMEL17 in melanosome.
5. Melanocortin 1 Receptor –
6. It is a G-protein coupled receptor + extracellular ligands ⟶ activation of Gs protein. ⟶ Increase activity of adenylate cyclase

   ATP ⟶ cyclic AMP ⟶

   Increase melanin synthesis and prevent apoptosis of melanocytes formation of eumelanin and phaeomelanin are regulated by α-MSH and adrenocorticotropin hormone (ACTH) which are the agonists of the MC1R .

Melanin is of two types, eumelanin, and pheomelanin. Synthesis of melanin is a multistep process derived from the amino acid tyrosine. The enzyme tyrosinase (tyrosine oxidase) catalyses tyrosine to form DOPA (3,4-dihydroxyphenylalanine), a rate-limiting step. DOPA is then converted to DOPAquinone which changes to 5,6-dihydroxyindole (DHI) or to 5,6-dihydroxyindole-2-carboxylic acid (DHICA). DHI will form eumelanin black through indole 5,6-quinone and DHICA to eumelanin brown via intermediate product Indole 5,6-quinone carboxylic acid. When DOPAquinone reacts with L- Cysteine results in the formation of cysteinyl-DOPA (CD), which latter form red/yellow, soluble, low molecular weight Pheomelanin through Alanyl-hydroxy- benzothiazine intermediate.

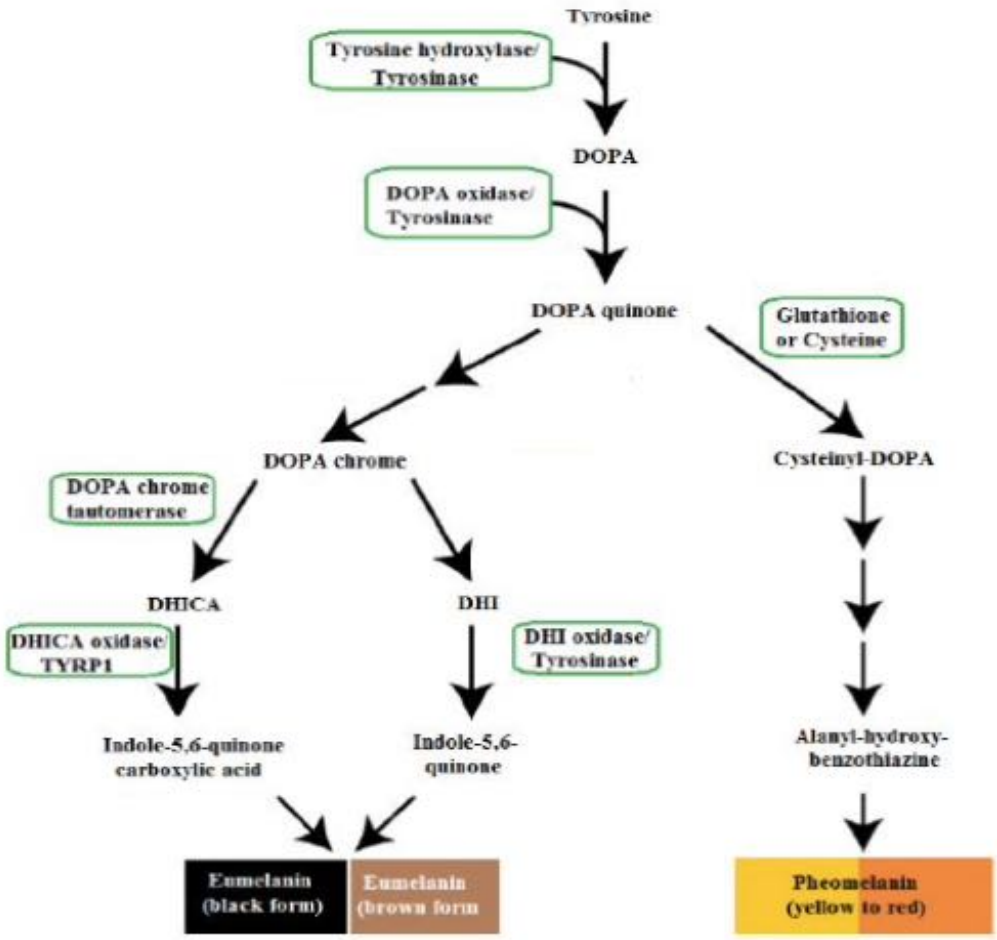


Figure 4: Pathway of synthesis of melanin[21]

ETIOPATHOGENESIS OF VITILIGO

Etiopathogenesis of vitiligo is not very clear and complex. Many hypothesis has been proposed.

1. Genetics:

In vitiligo, familial clustering is observed with 0.14% to 20% frequency among first degree relatives of vitiligo patients.[22,23] This clearly shows the role of genetic involvement in the etiopathogenesis of vitiligo. But among the monozygotic twins, only

23% concordance has been found, which indicates the non-genetic component in its pathogenesis.[22] Vitiligo is related to several genes, namely, major histocompatibility complex (MHC), cytotoxic T lymphocyte antigen-4 (CTLA-4), angiotensin-converting enzyme (ACE), catalase (CAT), catechol-O-methyltransferase (COMT), mannan-binding lectin (MBL2), protein tyrosine phosphatase, non-receptor type 22 (PTPN22), estrogen receptor (ESR), human leukocyte antigen (HLA), X-box binding protein 1 (XBP1), forkhead box P1 (FOXP1), NACHT leucine-rich repeat protein 1 (NALP1), and interleukin-2 receptor A (IL-2RA)[24,25]

Three of the autoimmune susceptibility (AIS) loci, AIS1, present on chromosome 1p31.3–p32.2, AIS2 on chromosome 7, and AIS3 on chromosome 8.[26,27] Systemic lupus erythematosus vitiligo-related gene (SLEV1) positioned on chromosome 17, was established to be linked with vitiligo patients along with other autoimmune diseases.[28]

2. Autoimmune hypothesis:

Presence of other associated autoimmune disorders like thyroid diseases, pernicious anaemia, Systemic lupus erythematosus etc in vitiligo patients support autoimmune hypothesis.[29] There is remarkable role of both cellular and humoral immune system in the evolution of vitiligo.

Cellular immunity

It has shown an accumulation of cellular infiltrate and an increased CD8+/CD4+ ratio in the perilesional skin of the patient. These cytotoxic cells cause the destruction of melanocytes, thereby resulting in basal cell vacuolization in the perilesional area. There

is also increased expression of CD25, MHC II, and interferon-gamma, leading to enhance expression of intercellular adhesion molecule-1 (ICAM-1), which in turn trafficking of T cells to the lesion. This formed a vicious cycle.[30,31]

In patients with vitiligo, an increased number of Melan-A-specific CD8 T cells have been found, corresponding to the disease extent.[32,33] Interferon-gamma (IFN γ) level has found to be increased both in vitiligo patch and perilesional, increasing expression of ICAM-1 attracting T cells.[34]

Cytokines

IL 17 level has been found to be increased in blood and tissue samples and showed association with disease activity.[35] There is also increased expression of IL-6 and tumor necrosis factor α (TNF-α) and decreased expression of granulocyte monocyte colony-stimulating factor (GM-CSF), fibroblast growth factor(FGF), and stem cell factor (SCF).[36]

Keratinocytes derived from GM-CSF and bFGF are involved in maintaining proliferation of melanocyte and UVA-induced pigmentation in the epidermis.[37] IL-6 and TNF-α induced decreasing tyrosinase activity and also melanocyte proliferation inhibition.[38] TNF-α induce B cell differentiation and antibody production through increased expression of ICAM-1 and IL1a, destroying melanocytes.[39,40] Also, TNF-α and IL1a have the potential to cause direct apoptosis.[40]

Humoral Immunity

The role of humoral response in the pathogenesis of vitiligo is supported by the presence of high circulating autoantibodies to cytoplasmic melanocyte and surface antigens.[41] These antibodies are grouped as those against cell surface pigment, cell antigens, intracellular pigment cell antigens, and non-pigment cell antigens.[42] Circulating antibodies are seen against antigens like VIT 40, VIT 75, and VIT 90 in around 83% of the patients.[43] Antibodies to enzyme Tyrosinase, tyrosinase-related protein-1, and tyrosinase-related protein-2, which are important enzymes in the synthesis of melanin, have also been found in vitiligo patients.[44,45]Also, some recent studies showed the presence of antibodies to melanocytes, Lamin A/C, and Vimentin X in the patient's serum.[46,47]

3. Oxidative stress theory

Free oxygen radicals are believed to play a key role in the pathogenesis of vitiligo disease. Superoxide dismutase (SOD), hydrogen peroxide (H2O2), and hydroxyl radical (OH) are the main reactive oxygen species causing injury to the cell and apoptosis of the cell. In vitiligo, there is an alteration of the redox state, leading to the accumulation of free radicals, causing the death of pigment-producing cells. Malondialdehyde (MDA) is the end result of lipid peroxidase, which corresponds to the degree of oxidative stress. Selenium is a major cofactor for the glutathione peroxidase (GPx) enzyme, which has a potent antioxidant property converting H2O2 and other peroxides into water. SOD catalyses superoxide radicals reducing O2– to O2 and H2O2, and Catalase converts H2O2 to O2 and H2O. In the case of vitiligo, there are higher serum malondialdehyde and selenium and superoxide dismutase activities in erythrocytes. In contrast, there is a notable decrease in GPx activity, normal Erythrocyte CAT activity, and serum vitamin

A and E levels.[48] Other studies showed remarkably increased SOD, decreased activity of GPx, low levels of Catalase, vitamins C and E levels.[49,50]

Haptenation theory has explained the role of oxidative stress in the pathogenesis of vitiligo. Under oxidative stress, increased H2O2 triggered the level of surrogate substrates (ortho-phenols) for tyrosinase like noradrenalin, tri-iodothyronine, and estrogen, which are catalysed by tyrosinase to form ortho quinone metabolites. These ortho quinone metabolites bind with tyrosinase because of polymorphism to make more affinity for the surrogate substrate. It brings about inactivation of normal death and dysfunction of tyrosinase enzyme render to become neoantigen causing an autoimmune reaction.[51]

4. Melanocytorrhagy hypothesis

This hypothesis propose that loss of pigmentation in vitiligo is due to detachment and death of melanocytes. Friction, trauma promote detachment of melanocytes from the basement membrane, moving upward to the upper epidermis and later transepidermal elimination.[52] Tenascin is an extracellular matrix molecule that hampers the adhesion of melanocytes to fibronectin, has been observed to be over-expressed in vitiligo give rise to further melanocyte detachment.[53] In patients with unstable vitiligo, melanocytes showed loose adhesion to collagen type IV compared to normal skin and stable vitiligo. Also, in unstable type, dendrites of melanocytes are small with clubbed ends and retracted unfit for adhesion to surrounding structures leading to loss of melanocytes.[54] Increased expression of Liver X receptor alpha (LXR α) around perilesional skin than uninvolved skin decreases adhesion of melanocytes to collagen VII and proliferation. It also

decreases the expression of matrix metalloproteinases and increases apoptosis of melanocytes showing a vital role in the pathogenesis of vitiligo.[55]

5. Autocytotoxicity

Various toxic intermediate metabolites such as phenol, quinone, and related compounds formed during melanin synthesis, causing the destruction of melanocytes in genetically susceptible individuals.[56] High mobility group box 1 (HMGB1) is a non-histone DNA-binding protein secreted by keratinocytes under stress conditions that have the capacity to take part in cell proliferation, angiogenesis, and cell knockdown. In active vitiligo lesions, an increased HMGB1 level triggers apoptosis of melanocytes by upregulating cleaved caspase 3 and melanogenesis-related molecules. Hence it explains the autocytotoxicity hypothesis of vitiligo.[57]

6. Neurohumoral hypothesis

This hypothesis is supported by melanocytes are originated from neural crest cells, dermatomal distribution, change in sweating and expression of specific neuropeptides in vitiligo skin lesions.[58,59] Stress is known to release catecholamine from presynaptic cells and also stimulate nervous system to increase the production of neuroendocrine hormones.[60] These increase neurotransmitters cause destruction of melanocytes through two mechanisms, first by direct cytotoxicity and secondly by causing vasoconstriction resulting in epidermal and dermal hypoxia with toxic free radicals.[61] It was also found to be increased levels of homovanillic and vanillylmandelic acids in the 24-hour urine samples in patients with unstable vitiligo.[61] The increased expression of corticotropin releasing hormone (CRH) and corticotropin releasing hormone receptor 1 (CRHR 1) in patient with vitiligo is remarkably associated with psychological stress.[62]

7. Vitamin D deficiency

Vitamin D is a fat-soluble vitamin derived from diet and also produced in the skin from 7-dehydroxycholesterol with the help of sunlight. It is required for the absorption of calcium and the metabolism of bone. It also helps in the proliferation of cells and has immunomodulatory and anti-inflammatory properties.[63] Different studies have proposed that 1,25-dihydroxyvitamin D3 escalates melanogenesis and tyrosinase activity. It also prevents ultraviolet radiation-induced death of melanocytes, helps in restoring repigmentation of the skin.[64] Calcium has an inhibitory effect on thioredoxin reductase (TR), which acts on 6-biopterin to form (6R)-L-erythro 5,6,7,8 tetrahydrobiopterin (6BH4) which inhibits the function of tyrosinase. Decreased intracellular calcium levels are found in vitiligo lesions leads to increased 6BH4 resulting in inhibition of melanogenesis.[65] Vitamin D has been shown to hinder the release of proinflammatory cytokines like IL-6, IL-8, TNF-α, and TNF-γ which are known to involve in the pathogenesis of vitiligo.[66]

8. Hyperhomocystinemia

Vitamin B12 and folic acid are the co-factors of homocysteine (Hcy) methyltransferase which converts homocysteine to methionine and s-adenosylhomocysteine.[67] Vitamin B12 and folic acid levels are low in patients with vitiligo[68]; consequently, there are high levels of homocysteine and low level of methionine.[69] A pilot study by OG Shaker and S M R El-Tahlawi also showed an increased homocysteine level in vitiligo and related to disease activity.[70] Homocysteine inhibits melanogenesis by blocking the enzyme tyrosinase after its interaction with copper[71] and by releasing reactive oxygen species, which contribute to the destruction of melanocytes.[72]

9. Tumor necrosis factor alpha

Tumor necrosis factor-alpha (TNF-α) also takes part in the immunopathogenesis of vitiligo by causing melanocytes dysfunction and death. TNF-α is secreted by various cells like macrophages, T cells, fibroblasts, and keratinocytes.[73] In a study by Moretti S, Spallanzani A, Amato L, Hautmann G, Gallerani I et al., showed that expression of TNF-α was increased in lesional area than non-lesional skin of vitiligo patients and normal skin of healthy subjects. TNF-α has an inhibitory effect on surrounding melanocytes, thereby hindering its proliferation and differentiation and melanin synthesis.[73] Another study by Naresh C. Laddha, Mitesh Dwivedi, Rasheedunnisa Begum found that TNF-α was more abundantly present in lesional skin of active vitiligo than stable vitiligo.[74]

10. Convergence theory

The Convergence theory states that all the theories mentioned above i.e., genetics, autoimmune hypothesis, oxidative stress theory, melanocytorrhagy hypothesis, autotoxicity, neurohumoral hypothesis**,** vitamin d deficiency, hyperhomocysteinemia, and tumor necrosis factor-alpha, each contribute to the pathogenesis of vitiligo and none of them are mutually exclusive.[75,76]

CLINICAL FEATURES

Patients with vitiligo present with asymptomatic depigmented milky white or chalky white macules or patches with well-defined margins, and the convex border with convexity is towards the normal healthy skin. The shape may be oval, round, irregular, or linear and often have variable sizes. In those individuals with fair skin, sometimes

lesions are faint, barely seen by naked eyes, but it becomes distinct with an examination of wood's lamp. There is a striking difference between normal skin and vitiligo lesions in darkly pigmented individuals, which affect the patient's emotional status, marital issues, and quality of life, sometimes leading to psychiatric illness.[14]

Vitiligo may appear anywhere on the body, but most commonly those areas that are more prone to trauma, pressure, or friction. More frequently, it is seen over the face, especially over periorbital and peri-oral areas, dorsum of the hands, axilla, inguinal, anogenital, elbows, knees, fingers, shin, and ankle. The macules may be localised to one side of the body, called segmental vitiligo, or may present discretely anywhere over the body. Segmental vitiligo is almost always present in childhood vitiligo, and non-segmental vitiligo is most commonly seen in adults. The hair present over the macules may be normally pigmented or depigmented (poliosis/leukotrichia). Vitiligo lesions may present as different shades of colour according to the amount of melanin loss in the same area.[77] Trichrome vitiligo has three colours, normal skin, hypopigmented (middle), and depigmented colour. Quadrichrome vitiligo when there is a fourth colour present, i.e., perifollicular or macular hyperpigmentation. There is a rare variant, pentachrome vitiligo when white, tan, brown, blue-gray colour and normal skin in the same area.[10]

