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ABSTRACT

Vitiligo is a common depigmentation disorder characterized by patchy white macules. It has been reported that vitiligo lesions, particularly in exposed areas, such as the face and hands, cause severe psychological distress. Although the classification and outcome of facial vitiligo have been proposed, clinical analyses featuring hand vitiligo are very limited, irrespective of its severe psychological impact. In this study, we investigated hand lesions in nonsegmental vitiligo patients and found that the distribution of hand vitiligo was symmetric, whereas the dominant hand was more frequently affected. Moreover, our clustering analysis newly classified hand vitiligo lesions into four distinct subtypes ($n = 140$): focal/scattered (46.4%), distal digit (31.4%), universal (12.9%), and proximal digit (9.2%) and their clinical characteristics. The focal/scattered type is the most common subtype and exhibits a distinctive prevalence in pediatric cases. The distal digit type was suggested to be associated with smoking or the Koebner phenomenon. The universal type is a distinct subtype, with onset in older age and a poor response to treatment. The proximal digit type is the rarest subtype, with onset at a young age. In conclusion, these findings deepen our understanding of the heterogeneity of hand vitiligo and support the development of personalized treatment strategies.

1 | Introduction

Vitiligo is a common depigmentation disorder characterized by patchy white macules. It is caused by selective loss of melanocytes and is currently considered an autoimmune disease. Vitiligo is classified into two major forms: segmental vitiligo (SV), which occurs unilaterally along the innervation area, and non-segmental vitiligo (NSV), which occurs independently of innervation areas. NSV lesions are often symmetrically distributed; however, the details of this distribution pattern remain unclear. The proposed mechanisms of selective loss of melanocytes include autoimmune responses, melanocyte detachment, and vulnerability of melanocytes to oxidative stress. However, it is not clearly understood how NSV lesions are distributed symmetrically on acral sites such as the hands and feet.

The prevalence of vitiligo has been historically estimated at 0.5%–2% in the worldwide population (Krüger and Schallreuter 2012). However, a recent systematic review and modelling study based on physician-diagnosed cases reported a lower lifetime prevalence of 0.36% (Akl et al. 2024), with notable regional variability and underrepresentation of data from low- and middle-income countries. These findings underscore the need for more inclusive and standardized epidemiological data to better understand the global burden of vitiligo.

Vitiligo not only causes visible pigment loss but also leads to significant psychosocial consequences. The presence of lesions on exposed areas such as the face and hands is associated with greater emotional distress, including shame, anxiety, and depression, which can lead to social withdrawal and low

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Summary

- Hand vitiligo is challenging to treat, with a poorer response to therapy compared to other body sites. Along with facial lesions, hand lesions have a significant psychological impact on patients.
- The lack of a standardized classification hinders precise diagnosis and treatment optimization.
- This study expands on existing knowledge by classifying hand vitiligo into distinct subtypes, revealing differences in distribution and clinical characteristics.
- The findings highlight the need for subtype-specific treatment strategies to enhance therapeutic outcomes in vitiligo management.
- This study introduces a proposed categorization of hand vitiligo lesions into four distinct subtypes: focal/scattered, distal digit, universal, and proximal digit type, providing insights into their distribution patterns and clinical characteristics.

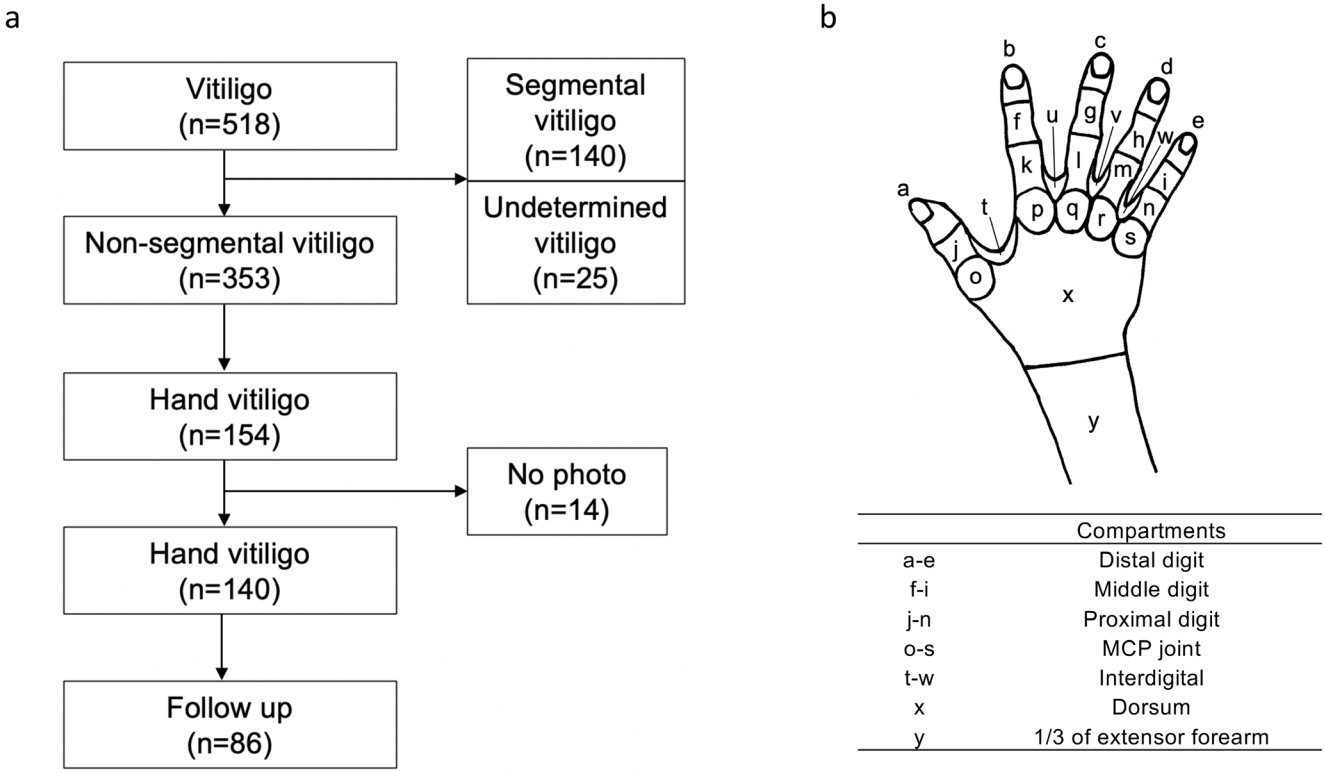
self-esteem (Ezzedine et al. 2015). It has been reported that the hands, in particular, are the most bothersome location among affected sites (Florez-Pollack et al. 2017). A recent study also suggested that psychological burden was particularly high in patients with more than 5% affected body surface area, darker skin color, and lesions on the face and hands (Bibeau et al. 2023). Unfortunately, the face, followed by the acral areas, was reported to be the most frequently affected area (Speeckaert and van Geel 2014). Moreover, lesions on exposed areas, including the face and dorsal digits or dorsal hands, are less responsive to conservative treatment (Narayan et al. 2023). A recent study suggested that facial vitiligo can be classified into three distinct types and also defined the clinical characteristics of each type (Bae et al. 2018). However, a detailed analysis of their anatomical distribution patterns and clinical characteristics is limited, despite the fact that the associated mental burden is very strong, similar to the face.

Given the profound psychological burden and therapeutic challenges associated with acral lesions, we investigated vitiligo lesions from the dorsal digits to the hands and assumed their constant heterogeneity in terms of the distribution patterns and clinical changes using a cluster analysis.

2 | Methods

2.1 | Study Population

We retrospectively reviewed all available photographs and medical records of patients with vitiligo who were referred to our institute between October 2013 and January 2024. Patients with rhododenol-induced leukoderma were excluded from this study. The classifications of the 518 vitiligo patients were as follows: NSV ($n = 353$), SV ($n = 140$), and undetermined vitiligo ($n = 25$). A total of 154 NSV cases (43.6%) with NSV had hand lesions. Of these, 140 patients with NSV with hand lesions, for whom photographic data were available, were enrolled in this



	Compartments
a-e	Distal digit
f-i	Middle digit
j-n	Proximal digit
o-s	MCP joint
t-w	Interdigital
x	Dorsum
y	1/3 of extensor forearm

FIGURE 1 | 140 cases of hand vitiligo patients were enrolled in this study. (a) The flowchart of enrolling patients in this study. (b) The dorsal hand was divided into 25 parts and assessed using an 11- point scale ranging from 0 (uninvolved) to 10 (entirely involved).