In segmental vitiligo, one or more depigmented macules or patches usually occur on the line of Blaschko. It mostly occurs on one side and does not traverse the midline. This type of vitiligo mostly has an early age onset and quickly advances in the affected area. The disease course of this type of vitiligo can cease, and depigmented patches can stay for the rest of the patient's life. This type of vitiligo is less frequently associated with autoimmune disorders, especially thyroid disorder, than non-segmental vitiligo[78], which

their different underlying etiopathogenesis may explain. In non-segmental type, the increased menace to autoimmunity, which genome-wide analyses have exposed as contrary to segmental type.[79] The depigmented skin lesion of vitiligo change to pink colour during menstruation in young women and girls and return to the original colour after the menses; this sign is called Punshi's sign.[80] Psychological stress is the major provoking factor in those predisposed individuals.[81] In some cases, new lesion may appear after inducing physical trauma, which is termed as koebner's phenomenon, commonly seen in non-segmental vitiligo (47.19%) than in segmental vitiligo (24%)[82]

ASSOCIATED CO-MORBID DISEASES

Vitiligo is associated with several systemic diseases and skin diseases in various studies. One of the studies found that 23% of vitiligo patients had one or more comorbid autoimmune diseases like thyroid disorders, psoriasis, alopecia areata (AA), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), diabetes mellitus (DM), and inflammatory bowel disease (IBD). Out of these disorders, thyroid disorders were the most common association, followed by rheumatoid arthritis.[83] It was also found that there was a significant association of vitiligo with ocular and auditory aberration as compared with normal healthy individuals.[84] These associations are supported by the autoimmune theory of vitiligo. In a nationwide study in Taiwan, 14.4% of the patients had one or more comorbid autoimmune conditions or atopic dermatitis, and AA was the most significantly associated with autoimmune disease. Regarding sex, Graves' disease, Hashimoto thyroiditis, atopic dermatitis (AD), RA, SLE, and systemic sclerosis (SS) were commonly seen in females, while psoriasis was more common in the male group. In further stratification by the onset of age, SLE, SS, and RA in the elderly group and myasthenia gravis (MG) in younger vitiligo patients were established.[5] Another retrospective study

by Sheth et al. 23% had comorbidities, most common being thyroid-related followed by psoriasis, rheumatoid arthritis, alopecia areata, inflammatory bowel disease, systemic lupus, and type I diabetes milletus. In addition, the majority of the patients with comorbidities were belong to Caucasians followed by Hispanic/Latino.[85]

HISTOPATHOLOGICAL FEATURES OF VITILIGO

On hematoxylin and eosin sectioning of involved skin reveals that total absence of melanocytes related to a complete disappearance of epidermal pigmentation. At the margin of vitiliginous lesions, superficial perivascular and perifollicular infiltrates can be noted. It is consistent with a cell-mediated process destroying melanocytes, mainly in the progressive stage of the disease. In inflammatory vitiligo, with an erythematous border, there is the presence of lymphocytes and histiocytes infiltrate. In keratinocytes and melanocytes, degenerative changes have been noted in the border of lesions and nearby skin. Other changes include an increase in the number of Langerhans cells, thickening of the basement membrane, and epidermal vacuolization. Fontana-Masson staining and immunohistochemistry testing are done to highlight the pigment and melanocytes loss in the epidermis. Histochemical studies can demonstrate the lack of dopa-positive melanocytes in the basal layer. In immunohistochemical studies, it seldom shows the presence of melanocytes in the lesional skin. Electron microscopy studies can also show the loss of melanocytes.

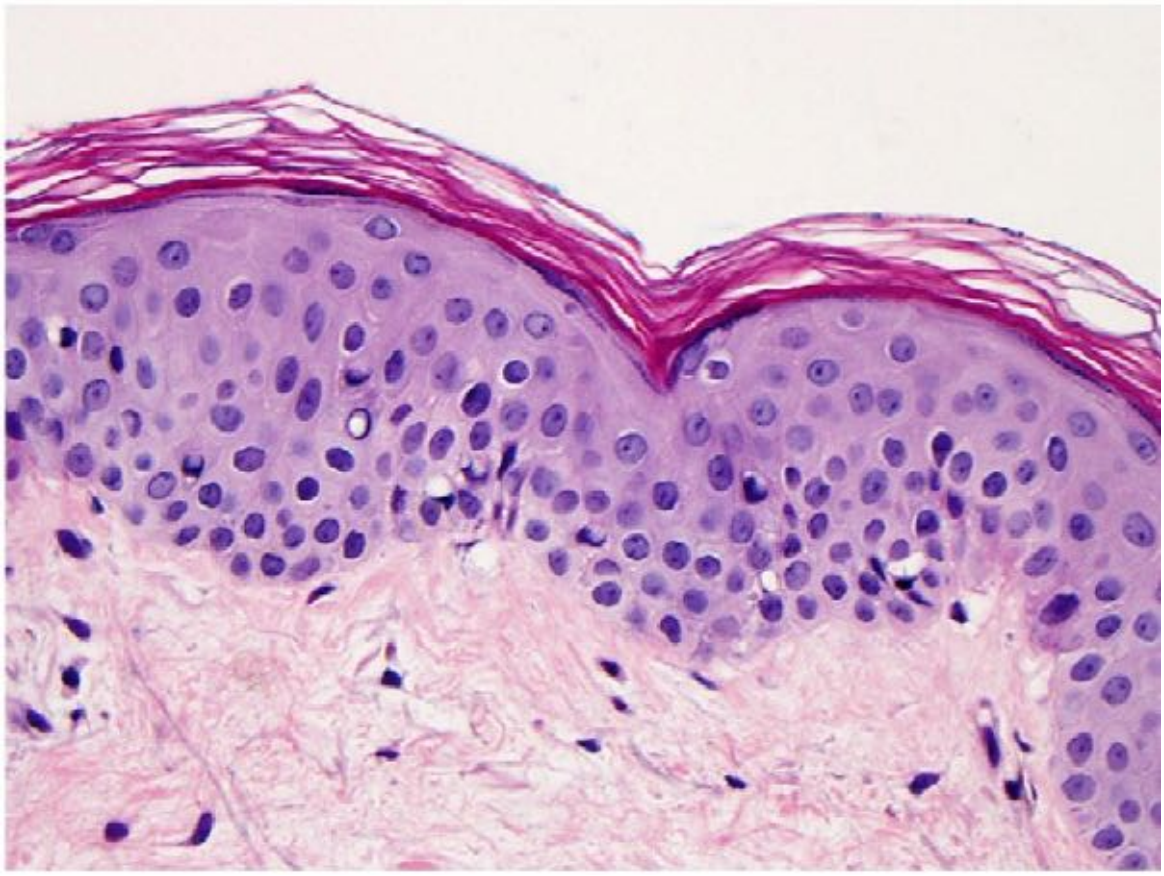


Figure 5: Histopathology of vitiligo lesion

H&E section (40x magnification) of vitiligo patch showing suprabasal vacuolization and occasional suprabasal clear cells, scant inflammatory cells in dermis and absence of melanin pigment. [86]

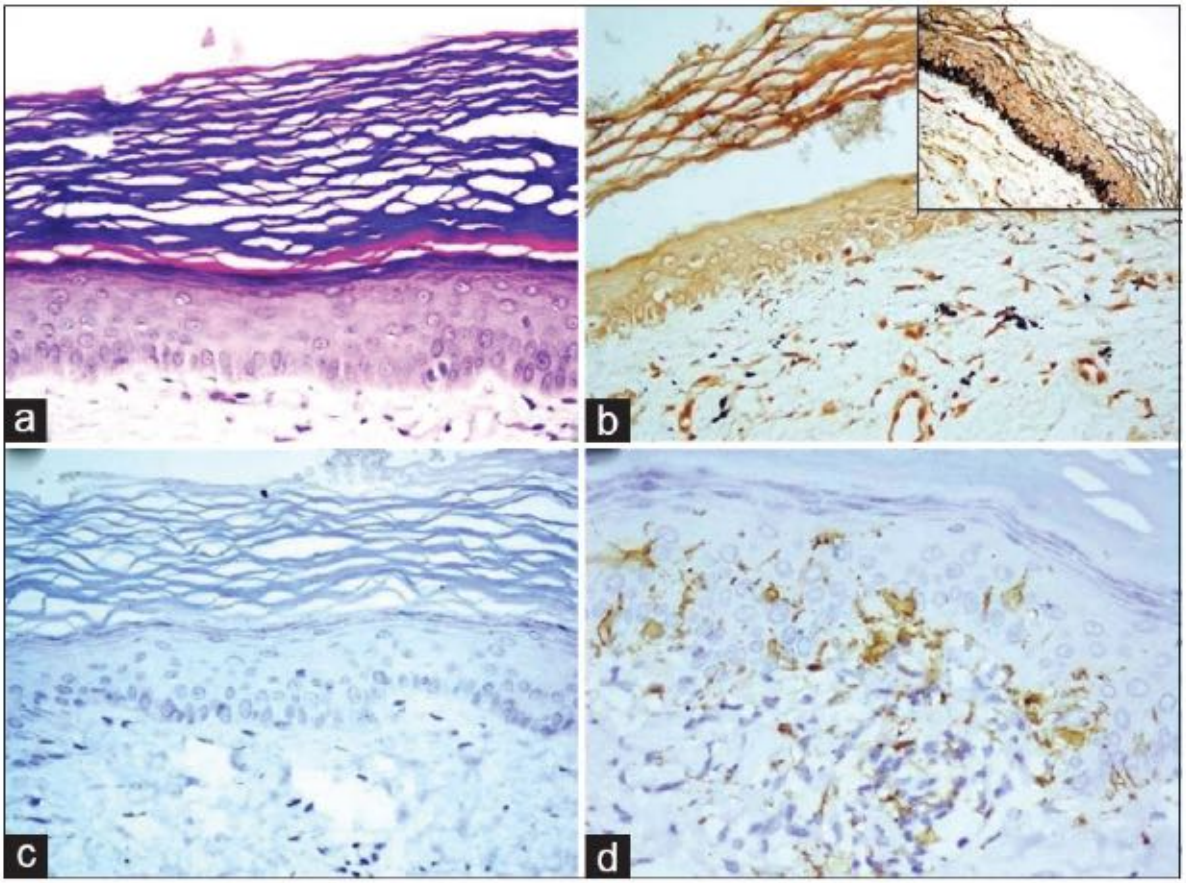


Figure 6: Active vitiligo (a) Total absence of melanin in basal epidermis with mild spongiosis (H and E, ×400). (b) The absence of melanin pigmentation (Masson Fontana ×400). Inset shows normal melanin pigment in the positive control section (MF, ×400). (c) Human melanoma black-45 immunostaining showing no melanocytes in the basal cell layer (IHC, ×400). (d) Increased number of Langerhans cells in epidermis on S-100 immunostaining (x400)[87]

DIFFERENTIAL DIAGNOSIS of vitiligo[77,88]

1. Halo naevi.

2. Naevus anaemicus

3. Naevus depigmentosus.

4. Inherited or genetically induced hypomelanosis (usually present at birth).

    a. Piebaldism.

    b. Tuberous sclerosis.

    c. Waardenburg syndrome.

    d. Pigmentary mosaicism (Hypomelanosis of Ito).

5. Progressive macular hypomelanosis.

6. Secondary hypomelanosis.

    a. Post-inflammatory hypomelanosis (e.g. pityriasis alba, lichen sclerosus, morphoea).

    b. Post-traumatic hypomelanosis.

    c. Post-infectious hypomelanosis (e.g. pityriasis versicolor, leprosy).

    d. Cutaneous lymphoma.

PROGNOSIS[89]

No reliable indicator is there for a good prognosis, but these are a few factors that usually indicate a poor prognosis:

1. Lesions that are present on the bony prominences, non-fleshy areas, non-hairy areas, and mucosal areas, for example, front of wrists, back of elbows, nipples, and areola, the sides of ankles, dorsum of feet and hands, palms, and soles.
2. More the presence of white hair worse is the prognosis.

3. Extensive, long-standing disease.
4. Other associated conditions, especially systemic diseases.
5. Heridofamilial background.
6. Elderly age group.
7. Iatrogenic factors (injudicious administration of topical and systemic
8. medications).

INVESTIGATIONS

The diagnosis of vitiligo is made mainly on clinical examination, as the lesions have a classic appearance. Sometimes lesions do not show the typical appearance of classical vitiligo; Wood's lamp examination can be beneficial in differentiating from other hypomelanotic disorders. In vitiligo, bright bluish-white fluorescence with sharp edges can be seen on Wood's lamp examination. The presence of koebner phenomenon, leukotrichia or poliosis, presence of vitiligo in the family, or presence of correlated autoimmune disorders such as thyroid disease can be helpful to support in clinical diagnosis of vitiligo.[77,88]

TREATMENT

In vitiligo, different treatment options are available such as topical, oral medications, phototherapy, laser therapy, and surgical therapy. However, treatment choice depends on the patient's compliance, affordability, availability, disease progression, type of vitiligo. Treatment response varies from individual to individual but is often unsatisfactory especially acral type of vitiligo. The risk of the spread of vitiligo lesion (koebnerization) from daily activities should be explained to the patients.

Response to treatment of vitiligo varies between individuals but is often unsatisfactory, especially for acral lesions. Patients are best advised to seek effective cosmetic camouflage and to use sunscreen. Furthermore, the risk of koebnerization resulting from everyday activities should be explained to patients.

Treatment modalities

1. Medical
    a. Topical
        i. Corticosteroids
        ii. Tacrolimus/Pimecrolimus
        iii. Pseudocatalase
        iv. Basic fibroblast growth factor
        v. Placental extract preparation
        vi. Combination
    b. Systemic
        i. Corticosteroids (OMP with betamethasone/ methylprednisolone)
        ii. Cyclophosphamide
        iii. Azathioprine
        iv. Levamisole
2. Phototherapy
        i. Topical PUVA
        ii. NB-UVB
        iii. Systemic PUVA (>12 years)
        iv. Phenylalanine + PUVA
        v. Khellin with UVA exposure (KUVA)

vi. Excimer laser

3. Surgical therapy
    i. Conventional – mini punch graft, Suction blister epidermal graft, Thin Thiersch graft.
    ii. Newer cellular transplantation techniques – Epidermal cell suspension, Cultured melanocyte suspension, Cultured epidermis.
4. Cosmetic camouflage.
5. Total depigmentation using Monobenzyl Ether of Hydroquinone [MBEH].

General Measures[77]

1. The condition of the disease and its unpredictable course and prognosis should be explained to the patient.
2. Reassurance.
3. Patient should be advised to take a diet rich in vitamin B complex, Vitamin E, proteins, and minerals such as copper, iron, and zinc.
4. Avoid physical, chemical, and emotional trauma as much as possible.
5. Avoid phenolic compounds containing substances, soaps, detergents, rubber goods, and contact with other chemical compounds.
6. Avoid exposure to the sun, and sunscreens should be prescribed.