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TABLE 1 | Clinical information of the patients enrolled in this study ($n = 140$).

Non-segmental vitiligo		Total, *n* (%)
Gender, *n* (%)		140
Male	75	53.5%
Female	65	46.4%
Age, years [range]	46.9 [1–84]	
Age of onset, years [range]	40.3 [0–84]	
Disease duration, years [range]	6.55 [0–30]	
Following duration, years [range]	2.3 [0–83]	86
Treatment response, *n* (%)		
Improved	28	32.5%
Unchanged	12	14.0%
Exacerbated	46	53.4%

study. We assessed a total of 140 patients with bilateral or unilateral vitiligo hand lesions and additionally evaluated disease activity signs, namely confetti-like depigmentation, the Koebner phenomenon, and hypochromic areas/borders. In addition, 86 patients were followed up with additional photographic data (Figure 1a). As this study did not have a prospective design, the 86 cases followed up with additional photographic data were treated with an undesignated treatment protocol. Therapeutic strategies include topical steroid ointment or topical tacrolimus ointment, mainly in combination with phototherapy (narrowband UVB or excimer light) once a week. Some progressive cases were treated with short-term systemic corticosteroid therapies, including oral minipulse corticosteroid therapy or intravenous methylprednisolone pulse therapy. This study was approved by the ethics committee of Osaka University Hospital (#13421-14). Written informed consent was obtained from all patients.

2.2 | Assessment of Hand Vitiligo Lesions

The entire dorsal hand was divided into 25 parts: (a–e) 1st–5th distal digit, (f–i) 2nd–5th proximal digit, (j–n) 1st–5th distal digit, (o–s) 1st–5th metacarpophalangeal (MCP) joint, (t–w) 1st-4th interdigital area, (x) dorsum, and (y) one-third of the extensor forearm (Figure 1b). Lesions on the palmar side of the hand were excluded from this study because of the difficulty in assessing vitiligo lesions in this area, even with a Wood's lamp, as it is naturally pale in color. The affected level in each compartment was scored on an 11-point scale ranging from 0 (not involved) to 10 (entirely involved). Three blinded dermatologists (K. Y., K. K., and A. T.) independently assessed the lesions, and the final score for each compartment was determined using the median of their points.

2.3 | Statistical Analysis

A clustering analysis was conducted using Shinyheatmap (http://shinyheatmap.com/) (Khomtchouk et al. 2017), with Ward's D2 method selected for its ability to minimize within-cluster variance, making it suitable for identifying lesion distribution patterns. Alternative methods, such as *k*-means and hierarchical clustering, were considered, but Ward's D2 provided the most stable and clinically interpretable results (accessed on 18th May 2024). For comparisons between two independent groups, Student's *t*-test or the Wilcoxon test was used, while the Friedman test and Dunn's multiple comparisons test were applied for comparisons across multiple groups. These group-level statistical analyses were performed using GraphPad Prism. Regarding the analysis of the distal digit score and smoking, we first conducted univariate analyses to examine crude associations. This was followed by an analysis of covariance (ANCOVA) including age, age at onset, disease duration, sex, clinical subtype, smoking history, and dominant hand as covariates. To identify the most informative predictors while avoiding overfitting, a variable selection procedure using the least absolute shrinkage and selection operator (LASSO) regression was subsequently applied. The variables selected through LASSO were then incorporated into a final ANCOVA model. Finally, stratified analyses across various age thresholds were performed to explore potential age-dependent associations. These multivariate analyses (LASSO and ANCOVA) and stratified analyses were performed using Python (version 3.10.5) on macOS (version 15.5, build 24F74). Code development and execution were conducted in Visual Studio Code (version 1.100.0). p values of < 0.05 were considered to indicate statistical significance.

3 | Results

3.1 | Clinical Information of Enrolled Patients

The mean age of the 140 NSV patients with hand involvement was 46.9 years (range: 1–84 years), and 46.4% of the patients were female. The mean age of onset and disease duration was 40.3 years (range: 0–84 years) and 6.55 years (range: 0–30 years), respectively. The mean follow-up period for the 86 cases with additional photographic data was 2.3 years (range: 0–8.3 years). Among them, 28 (32.5%) showed improvement, 12 (14.0%) remained unchanged, and 46 (53.4%) experienced disease progression during their clinical course (Table 1).