1. Medical

a. Topical therapies

i. Corticosteroids:

The topical corticosteroid is preferred as first-line therapy for localized vitiligo as it is easy and convenient for patients. Although potent corticosteroids give good results in 2-4 months, it is likely to develop side effects like atrophy, telangiectasia, striae, hypopigmentation, and hypertrichosis.[89] Furthermore, treatment requires prolonged therapy, which increases the chances of developing these local side effects, tachyphylaxis, glaucoma (prolonged application on periorbital vitiligo), suppression of hypothalamopituitary adrenal axis and growth retardation when used over large body surface area. In order to avoid the side effects, interrupted therapy has to be given (application of twice or once daily for 2 months followed by treatment-free period for 2 weeks if the treatment period is longer than 8 months). Hence patients should be cautioned against inadvertent use of topical steroids.[6]

ii. Tacrolimus/Pimecrolimus:

Topical calcineurin inhibitors (TCI), tacrolimus, and pimecrolimus are effective alternatives to topical corticosteroids in terms of avoidance of side effects of the latter. TCIs are slower to exert beneficial effects compared to topical corticosteroids. The best response is observed on the thinnest areas of the skin (eyelids). They are not approved for the treatment of vitiligo in children below 2 years.[90]

iii. Pseudocatalase:

Twice daily applications of pseudo catalase and calcium chloride with short-term suberythemogenic UVB showed repigmentation in 90% of the vitiligo patients in a study by Schallreuter KU et al.[91]

iv. Basic Fibroblast growth Factor:

It can multiply hair follicle melanocytes surrounding the vitiligo patch and direct the new melanocytes to the affected skin.[92]

v. Placental Extract Preparations:

The use of the human placental extract, both aqueous and alcoholic, has been widely propagated. It probably rectifies the block in the conversion of tyrosine to DOPA and DOPA to DOPAchrome. It is effective in focal and acral types of lesions and the segmental and vulgaris types. The extract is to be applied locally three times a day. It should be rubbed in for 3 to 5 minutes, then exposed to sunlight, infrared light, and UV lamp for 15 minutes.[93]

b) Systemic

i. Corticosteroids:

Systemic corticosteroid therapy has been advocated in pulse form to reduce the side effects. Oral mini pulse therapy, that is, smaller cyclical pulsed administration of a corticosteroid, has been considered a safe and highly effective domiciliary treatment for halting rapidly progressive vitiligo.[94] In a large, retrospective study, Kanwar et al found that mini pulse therapy with low-dose oral dexamethasone 2.5mg/day on 2 consecutive days/week stopped vitiligo progression in 91.8 percent of patients at a mean of 13 weeks. A certain amount of repigmentation was seen in all vitiligo patches at a mean of 16 weeks, and recurrence happened in 12.3 percent of patients. [95]

ii. Cyclophosphamide:

This drug has been tried in the dosage of 50 mg twice a day orally either alone or in combination with oral corticosteroids but due to its side effects, its use is not recommended. It has been reported to be useful in halting the disease activity and in repigmenting vitiligo lesions. [6]

iii. Azathioprine:

It may be promising in the treatment of vitiligo alone or combination with other modalities like UVB or oral PUVA.[96]

iv. Levamisole:

It has shown to be quite effective when used along with a topical corticosteroid in treating vitiligo; however, a double-blind trial undertaken did not show any significant benefit. It is used in the dose of 150 mg on two consecutive days a week in adults, 100 mg in children for a minimum duration of 4 months.[97]

2. Phototherapy

The mechanism of action of psoralens and UVA therapy is by increase of the following:-

1. Number of functional melanocytes.
2. Number and size of melanosomes.
3. Number of dendrites of melanocytes.
4. Transfer of melanosomes to keratinocytes.
5. Tyrosinase activity.
6. Amount of free melanin.
7. Thickness, density and adherence of the stratum corneum.

i. Topical PUVA

Generally, topical PUVA is the chemotherapy of choice if the vitiligo macule is less than 6 sq cm in size. 0.1% is applied a week initially, followed by UVA irradiation for 30-60 seconds after 2-3 hours. The time of exposure can be escalated by 30 seconds each visit and the rate of sitting to twice weekly to thrice-weekly sittings until the patch turns faint erythema.

Alternatively, the treated area is exposed to "black light" at a distance of 4 cm for 4–5 minutes. A Wood's lamp or fluorescent UVA light may be used. After the treatment, the treated area should be washed thoroughly with soap and water and proper sun protection with a broad-spectrum sunscreen and long sleeve clothing. The area must not be exposed to direct sunlight for the next 12 hours. The potential phototoxic side effects associated with PUVA therapy are attributed to the deeper penetration of UVA light than UVB. Hence, cautious application with proper counseling is crucial.[6]

ii. NB- UVB

Narrowband fluorescent bulbs of Philips TL-01, each of 100W with an emission spectrum of 311nm are used. It can be used in pregnancy and children. The advantages of this modality are that no post-exposure eye protection is required, and exposure time is short. Results are best in the face and neck areas, followed by the trunk and proximal extremities having moderate pigmentation. Acral areas and areas of bony prominences and lower hair growth density are hardly pigmented. The therapy should be terminated if there is no response after 6 months.[98]

iii. Systemic PUVA

The use of topical or oral psoralens and ultraviolet A radiation (UVA) is termed PUVA. It is contraindicated in children less than 12 years of age.[99] These phototoxic compounds enter cells and then absorb photons to produce photochemical reactions that alter the function of cellular constituents. It is used when more than 20-25% of the BSA is involved or in patients where other modalities fail to give optimum results.[99] Three psoralens are used :- Methoxypsoralen or 8-MOP, Bergaptan or 5-MOP and Trioxsalen or 4,5,8 trimethyl psoralen.[6] Psoralens (8-MOP or TMP) are given in the dose of 0.6mg/kg/day ingested with food 2 hours before sun exposure, preferably between 10 am and 2 pm.[6]

The first therapeutic dose is calculated from the minimal phototoxicity dose (MPD), which should be determined by photo testing. If photo testing is not feasible, then treatment is usually started at an initial dose of 1-9 J/cm^2; 2 – 3 sittings per week. The subsequent dose should be increased by 0.5 J/ cm^2. Side effects of this therapy include nausea, pruritus, epigastric discomfort, nervousness, erythema, blistering reaction, cataract, and photocarcinogenesis. If there is no response after 6 months or 50 treatments, PUVA should be discontinued.[6]

iv. Phenylalanine with UVA exposure

It has been used both topically and orally along with sun exposure. One hour before UVA irradiation, a 5% aqueous L- phenylalanine solution was given orally. Topically, it has been used as a 10 % L- phenylalanine cream over the vitiligo patch 20 min before sun exposure, given twice a week for six months. Arms, legs, knees, and eyelids are the most common areas of repigmentation and have no side effects.[100]

v. Khellin with UVA exposure (KUVA)

Khellin is a plant of the eastern Mediterranean area, isolated from the seeds of Ammi visnaga, has been used as an effective photosensitizer as psoralen. It is well-tolerated and has no toxic side effects.[101]

vi. Excimer laser (308nm)

The 308nm xenon chloride excimer laser is an effective and safe modality for treating chronic stable vitiligo, with good results achieved in a short duration of time—treatment given twice or thrice weekly for 10 to 15 sittings. Initial pigmentation is observed by 4 to 8 weeks. It acts through immunomodulation by affecting the T cells. Regimentation occurs fastest with thrice-weekly treatment. However, a treatment period of more than 12 weeks is required.[102]

3. Surgical therapy

- Only stable localized vitiligo lesions (segmental or nonsegmental vitiligo), unresponsive to other treatment modalities, are chosen for surgical treatment.
- Surgical procedures are not performed in very young children as segmental or stable focal lesions expand with body growth.
- Moreover, the success of many procedures depends on postoperative immobility of the operated part, which is challenging to maintain in young children.
- Older children and adolescents may be counselled about the procedure and possible surgery outcomes to achieve their cooperation. The restrictive factors

for surgery are the inability to treat larger sites and the risk of koebnerisation of the donor site.

- Among the various surgical techniques, suction blister epidermal grafting has been found to be the most convenient and effective for children; however, prolonged immobility is required.
- Non- cultured autologous epidermal transplantation has been used successfully in children and adolescents with stable vitiligo.
- Cultured melanocyte transplantation is a relatively tedious technique requiring specialised setup, trained staff, and a preparation time of 6 to 8 weeks. Cost may be a restrictive factor for low-income families in availing this treatment modality.[90]

4. Cosmetic camouflage

Good quality cover-up cosmetics (available in commercial names: Dermablend, Covermark, Dermacolor) may be used to cover localised vitiligo lesions overexposed body parts. Treatment of vitiligo at any age remains a challenge, more so during childhood. None of the available therapies is effective, and the disease runs a relapsing course.[90]

5. Depigmenting therapy for extensive vitiligo

Widespread recalcitrant vitiligo or universal vitiligo with only a few islands of normal skin may be considered for total depigmentation therapy with 20% mono benzyl ether of hydroquinone with the advice of lifelong stringent protection.[90]

MATERIALS AND METHODS

Source of data:

The present study was an Cross-sectional analytical study carried out in the Department of Dermatology at RL Jalappa Hospital and Research Centre attached to Sri DevarajUrs Medical College, Tamaka, Kolar from January 2020 to July 2021. Fifty three adult female patients who were diagnosed with vitiligo were included in the study.

Inclusion criteria

- All female patients aged above 18 years presenting with vitiligo

Exclusion criteria

- Leukoderma secondary to contact dermatitis
- Post inflammatory hypopigmentation/ depigmentation
- Albinism.

Methods of data collection:

After obtaining written informed consent, data was collected from all the patients who were included in this study. Detailed history taking and careful clinical examination were performed in all the patients. Data regarding age of onset, site of onset, duration, history including family history, history of associated diseases, any associated symptoms use of any drugs before onset of illness, any aggravating factors, any spontaneous re-pigmentation were noted down. Diagnosis will be made by clinical examination, Wood's lamp and biopsy in doubtful cases. The study was approved by the institution Ethical Committee. Relevant laboratory test was done wherever necessary. The data thus collected will be entered into a specially designed Case Record Form and subjected to statistical analysis.

STATISTICAL ANALYSIS:

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. **Chi-square test or Fischer's exact test** (for 2x2 tables only) was used as test of significance for qualitative data.

Continuous data was represented as mean and standard deviation. **Independent t test** was used as test of significance to identify the mean difference between two quantitative variables.

Graphical representation of data: MS Excel and MS word was used to obtain various types of graphs.

P value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

Statistical software: MS Excel**,** SPSS version 22 **(**IBM SPSS Statistics, Somers NY, USA) was used to analyze data**.**

Sample size calculation:

Sample size of the present study was estimated based on the most common co morbidity seen in vitiligo patients in age group of 18 years and above reported to be 11.3% by the author D. S. Krupa Shankar, K. Shashikala, Rama Madala in 2019,[103] with alpha error of 5% and 95% confidence interval considering an absolute error of 10%. The estimated sample size was 39. A total of 53 subjects with female adult vitiligo were included in this present study.

$$\text{Sample size} = \frac{Z_{1-\alpha/2}{}^2 p(1-p)}{d^2}$$

Here

$Z_{1-\alpha/2}$ = Is standard normal variate (at 5% type 1 error ($P<0.05$) it is 1.96 and at 1% type 1 error ($P<0.01$) it is 2.58). As in majority of studies P values are considered significant below 0.05 hence 1.96 is used in formula.

p = Expected proportion in population based on previous studies or pilot studies.

d = Absolute error or precision – Has to be decided by researcher.

RESULTS

Table 1:- Distribution of subjects according to occupation.

Occupation	Frequency	Percentage
Housewife	40	75.5
Nurse	2	3.8
Student	9	17.0
Teacher	2	3.8
Total	53	100.0

Most of the participants (75.5%) were Housewives, followed by 17% of Students, 3.8% were Nurses, and 3.8% were Teachers.

Graph 1:- Graph showing distribution of subjects according to occupation.

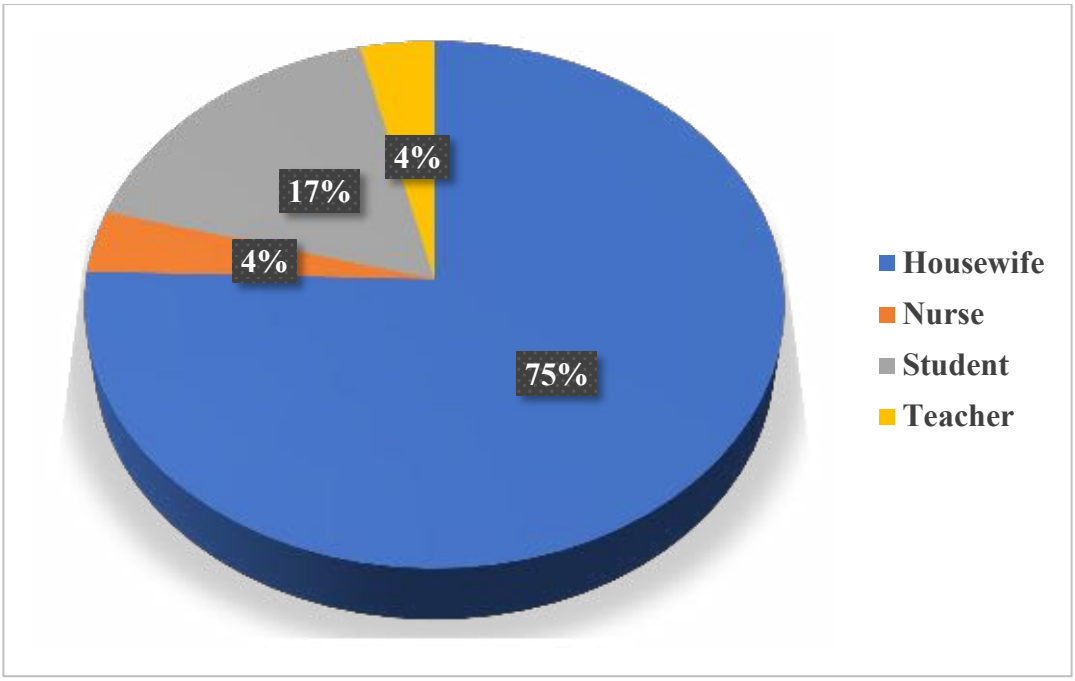


Table 2:- Distribution of subjects according to the types of vitiligo.

Types of vitiligo	Frequency	Percentage
Focal	12	22.6
Lip tip	16	30.2
Mucosal	2	3.8
Universalis	1	1.9
Vulgaris	22	41.5

The majority, 41.5% of the participants, had vulgaris followed by 30% of the subjects had lip tip, 22.6% of the subjects had focal, 3.8% of the subjects had mucosal, and 1.9% of the subjects had universalis.

Graph 2:- Graph showing distribution of subjects according to the types of vitiligo

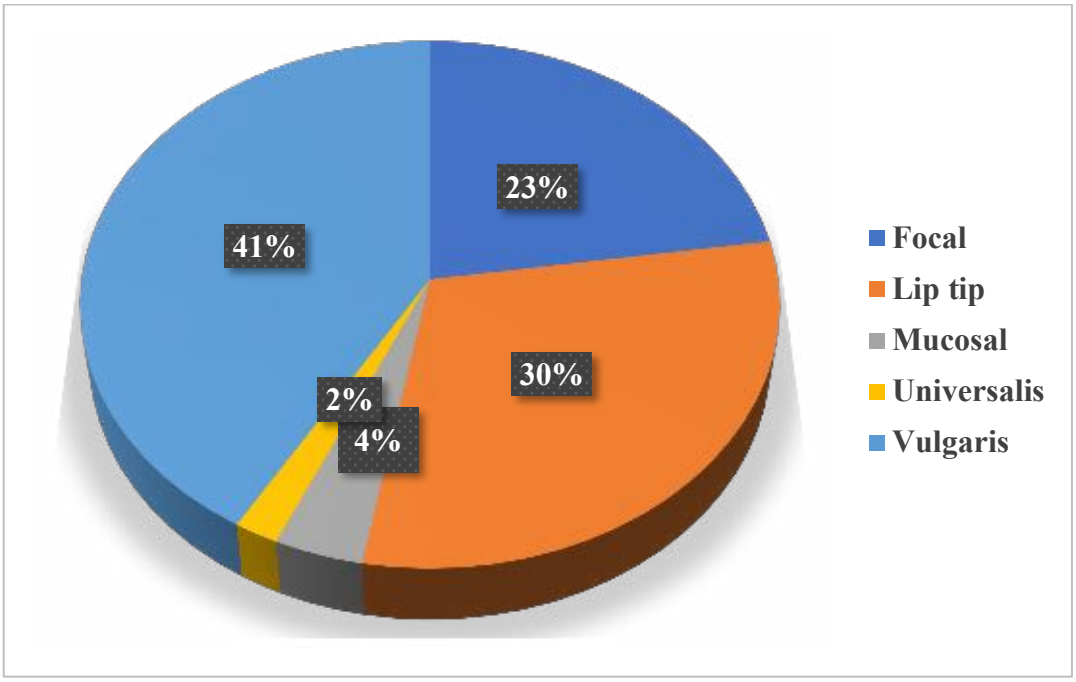


Table 3:- Descriptive statistics of age at presentation and age of onset.

	Minimum (years)	Maximum (years)	Mean (years)	SD
Age at presentation	19	65	37.89	12.394
Age of onset	8	53	25.55	9.583

The minimum age at presentation was 19 years, and the maximum was 65 years, with a mean age at presentation being 37.89 ± 12.3 years. The minimum age of onset was 8 years, and the maximum was 53 years, with the mean age of onset being 25.5 ± 9.5 years.

Graph 3:- Graph showing descriptive statistics of age at presentation and age of onset.

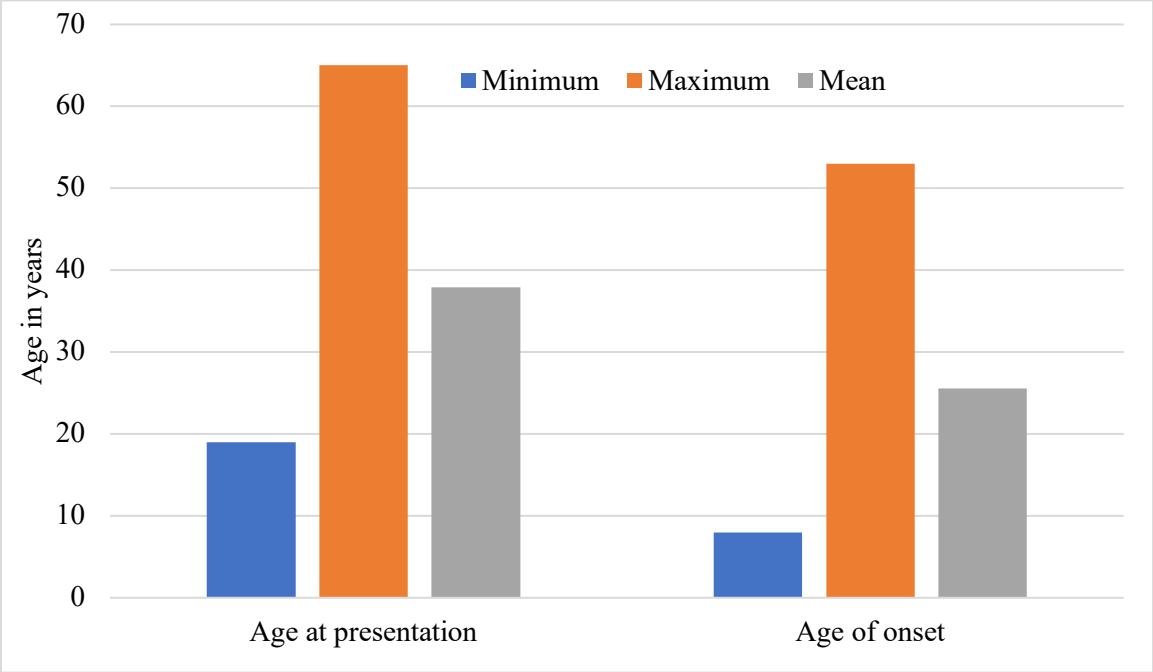


Table 4:- Distribution of subjects according to age at presentation

Age at presentation	Frequency	Percentage
11-20yrs	2	3.8
21-30yrs	14	26.4
31-40yrs	18	34.0
41-50yrs	11	20.8
>50yrs	8	15.1

The majority of the patients (34%) belonged to the age group between 31-40 years, followed by 21-30 years (26.4%), 41-50 years (20.8%), >50 years (15.1%), and 11-20 years (3.8%).

Graph 4:- Graph showing distribution of subjects according to age at presentation

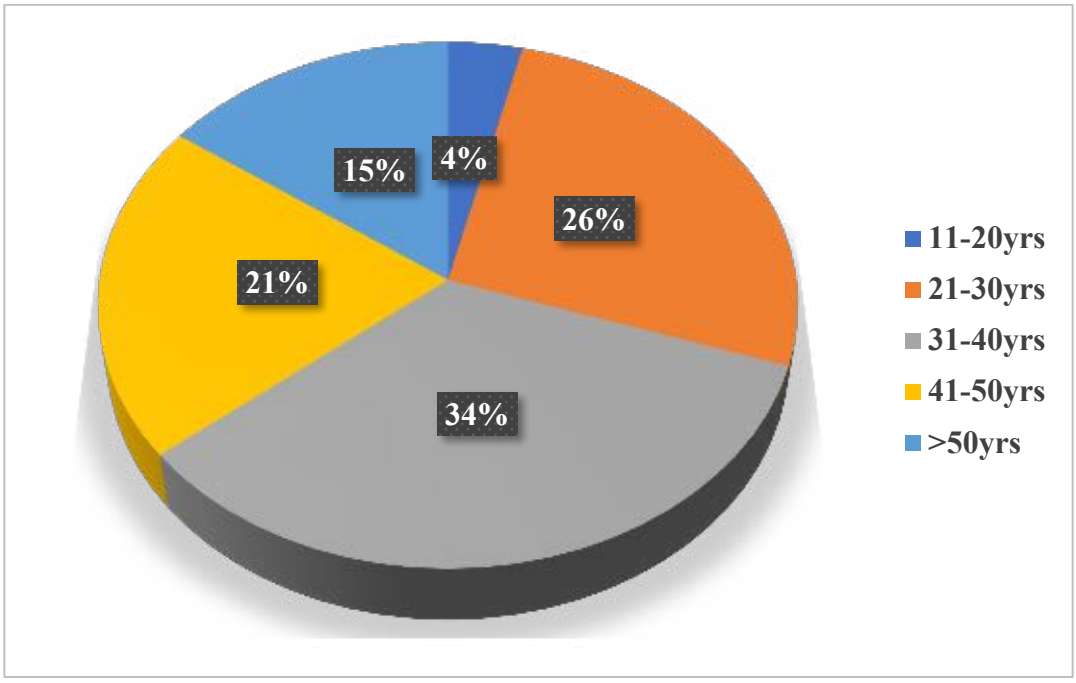


Table 5:- Distribution of subjects according to age of onset

Age of onset	Frequency	Percentage
<10yrs	2	3.8
11-20yrs	18	34.0
21-30yrs	19	35.8
31-40yrs	11	20.8
>40yrs	3	5.7

35.8% of the participants had the age of onset between 21-30 years, 34% had 11-20 years, 20.8% had between 31-40 years, 5.7% had > 40 years, and 3.8% had <10 years.

Graph 5:- Graph showing distribution of subjects according to age of onset.

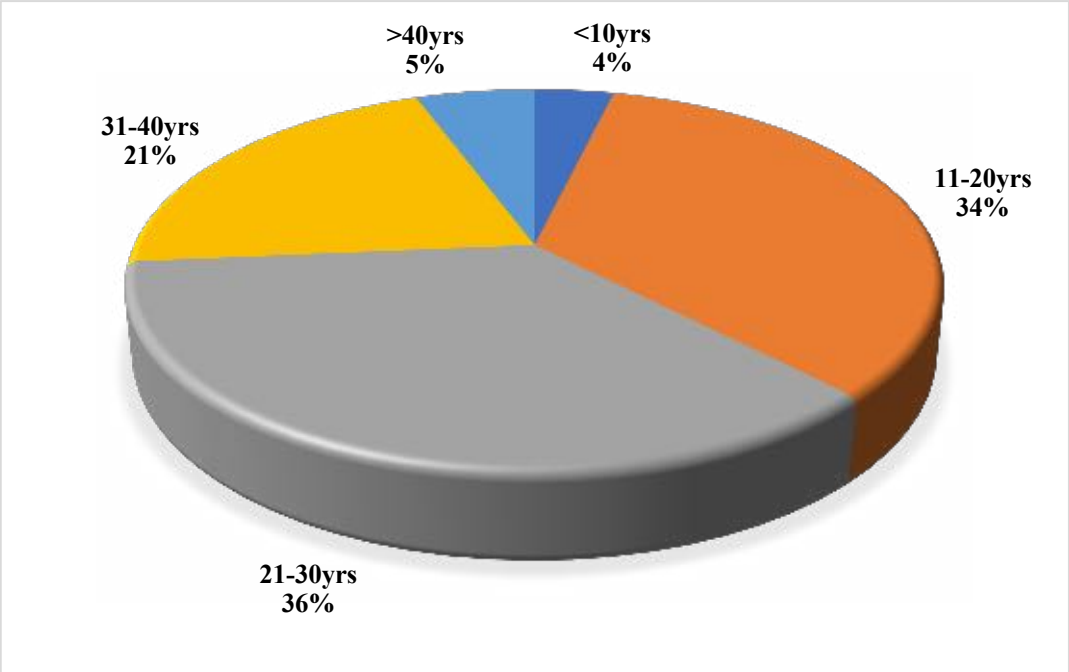


Table 6:- Frequency distribution according to the duration of the disease

Age of the patients	No. of patients	Percentage
<6 months	1	1.9
6 months – 1 year	7	13.2
>1 – 5 years	12	22.6
>5 years – 10 years	10	18.9
> 10 years	23	43.4

In this study, 43.4% of the patients had duration of the disease more than 10 years which is followed by 22.6% had between >1-5 years.

Graph 6:- Graph showing distribution according to the duration of disease

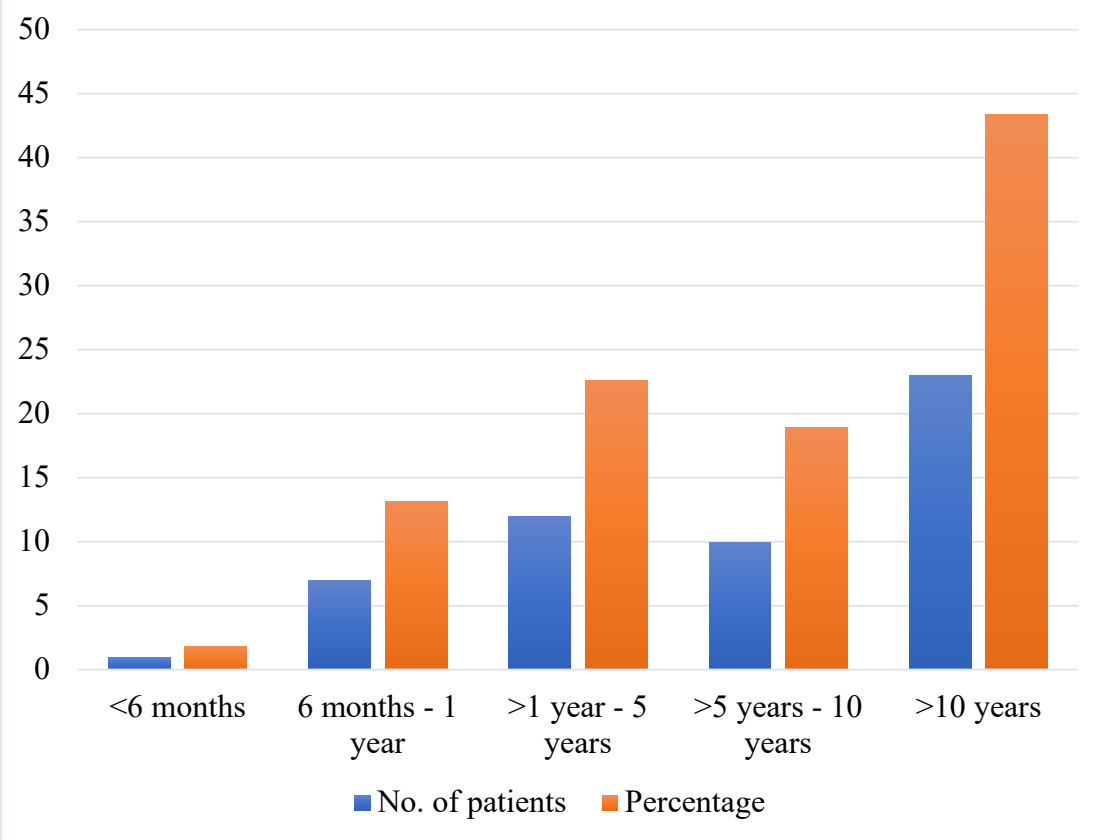


Table 7:- Distribution of patients according to the associated comorbid conditions.

Associated comorbidities	Frequency	Percentage
No	30	56.6
Yes	23	43.4
Total	53	100.0

43.4% of the participants had associated comorbid diseases, and 56.6% didn't have any comorbidities.

Graph 7:- Graph showing distribution according to the associated comorbid conditions.

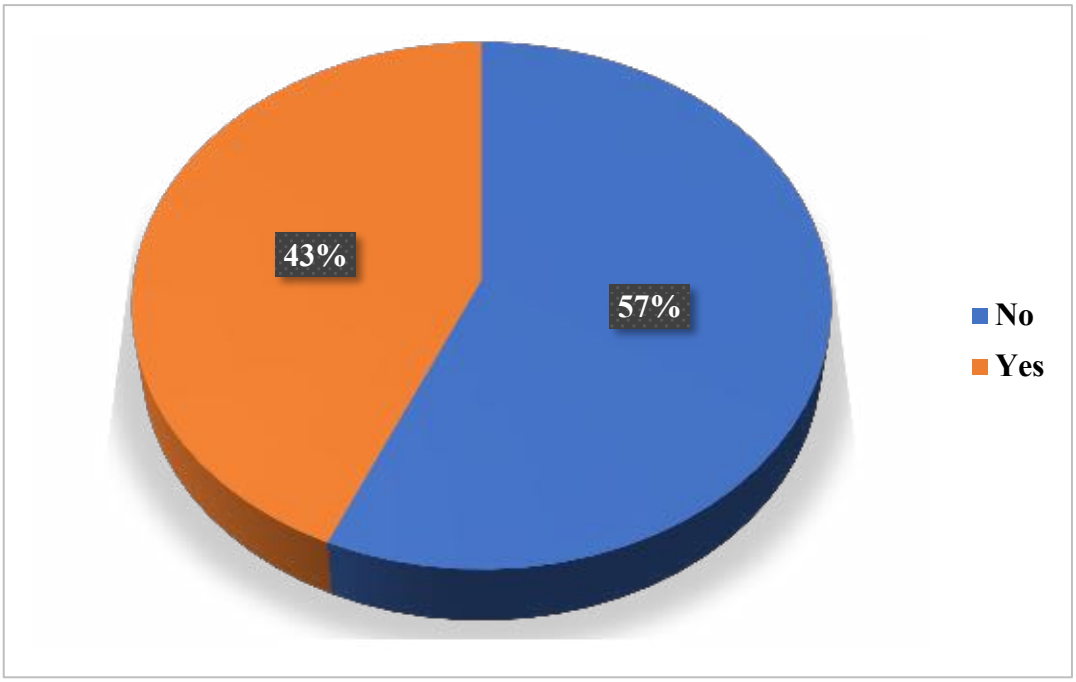


Table 8:- Frequency distribution of associated comorbidities.

Comorbid conditions	Frequency	Percentage
Alopecia areata	2	3.77
Guttate psoriasis	1	1.88
Canities	1	1.88
Diabetes mellitus	5	9.43
Hypertension	3	5.66
Leukotrichia	3	5.66
Hypothyroidism	13	24.52

24.5% of the patients had Hypothyroidism, 9.43% had Diabetes mellitus, 5.6% had Hypertension, 5.6% had Leukotrichia, 3.77% had Alopecia areata. 1.8% of the patients had Guttate psoriasis, and 1.8% had Canities.

Graph 8:- Graph showing Frequency Distribution of associated comorbidities.

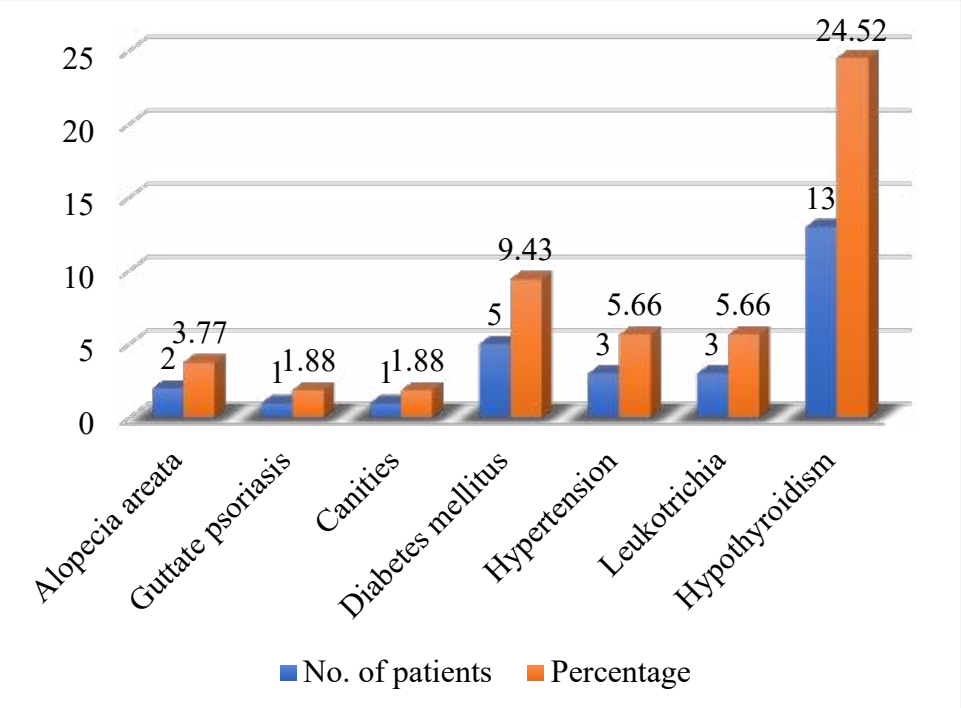


Table 9:- Distribution of patients according to family history.