3.2 | Distal Digits Were More Affected in Comparison to Proximal Areas

Visualization of hand vitiligo scores for 140 cases, presented as a heatmap, indicated that the digital area, particularly the distal digits, was affected more frequently (Figure 2a). A Wilcoxon test was performed for the 1st digit, whereas the Friedman test and Dunn's multiple comparisons test were used for the 2nd–5th digits. Each analysis indicated that the scores of the distal digits were significantly higher than those of the proximal digits in the 1st–4th digits (Figure 2b).

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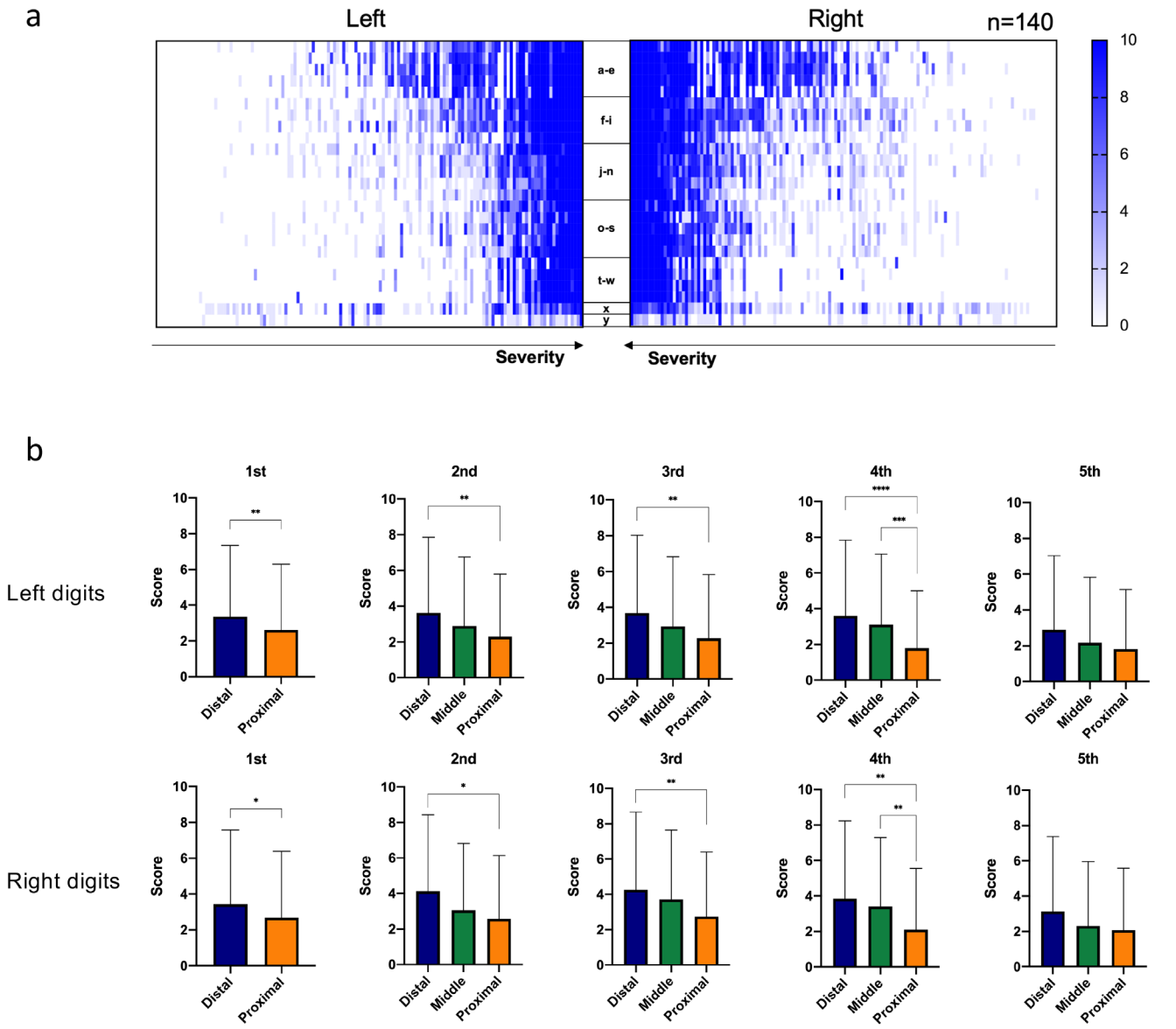