Family history	Frequency	Percentage
No	43	81.1
1st degree	7	13.2
2nd degree	2	3.8
3rd degree	1	1.9

13.2% of the patients had a positive 1st degree family history, 3.8% of the patients had 2nd degree, 1.9% had 3rd-degree family history, and 81.1% of the patients didn't have any positive family history.

Graph 9:- Graph showing distribution of patients according to family history.

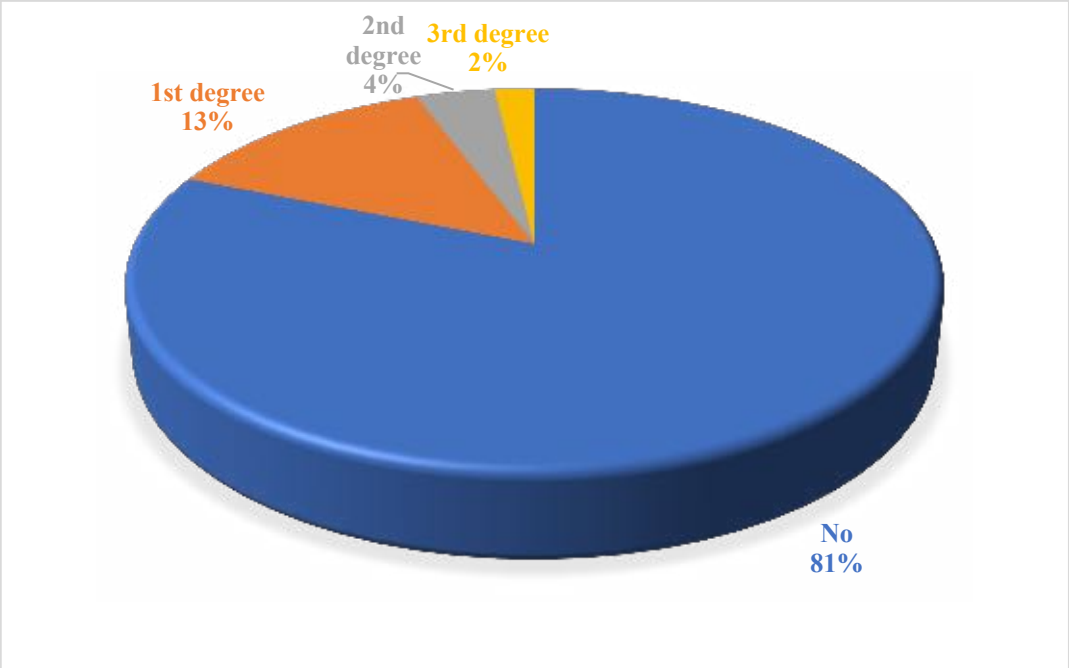


Table 10:- Distribution of subjects according to Koebner's phenomenon.

Koebner's phenomenon	Frequency	Percentage
No	43	81.1
Yes	10	18.9
Total	53	100.0

Koebner's phenomenon was present in 18.9% of the patients.

Graph 10:- Graph showing distribution of participants according to Koebner's phenomenon.

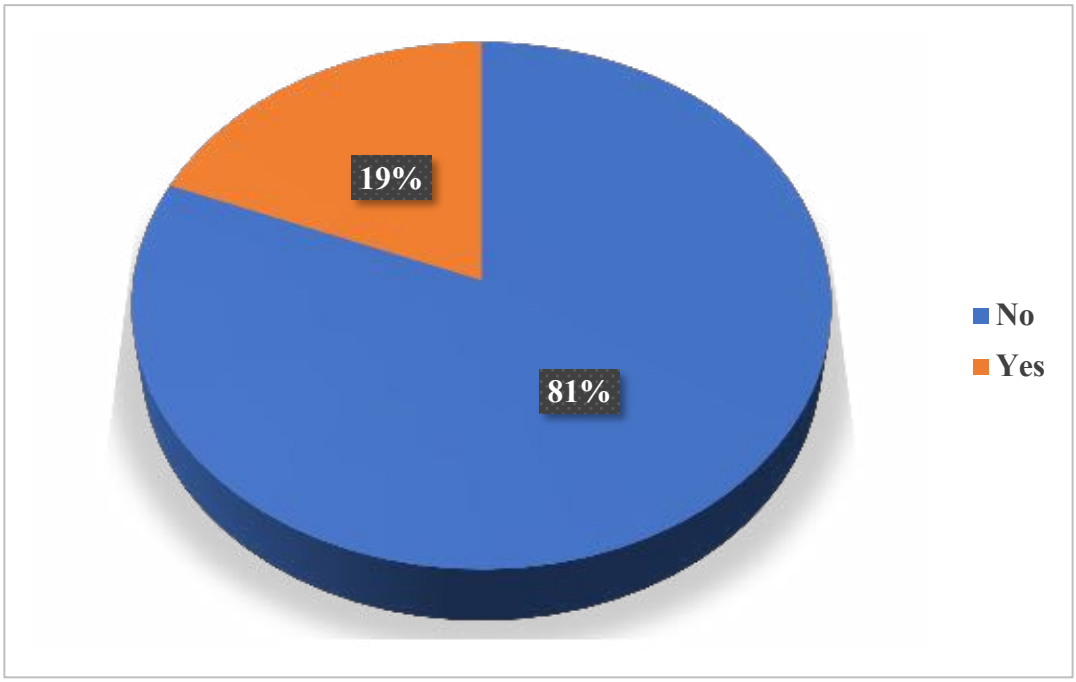


Table 11:- Distribution of patients according to Spontaneous repigmentation.

Spontaneous repigmentation	Frequency	Percentage
No	43	81.1
Yes	10	18.9
Total	53	100.0

Spontaneous repigmentation was present in 18.9% of the patients.

Graph 11:- Graph showing distribution of patients according to Spontaneous repigmentation.

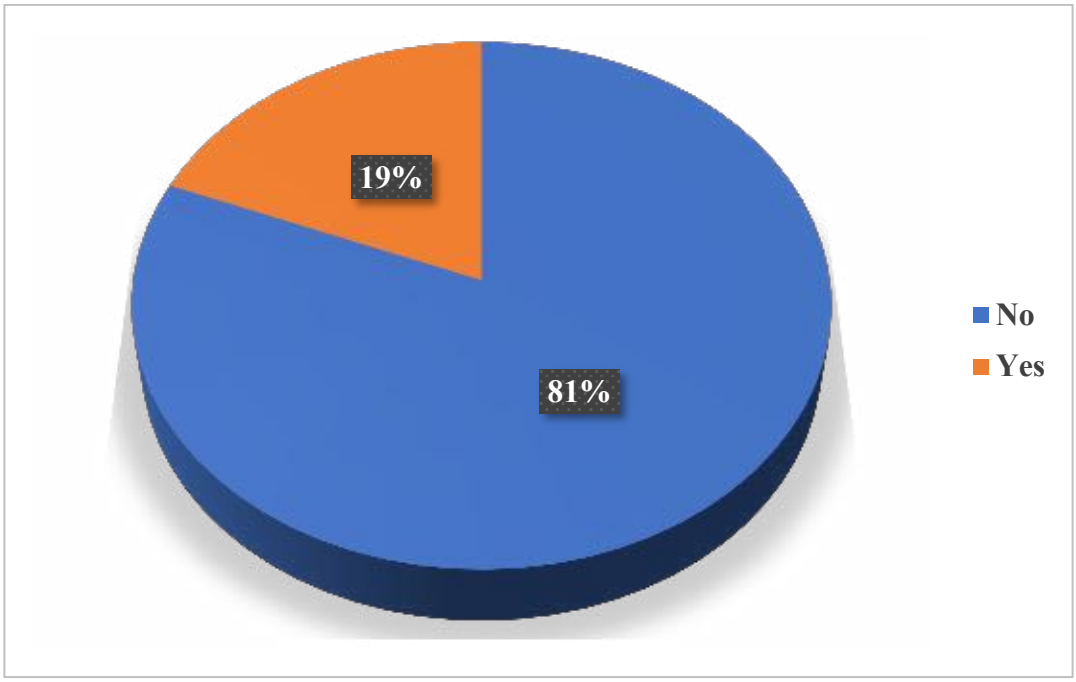


Table 12:- Frequency distribution of site among patients.

Sites	Frequency	Percentage
Face	9	17
Lip	13	24.5
Ear	2	3.8
Chin	1	1.9
Acral	16	30.1
Chest	2	3.78
Abdomen	9	17
Back	9	17
Shoulder	1	1.9
Arm	6	11.3
Forearm	10	18.9
Hand	5	9.4
Thigh	4	7.5
Legs	19	35.8
Feet	2	3.8
Genital	2	3.8

Most common site involved was legs (35.8%) followed by acral region (30.1%) and lips (24.5%).

Graph 12:- Graph showing Frequency Distribution of site among subjects.

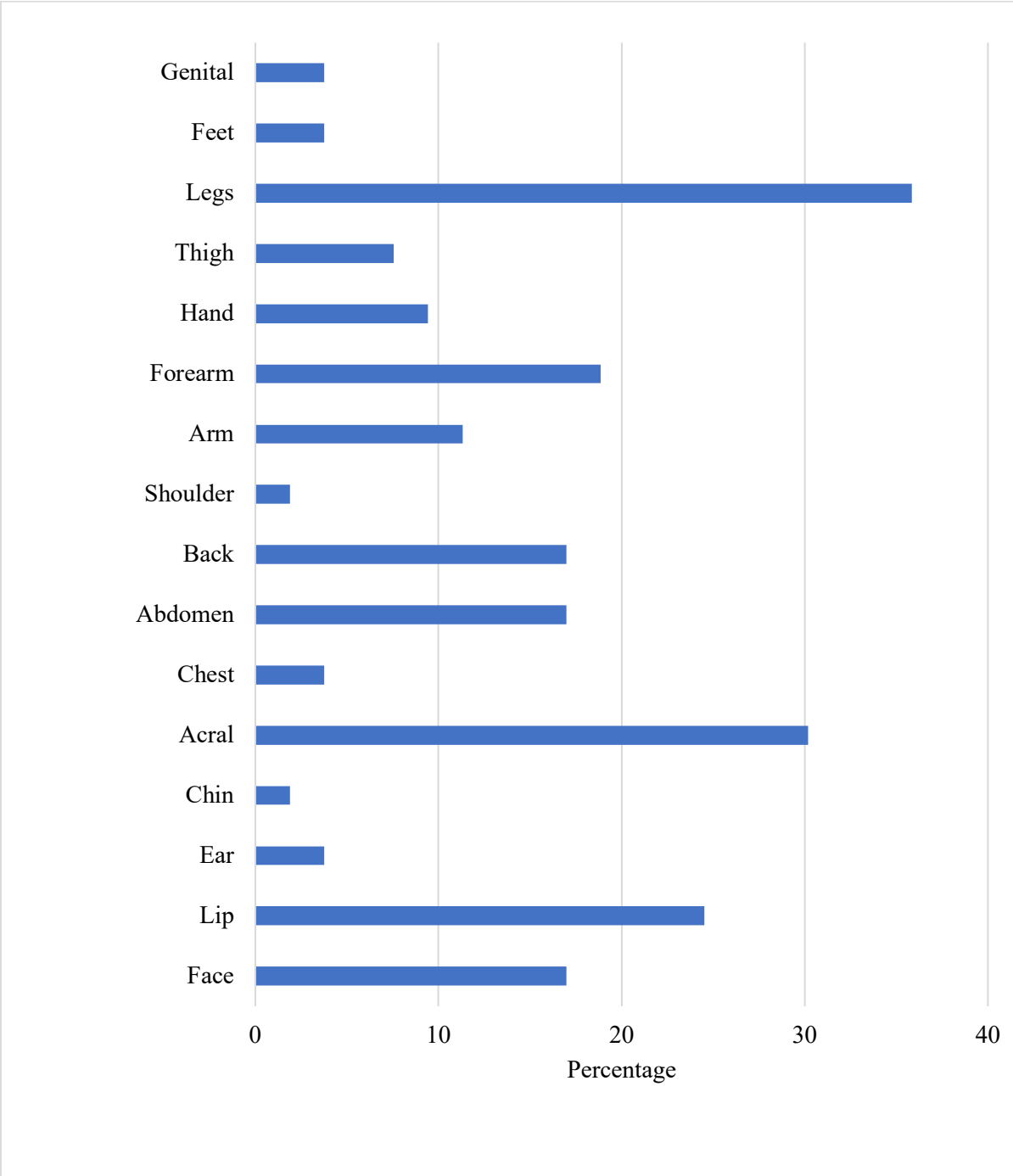


Table 13:- Comparison of Age at presentation, Age of onset according to associated diseases

	Associated diseases	Mean	SD	P value
Age at presentation	Yes	42.57	13.238	0.018
	No	34.30	10.574	
Age of onset	Yes	25.65	10.426	0.945
	No	25.47	9.066	

The mean age at presentation was 34.30 years in patients who didn't have associated comorbidities, and the mean age at presentation was 42.57 years in the patients who had associated comorbid conditions. There was a statistically significant difference between the age at presentation and associated diseases. The mean age of onset was 25.47 years in those patients who didn't have associated comorbidities, and the mean age of onset was 25.47 years in patients who had associated diseases. There was no statistically significant difference between the age of onset and associated diseases.

Graph 13:- Graph showing Comparison of Age at presentation, Age of onset according to the associated diseases

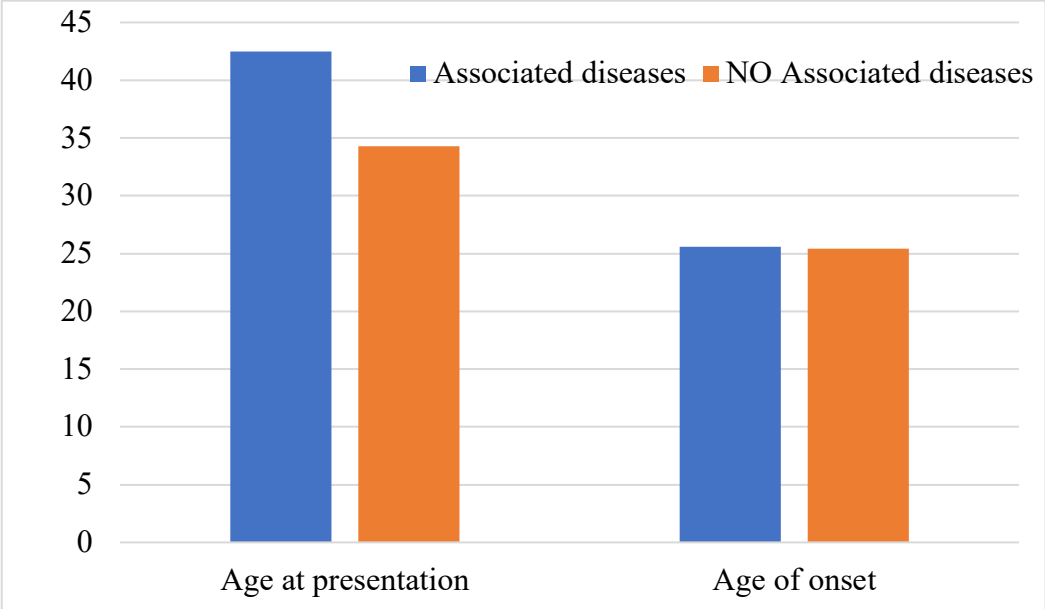


Table 14:- Comparison of Spontaneous re-pigmentation, Koebner's phenomenon according to the associated diseases

	Associated diseases		P value
	No	Yes	
Spontaneous re-pigmentation	5	5	0.730
	50.0%	50.0%	
Koebner phenomenon	3	7	0.082
	30.0%	70.0%	

There was no statistically significant difference between Koebner's phenomenon and associated diseases. There was no statistically significant difference between Spontaneous re-pigmentation and associated diseases.

Graph 14:- Graph showing Comparison of Spontaneous re-pigmentation, Koebner phenomenon according to the associated diseases

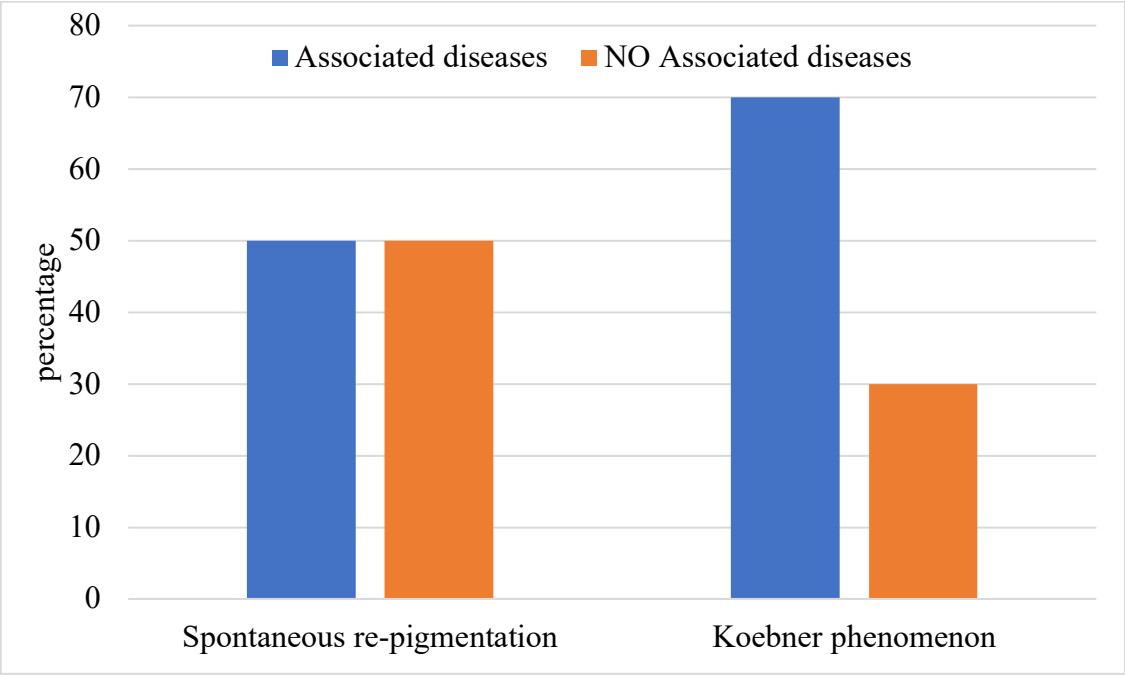
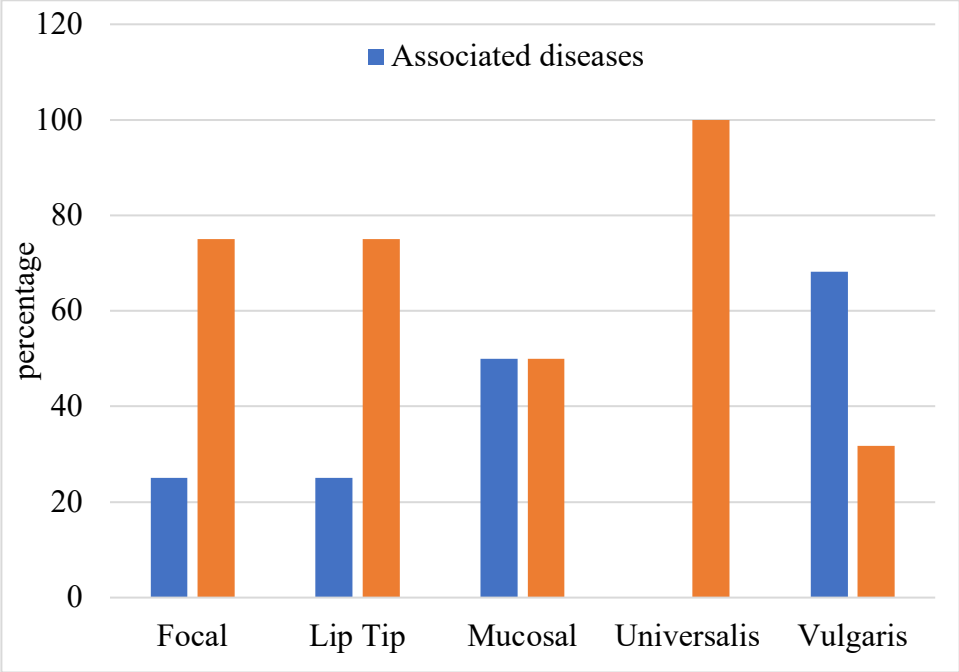


Table 15:- Comparison of types of vitiligo according to the associated diseases

Types of vitiligo	Associated diseases	
	No	Yes
Focal	9	3
	75.0%	25.0%
Lip tip	12	4
	75.0%	25.0%
Mucosal	1	1
	50.0%	50.0%
Universalis	1	0
	100.0%	.0%
Vulgaris	7	15
	31.8%	68.2%

68.2% of the patients with vitiligo vulgaris had associated comorbidities, 25% of the patients with Focal and Lip tip type had associated comorbidities. There was a statistically significant difference between types of vitiligo and associated diseases (P value 0.032).

Graph 15:- Graph showing Comparison of types of vitiligo according to the associated comorbidities.



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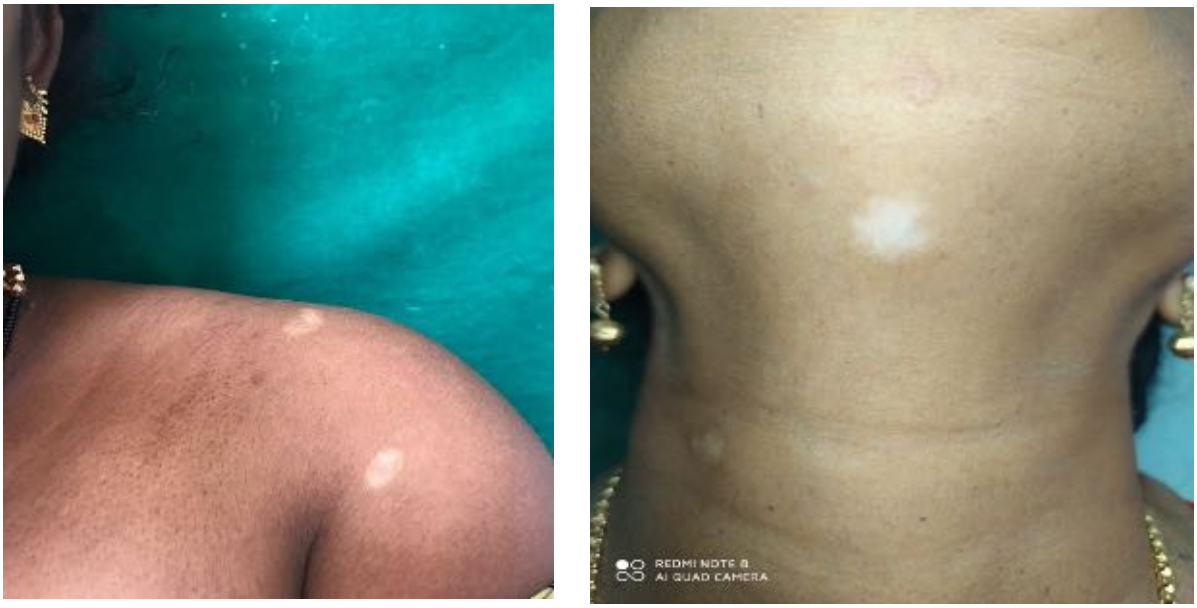

Figure 7: Focal vitiligo over the shoulder and neck

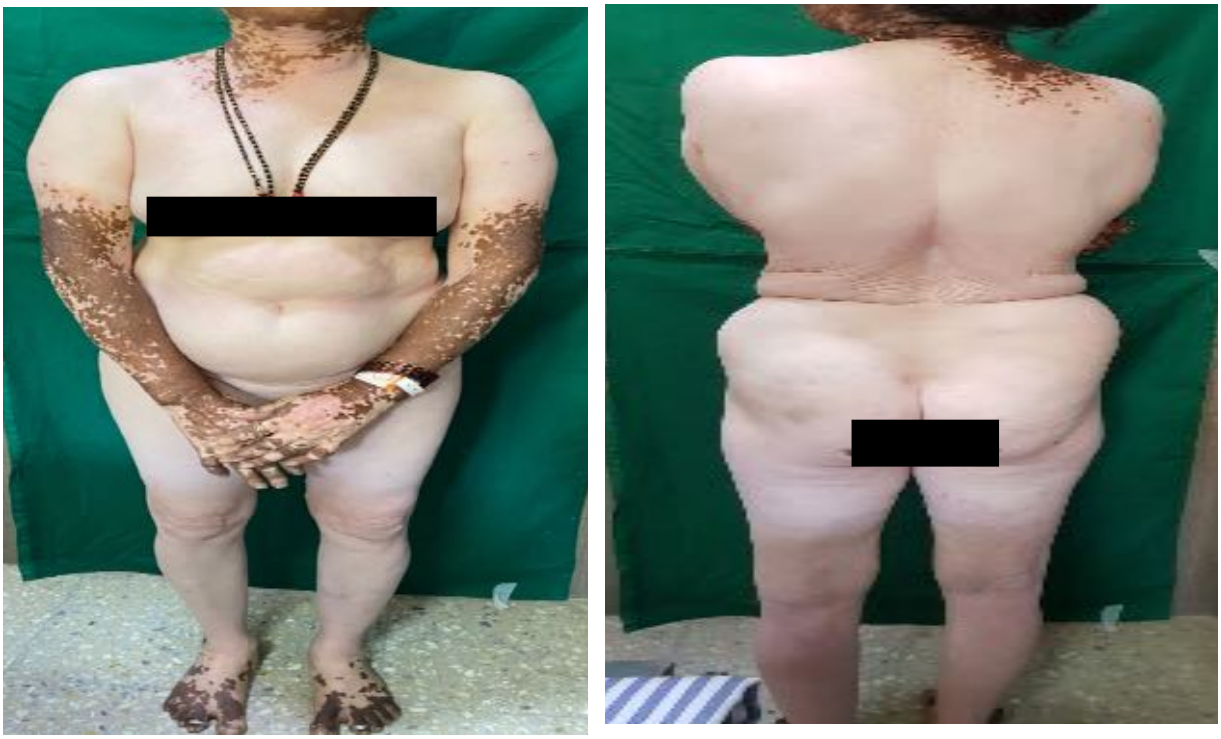

Figure 8: Vitiligo universalis

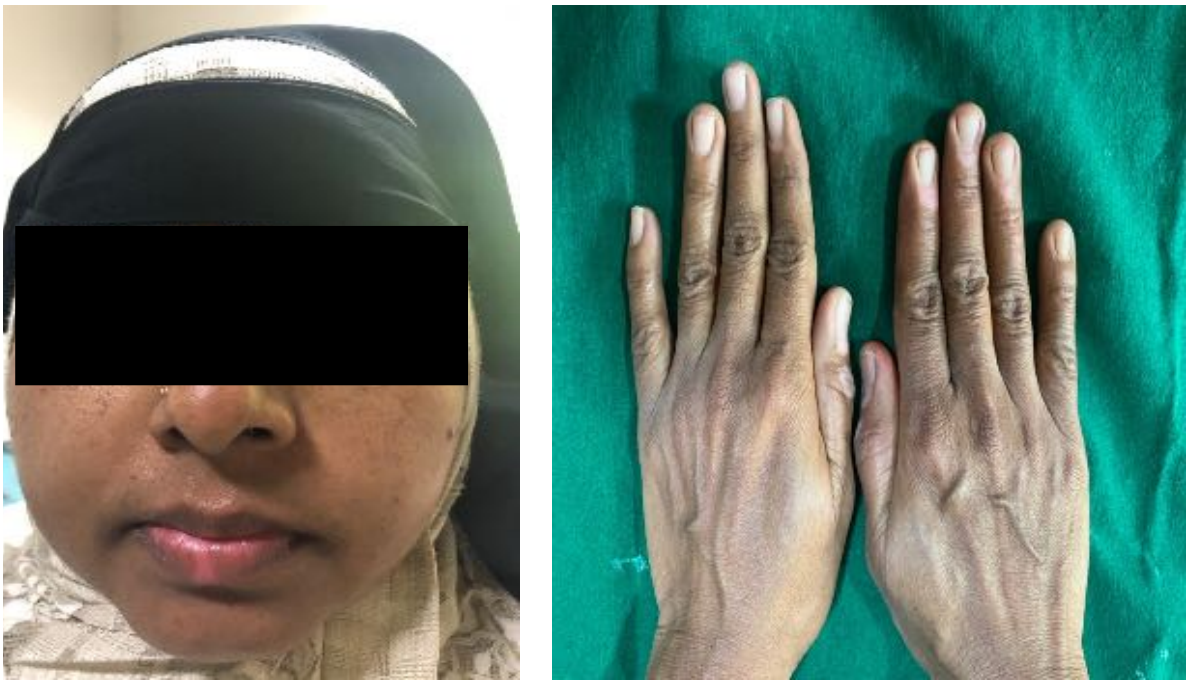

Figure 9: Lip tip vitiligo

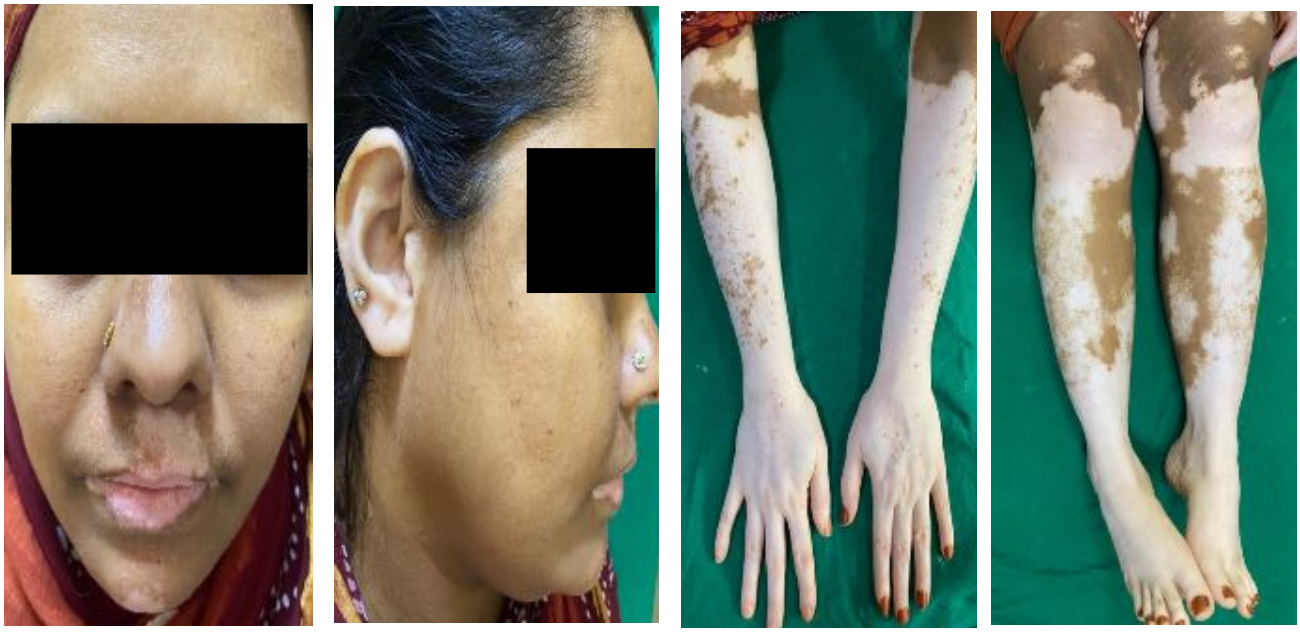

Figure 10: Vitiligo vulgaris

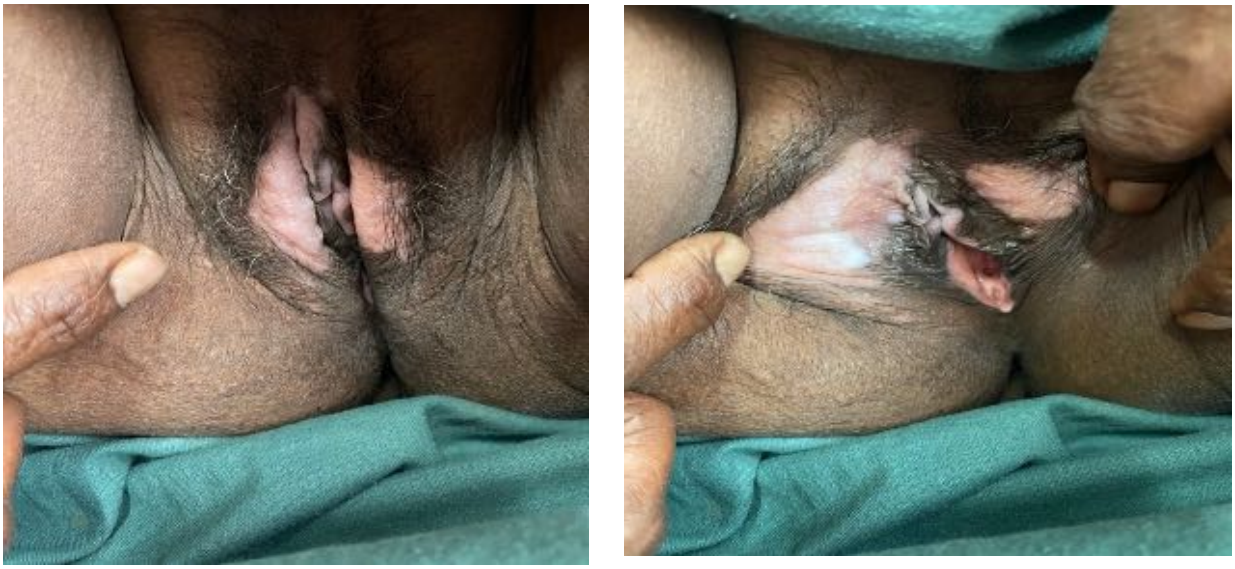

Figure 11: Mucosal vitiligo

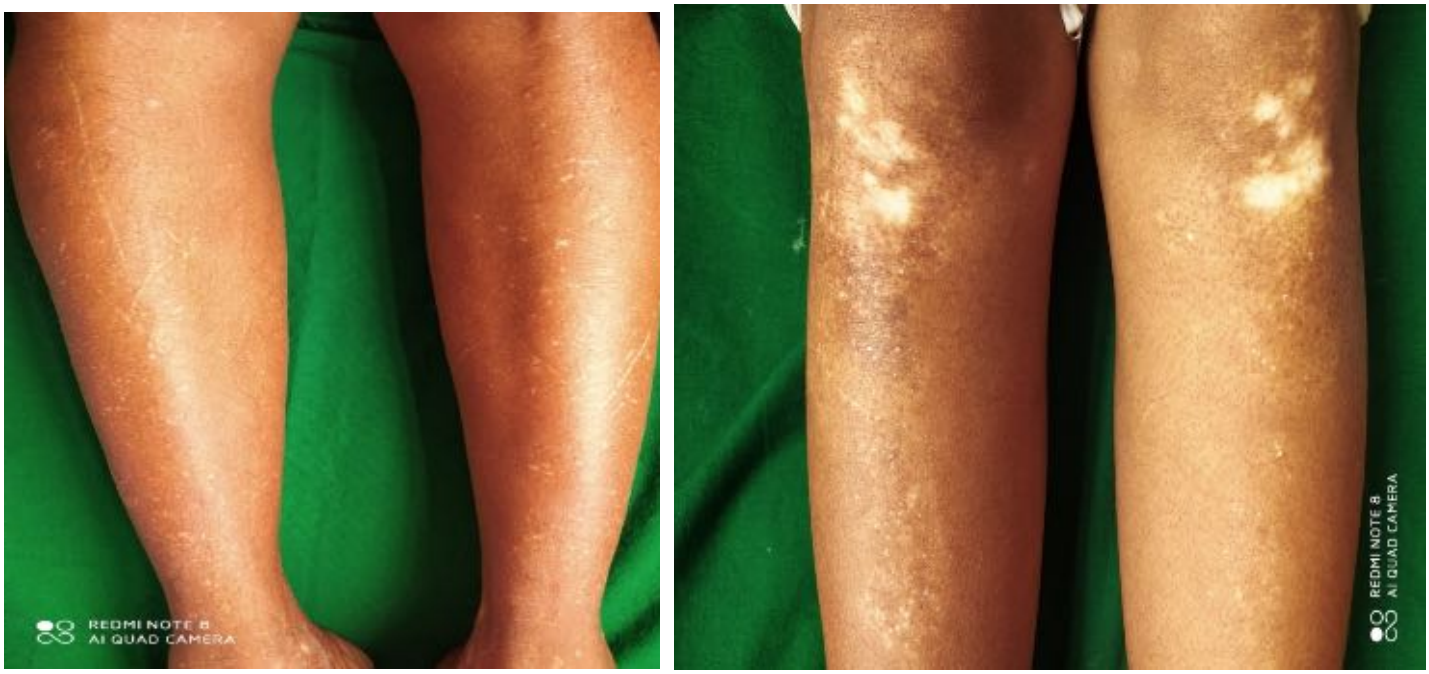

Figure 12: Koebner's phenomenon

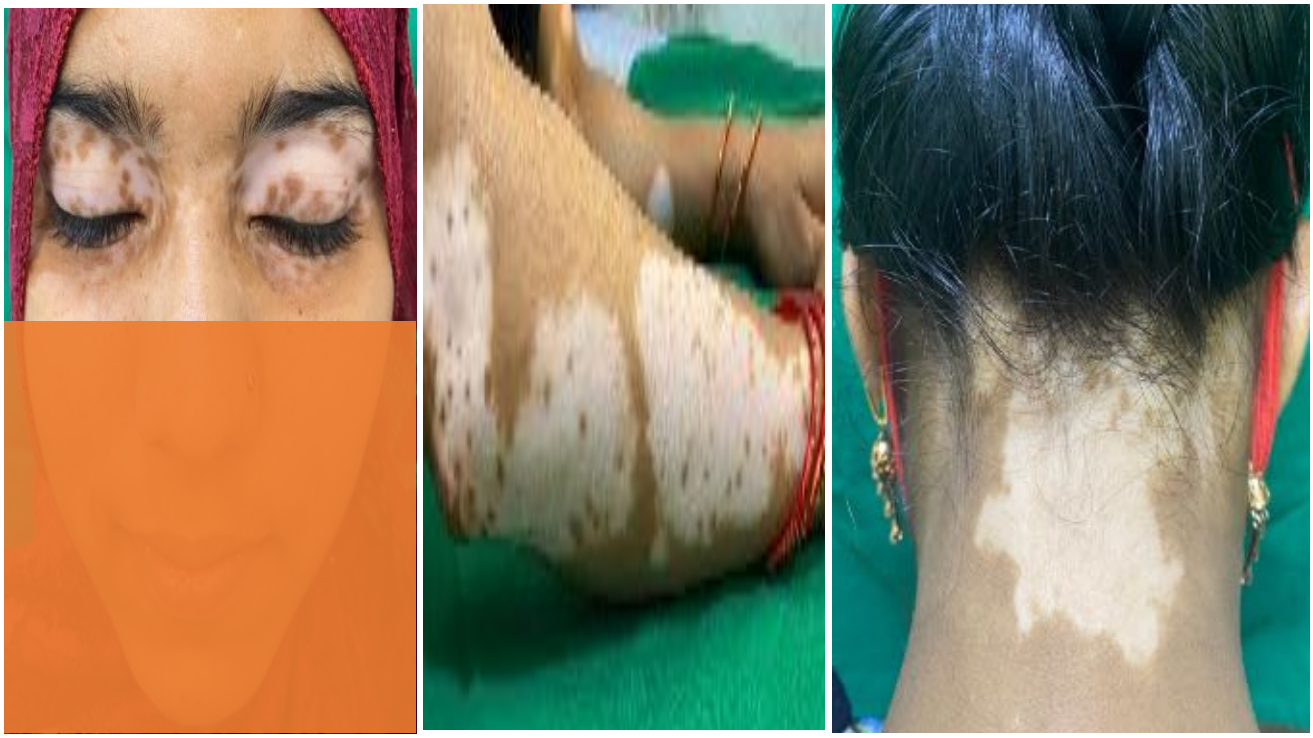

Figure 13: Spontaneous repigmentation

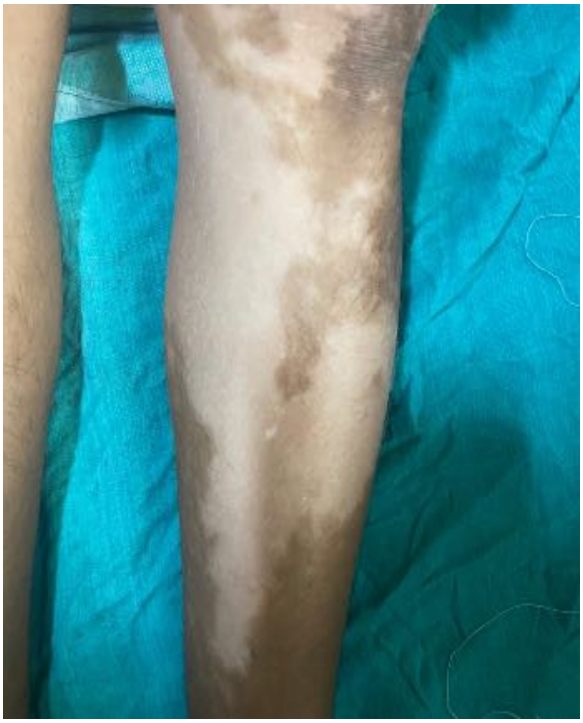

Figure 14: Leukotrichia over the vitiligo patch

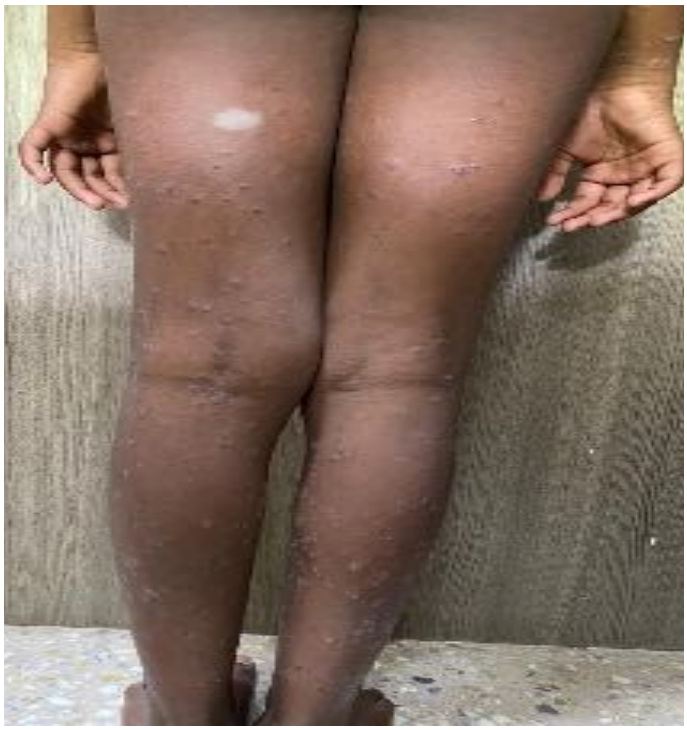

Figure 15: Vitiligo patch over the left thigh with guttate psoriasis

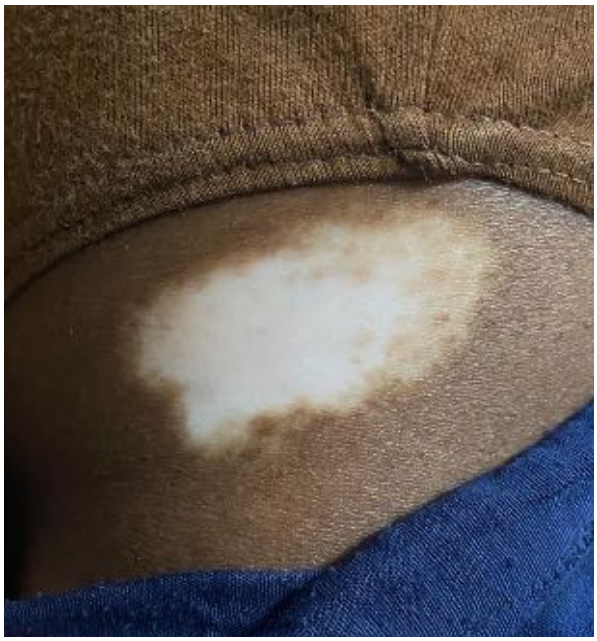

Figure 16: Trichrome vitiligo with leukotrichia

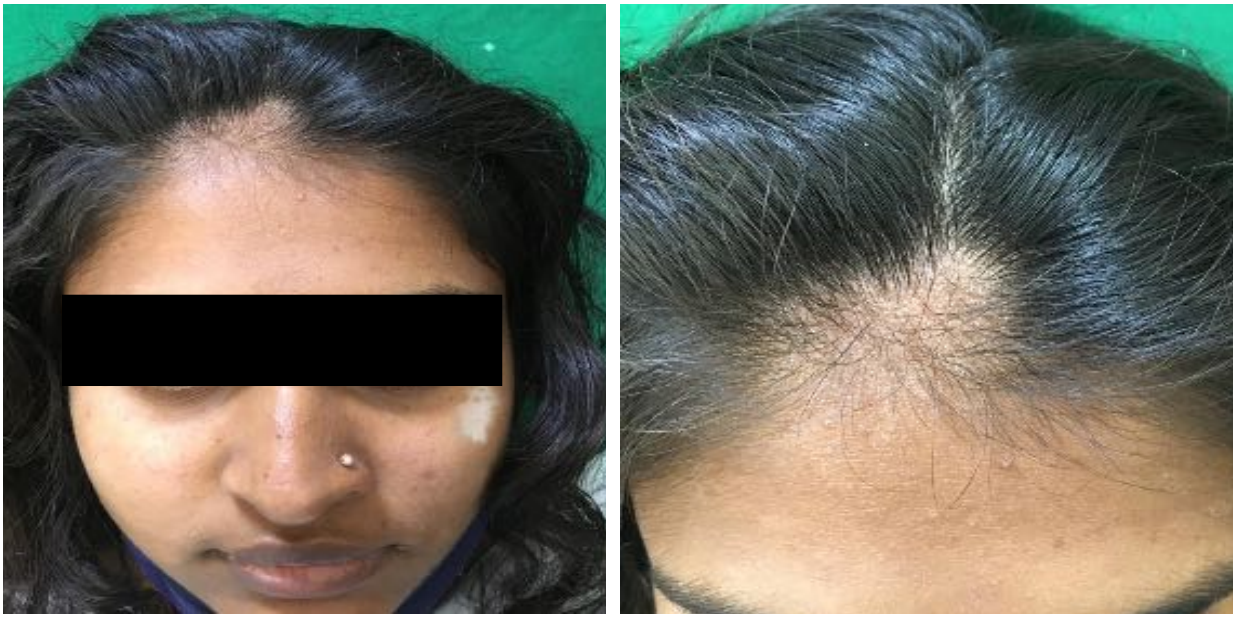

Figure 17: Focal vitiligo with alopecia areata

DISCUSSION

Vitiligo is an acquired pigmentary disorder with well-defined macules and patches, characterized by depigmentation due to loss of melanocytes.[9] There is no difference in the rate of occurrence according to race or skin type. Women are more affected two times than males, which may be attributed to their health-seeking behaviour for cosmetic reasons.[4] The change in skin color in this disease condition causes a significant psychological impact on the patient's quality of life, especially in female patients with dark-skinned. The etiology of vitiligo is multifactorial.[4]

This cross-sectional analytical study was aimed to explore the clinical types of vitiligo and associated co-morbidities in adult female patients with vitiligo.

A study conducted by Mahajan VK et al. observed that the prevalence of vitiligo was higher in female than male patients, and most of the patients belonged to the age group of ≤ 20 years, followed by aged ≤ 12 years, mean age of onset was 20.5 years.[104] Similarly Vora RV et al. observed that female constituted more than male, maximum patients were in the age group between 21-30 years of age, 11-20 years were the most common age group where age of onset was seen.[105]

But in our study, most of the participants belonged to 31-40 years, subsequently 21-30 years of age. This is in concordance with a study by Chinthaamani KPR. where increased prevalence was seen in the age group of 31-50 years; the majority were female patients, commonest age of onset was 11-30 years which was seen earlier in males than females.[106]

We found that the age of onset varies from 8 years to 53 years, with the mean age of onset 25.55 $\pm$ 9.583 years in our study, which is comparable with a hospital-based study in Saudi Arabia conducted by Fatani M.I. et al. where the mean age of onset was 24.5 years.[107] These values were lower than the mean age of onset 29.6 ± 20.6 years which was observed in one of the tertiary care center, Kerala.[108]

Another study showed that most of the patients had late-onset vitiligo i.e., onset after 10 years of age. However, patients with early-onset vitiligo (onset before 10 years of age) had involved more body surface area, moderately to extremely severe disease, longer disease duration, Koerner's phenomenon, and halo nevus.[109]

In a study conducted in Turkey, most of the participants were females, 37 and 10 years were the mean age at presentation and age of onset, respectively. The most common type was vulgaris; 55% of the patients had associated autoimmune disease, amongst which Hashimoto thyroiditis was the most common.[110]

Duration of the disease varies from 4 months to 45 years, 43.4% of the patients had duration of more than 10 years in this study. In our study, the most common type of vitiligo was vitiligo vulgaris; similar findings were found in other studies.[111,112]

18.9% positive family history was observed in this study, among which 13.2% were in first-degree relatives, 3.8% in 2nd degree, and 1.9% in 3rd degree. It is comparable to the survey by Shanker SK et al. showed 20% of the patients had a positive family history, 8.75% had first-degree relatives, second-degree relatives 7.5%, and third-degree relatives

3.5%.[103] Whereas in a study by Dave S et al., the percentage of positive family history was low; it was seen in only 15 patients out of 199 total patients (7.5%).[113]

In this study, the most common triggering factor was physical trauma, i.e., Koebner's phenomenon, seen in 18.9% of the patients. This finding is high as compared to other studies. Fatani M.I. et al. found that 2% of the patients shown to have physical factors were the commonest precipitating factors.[107]

Trichrome vitiligo was seen in only three patients (5.7%) in our study, which is equivalent to 7.3% found in female vitiligo patients shown in a survey conducted by Altaf H et al.[114] In contrast, Arycans' et al. reported 66.3% of the participants had trichrome lesions in their study sample.[115]

Spontaneous repigmentation was seen in 18.9% of the female adult vitiligo patients in our study, which indicates a good prognosis. This finding is comparable with the previous research, which showed the rate of repigmentation was 22% of the vitiligo patients.[107]

Because easy visibility of depigmented white vitiligo patches, especially in darker toned skin, may significantly impact patients' quality of life and psychological trauma. Social stigma leads to discrimination, a marital problem, low self-esteem, prevent from job opportunities and social isolation, especially in female patients.[116]

In our study, 43.4% of the participants had associated comorbid conditions, and we noted that hypothyroidism (24.52%) was the most common association with vitiligo, followed by Diabetes milletus (9.43%), Hypertension, and Leukotrichia (5.66%). Suman S et al. reported that 18.5% of the total participants had associated comorbidities, among which

thyroid disease was 12%, following which leukotrichosis in 9.5% and diabetes mellitus in 3% patients.[117]

The percentage of association of comorbidities is higher in one of the Italian studies, as shown by Ingordo V et al.; they reported that 41.5% had associated comorbidities and that autoimmune thyroiditis was the primary association.[118]

A nationwide study in Taiwan showed an increased chance of psychiatric morbidities and increased risk of obsessive-compulsive disorders, manic disorder, bipolar disorder, and schizophrenia in patients with vitiligo.[119] A case-control study reported hearing loss in 12 ears of 7 patients (17.5%). With the optical coherence tomography (OCT), ocular abnormalities were found in 19 eyes of 15 patients (37.5%).[120]

In this study, we found the most common site involved was the legs, followed by the acral region. But another study showed that the face and upper limbs were the most common site of onset. In a study in Saudi Arabia, the most common site was the right lower limb and face.[107]

A study in Gujarat conducted by Laddha NC showed significantly higher TNF-α levels in female patients and patients with active vitiligo. Its levels were elevated in generalized vitiligo as compared to localized vitiligo. Also revealed that TNF- α promoter polymorphisms may be genetic risk factors for susceptibility and progression of the disease.[74]

Several different treatment modalities have been tried. A study by Sriram R showed that the efficacy of 0.03% tacrolimus with topical corticosteroids (mometasone furoate) is better than 0.03% tacrolimus alone in terms of reduction in total body VASI score.[121]

In one of the retrospective studies, an oral mini pulse dose of dexamethasone 2.5 mg twice weekly was given until the cessation of disease activity (or for a maximum of 6 months). It showed that improvement was achieved by 91.8%, with varying degrees of repigmentation observed in all patients, and relapse was seen only in 12.3%.[122]

An open-label single-arm interventional study conducted with ciclosporin 3 mg/kg for 12 weeks was shown to halt the progression of vitiligo in 61% of patients and reported being improved remarkably Vitiligo Area Scoring Index (VASI).[123]

CONCLUSION

- Our study suggests that the majority, 41.5% of the participants, had vitiligo vulgaris followed by lip tip type (30%).
- 43.4 % of all female adult patients with vitiligo had associated co-morbidities.
- Among all co-morbidities, hypothyroidism (24.52%) was the most common associated condition.
- Associated co-morbidities were frequently observed in vitiligo vulgaris patients than in any other clinical types of vitiligo.
- Early screening for these comorbid diseases is essential to start early diagnosis and prompt treatment, especially in patients with vitiligo vulgaris.
- Clinicians should explain and counsel the patients with vitiligo about its associations with other diseases and the importance of its screening.

SUMMARY

- Patients with adult female vitiligo attending the Department of Dermatology at R.L Jalappa Hospital attached to Sri Devaraj Urs Medical College, Tamaka, Kolar from January 2020 to July 2021 were identified and a total of 53 cases satisfying the inclusion criteria were included in the study.
- A detailed history was taken, a thorough examination was done, and all the findings were documented as per proforma.
- The majority of the participants belonged to the age group of 21-30 years.
- Age of onset varies from 8 years to 53 years of age.
- The majority 43.4% had a duration of the disease >10 years.
- Positive family history was seen in 18.9% of the patients, and most of them were first-degree relatives.
- The majority, 41.5% of the patients had vitiligo vulgaris.
- 43.4% of the participants had associated comorbidities among which Hypothyroidism was seen in 24.52%, Diabetes mellitus in 9.43%, Hypertension in 5.66%, Leukotrichia in 5.66%, Alopecia areata in 3.77%, Guttate Psoriasis in 1.8% and canitis in 1.8%.
- Koebner's phenomenon was seen in 18.9%.
- Legs was the most common site involved (35.8%).
- Spontaneous repigmentation was seen in 18.9% of the patients.
- 31.8% of the vitiligo vulgaris patients had associated comorbidities.

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ANNEXURE I

PROFORMA

Patient particulars **Case number**

NAME:	**OP/IP NUMBER**
AGE& GENDER:	**DATE:**
ADDRESS:	**Occupation:**

CHIEF COMPLAINTS:

HISTORY OF PRESENT ILLNESS:

1. Age of Onset:
2. Site of onset:
3. Duration:
4. Any Associated Symptoms: itching/ burning/ pain
5. Mode of spread: static/ growing/ receding
6. Use of any drugs before onset of illness
7. Aggravating factors: Occupational/ hobbies/ trauma/ drug/ work/ sunlight/ emotional factors/ menstruation/ pregnancy/ food/ cosmetics/ chemicals/ any other:
8. Recovery: Some/ good/ poor/ no response
9. Sudden re-pigmentation: yes/ no

PAST HISTORY:

Associated systemic diseases: DM/ HTN/ Thyroid disease/ SLE/ Alopecia areata etc.

Associated cutaneous diseases:

H/o recent major surgery/ major trauma

FAMILY HISTORY:

A. Similar complaints:

B. Other skin problems:

PERSONAL HISTORY:

Diet: veg/ nonveg/ mixed

Bowel/ Bladder habits: regular/ altered.

Sleep- adequate/ disturbed

Appetite-

Habits: smoking/ tobacco chewing/ alcoholism

H/o recent major surgery/ major trauma

TREATMENT HISTORY:

<u>ON EXAMINATION:</u>

1)General physical examination:

Built and Nourishment:

Pallor/ Icterus/ Clubbing/ Cyanosis/ Significant lymph node enlargement/ Edema

Vitals: Temperature-

Pulse -

Blood pressure-

Respiratory rate-

2)Systemic examination:

1. CVS
2. RS
3. PER ABDOMEN
4. CNS

1) Cutaneous examination:

Types of vitiligo

a. Generalized/ Localized
b. Unilateral/ Bilateral
c. Symmetrical/ Symmetrical
d. Universal
e. Acrofacial
f. Segmental
g. Focal
h. Liptip vitiligo
i. Trichrome
j. Quadrichrome

Sites of involvement –

Face

Upper limb

Lower limb

Trunk

Koebner's phenomenon: Yes/ No

Other cutaneous findings if any:

4)Hair examination-

5)Nail examination-

6)Oral / mucosal examination –

INVESTIGATIONS:

1. Complete haemogram,
2. RBS
3. Thyroid function tests
4. CRP, RA
5. ANA
6. Skin biopsy wherever required
7. Other tests if required

ANNEXURE II

Consent form – A CROSS SECTIONAL STUDY ON THE ASSOCIATION OF CO-MORBIDITIES IN ADULT FEMALE PATIENTS WITH VITILIGO IN TERTIARY HEALTH CARE CENTRE, KOLAR

I, Mr./Mrs./Ms._____, aged _____years, S/D/o _____, & a resident of _____

_____
_

, do hereby declare that I am voluntarily giving my consent to participate/ let my son/ daughter to participate in the study of "A CROSS SECTIONAL STUDY ON THE ASSOCIATION OF CO-MORBIDITIES IN ADULT FEMALE PATIENTS WITH VITILIGO IN TERTIARY HEALTH CARE CENTRE, KOLAR".

I have been explained in my own language about the nature of my skin condition, its prognosis, the treatment options available & their respective side effects. I have also been explained to my full satisfaction, in my own language about the procedure involved in the study. I have been explained that my refusal to consent is however not going to affect my / my patient's right to receive treatment from the department.

I do hereby declare that I will provide complete medical history of the disease, allow myself/ my patient to undergo clinical examination & allow collection of necessary clinical material by the treating Doctor.

I also hereby accord consent to be photographed as & when necessary for the purpose of the study. However, these photographs have to be used only for teaching purposes,

clinical presentations & publications but not for advertisements or any other commercial purposes.

Name of the declarant / guardian _____

Signature of the declarant / guardian _____

Name of the witness:
_____

Signature of the witness: _____

Name & Signature of the investigator: _____

Date:_____
Place: SDUAHER, KOLAR

ANNEXURE III

PATIENT INFORMATION SHEET

Study title: A CROSS SECTIONAL STUDY ON ASSOCIATION OF CO MORBIDITIES IN ADULT PATIENTS WITH VITILIGO IN TERTIARY HEALTH CARE CENTRE, KOLAR.

Study site: R.L Jalappa Hospital, Tamaka, Kolar.

Aim:

1) To assess association of co morbidities in adult female patients with vitiligo.
2) To evaluate various clinical patterns in adult female vitiligo patients.

Vitiligo is the whitish discolouration of skin and mucous membrane affecting both gender, which gives psychological distress affecting quality of life of the patient, and it is also associated with other diseases. It is not contagious and not transmitted from one person to another by touching, eating together, sharing clothes.

Vitiligo can be diagnosed by clinical examination and biopsy in doubtful cases. Other associated diseases can be diagnosed by clinical history, examination and blood test. So early diagnosis of vitiligo with other associated diseases can be made and an early intervention is worthful.

Please read the following information and discuss with your family members. You can ask any question regarding the study. If you agree to participate in this study we will collect information (as per proforma) from you. Relevant blood investigations will be

carried out if required. This information collected will be used for dissertation and publication only.

All information collected from you will be kept confidential and will not be disclosed to any outsider. Your identity will not be revealed. The expenses required for the above investigations will be funded by the study investigator. This study has been reviewed by the Institutional Ethics Committee and you are free to contact the member of the Institutional Ethics Committee. There is no compulsion to agree to this study. The care you will get will not change if you don't wish to participate. You are required to sign/ provide thumb impression only if you voluntarily agree to participate in this study.

For any further clarification you can contact the study investigator:

Dr. Savana Waikhom

Mobile no: 7005747392

E-mail id: sabanawaikhom@gmail.com

ANNEXURE IV

KEY TO MASTER CHART

1) Occupation

Housewife – 1

Nurse – 2

Student – 3

Teacher – 4

2) Types of vitiligo

Focal – 1

Lip tip – 2

Mucosal – 3

Totalis – 4

Vulgaris - 5

3) Age at presentation (years)

11-20yrs – 1

21-30yrs – 2

31-40yrs – 3

41-50yrs – 4

>50yrs – 5

4) Age of onset (years)

<10yrs – 1

11-20yrs – 2

21-30yrs – 3

31-40yrs – 4

>40yrs – 5

5) Duration of the disease

<6 mnths – 1

6 mnths – 1 yr – 2

>1 – 5 yrs – 3

>5 yrs – 10 yrs – 4

> 10 yrs – 5

6) Associated comorbidities

Alopecia areata – 1

Guttate psoriasis – 2

Canitis – 3

Diabetes mellitus - 4

Hypertension – 5

Leukotrichia – 6

Hypothyrodism – 7

7) Family history

1st degree – 1

2nd degree – 2

3rd degree – 3

8) Spontaneous repigmentation

Yes – 1

No – 2

9) Koebner's phenomenon

Yes – 1

No – 2

10) Sites involved

Face – 1

Lip – 2

Ear – 3

Chin – 4

Acral – 5

Chest – 6

Abdomen – 7

Back – 8

Shoulder – 9

Arm – 10

Forearm – 11

Hand – 12

Thigh – 13

Legs – 14

Feet – 15

Genital - 16

SL NO	UHID NO.	OCCUPATION	AGE AT PRESENTATION	AGE OF ONSET	DURATION	TYPES OF VITILIGO	ASSOCIATED DISEASES	FAMILY HISTORY	KOEBNER PHENOMENON	SPONTANEOUS REPIGMENTATION	SITES INVOVED
1	693043	3	2	2	3	5	0	0	2	1	1,7,8,10,13,14
2	678930	1	2	3	2	2	0	0	2	2	2,12
3	712862	3	2	2	3	2	0	0	2	2	2,12
4	835622	2	2	2	3	5	7	2	1	2	1, 12, 11, 10, 14,13
5	714819	1	3	4	2	1	0	0	2	2	4
6	820136	1	3	4	3	1	0	0	2	2	8,11
7	806853	1	2	3	3	2	0	1	2	2	2,12
8	839248	1	3	3	4	1	2,7	0	1	2	8
9	849702	4	2	2	3	2	0	3	2	2	3,12
10	849400	1	3	2	5	5	7	0	2	2	7, 10,11,14
11	589071	1	5	4	5	3	4	0	2	2	16
12	122686	1	2	3	1	2	0	1	2	2	2,12
13	122687	1	5	3	5	5	7	0	2	2	5, 8,13,14
14	882674	1	3	3	5	4	0	0	1	2	1, 6,7,11, 13,14
15	638907	1	4	4	5	1	0	0	2	2	9
16	786731	4	4	5	2	1	1	0	2	2	11, 14
17	838404	1	5	2	5	5	4	0	2	2	7,8,10, 11
18	848093	1	3	2	5	5	7	0	2	2	1, 11,12,14,15
19	862193	1	2	3	4	2	0	0	2	2	2,12
20	634778	1	5	2	5	5	3	1	2	2	1
21	459292	1	3	2	5	5	0	0	2	2	10, 12, 14,15 A
22	893974	1	4	3	5	5	5	0	2	1	5, 11,12
23	588255	1	3	2	5	2	0	0	1	2	2,12
24	943969	1	5	3	5	3	0	0	2	2	16
25	846481	3	2	2	3	2	0	0	2	2	1,15
26	849033	1	3	3	4	5	7	0	1	2	7,14
27	848093	2	3	2	5	1	0	2	2	1	14
28	854840	3	1	1	5	2	6	0	2	2	2
29	778248	3	1	2	2	2	0	0	2	2	2,12
30	608235	1	3	2	5	5	7	1	2	1	7,11,12

31	591744	1	3	3	4	2	0	0	2	2	3,5
32	747752	1	4	3	5	5	7	0	2	2	6,10
33	832376	1	4	3	5	5	4	0	2	2	7,8
34	824831	3	2	1	5	5	0	0	2	1	1,11
35	941910	3	4	4	4	2	5,7	0	2	2	2,14
36	793048	1	2	3	4	5	6,7	1	1	1	13,14
37	911603	1	2	3	2	1	0	0	2	2	1
38	885062	1	3	4	2	2	7	1	1	2	5
39	853907	1	5	5	3	1	0	0	2	2	11
40	590426	1	3	4	3	5	0	0	1	1	14
41	862335	1	5	2	5	5	7	0	1	2	13,14
42	937476	1	5	2	5	5	1,4	0	1	2	11,13,14
43	603346	1	4	3	5	2	0	0	2	2	2,5
44	647401	1	3	4	3	1	0	0	2	2	8
45	679594	1	4	3	5	5	0	0	2	2	1,11
46	678901	3	2	2	3	5	6	0	2	2	2,5,14
47	765980	1	3	2	5	1	0	0	2	2	8
48	675894	3	2	2	4	5	0	0	2	2	7,13,14
49	546783	1	4	4	4	2	7	1	2	2	2,5
50	679805	1	3	3	4	5	0	0	2	1	1,11,14
51	786123	1	3	4	2	5	0	0	2	2	7,8,13,14
52	834185	1	4	4	4	2	I	0	2	2	2,5
53	801262	1	4	5	3	1	5	0	2	2	5

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INTRODUCTION

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