FIGURE 2 | Distal digits were more affected in comparison to proximal areas. (a) The distribution patterns of vitiligo on hands were presented with a heat map. The cases with higher scores were indicated inside each hand. (b) Comparison of scores between distal, middle, and proximal digits. The scores for distal digits were significantly higher than those for proximal digits in the 1st-4th digits. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

3.3 | Although the Distribution of Hand Vitiligo Was Symmetric, the Dominant Hand Was More Frequently Affected

A strong correlation was observed between left and right scores ($R^2 = 0.9319$, $p < 0.0001$) (Figure 3a). The scores for the right hand were significantly higher than those for the left hand ($p < 0.0001$) (Figure 3b). While 63.1% of the cases showed higher scores in their dominant hands, only 27.7% of the cases showed lower scores in their dominant hands (Figure 3c).

3.4 | Lesions on the Distal Digits Were More Severe in Smokers Than in Non-Smokers

Among the 140 patients, clinical records of smoking history were available for 73 patients. In the initial univariate analysis, smokers ($n = 17$) had significantly higher distal scores than non-smokers ($n = 56$) ($p = 0.0443$) (Figure 4a). However, this association did not remain statistically significant in the subsequent multivariate ANCOVA. While the ANCOVA indicated a positive trend between smoking and distal digit score, the association did not reach statistical significance after adjusting for potential confounders. In the LASSO-based ANCOVA model, age, disease duration, involvement of other anatomical sites, and universal-type distribution pattern (identified in the subsequent cluster analysis) were selected as predictors. Among these, only disease duration showed a statistically significant association with the distal digit score ($p = 0.00042$) (Figure 4b). Finally, stratified analysis by age group (≥ 56 vs. < 56 years) revealed a statistically significant association between smoking and distal digit score exclusively in patients under 56 years of age (Figure 4c).

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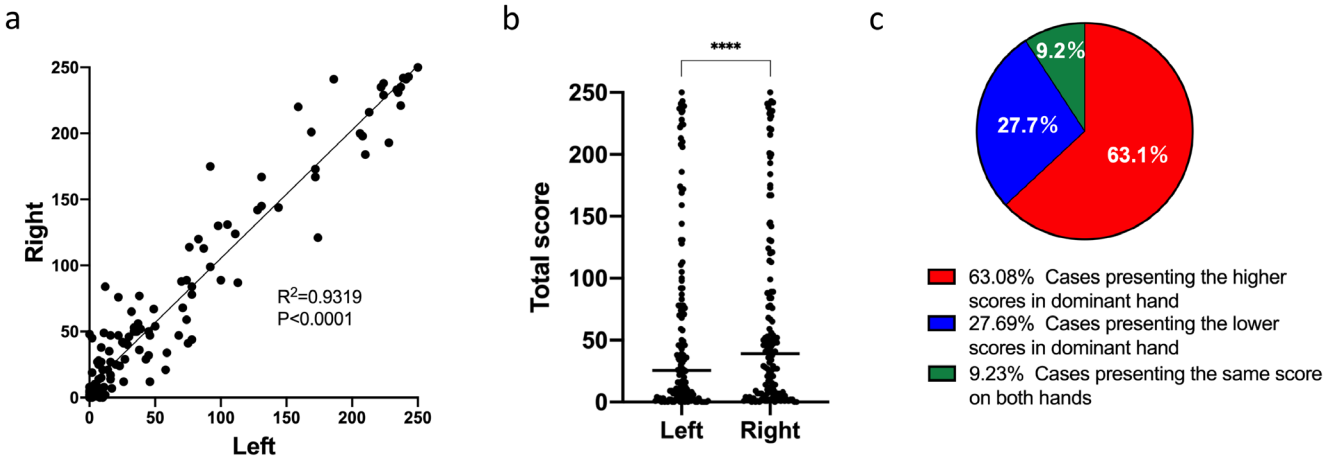
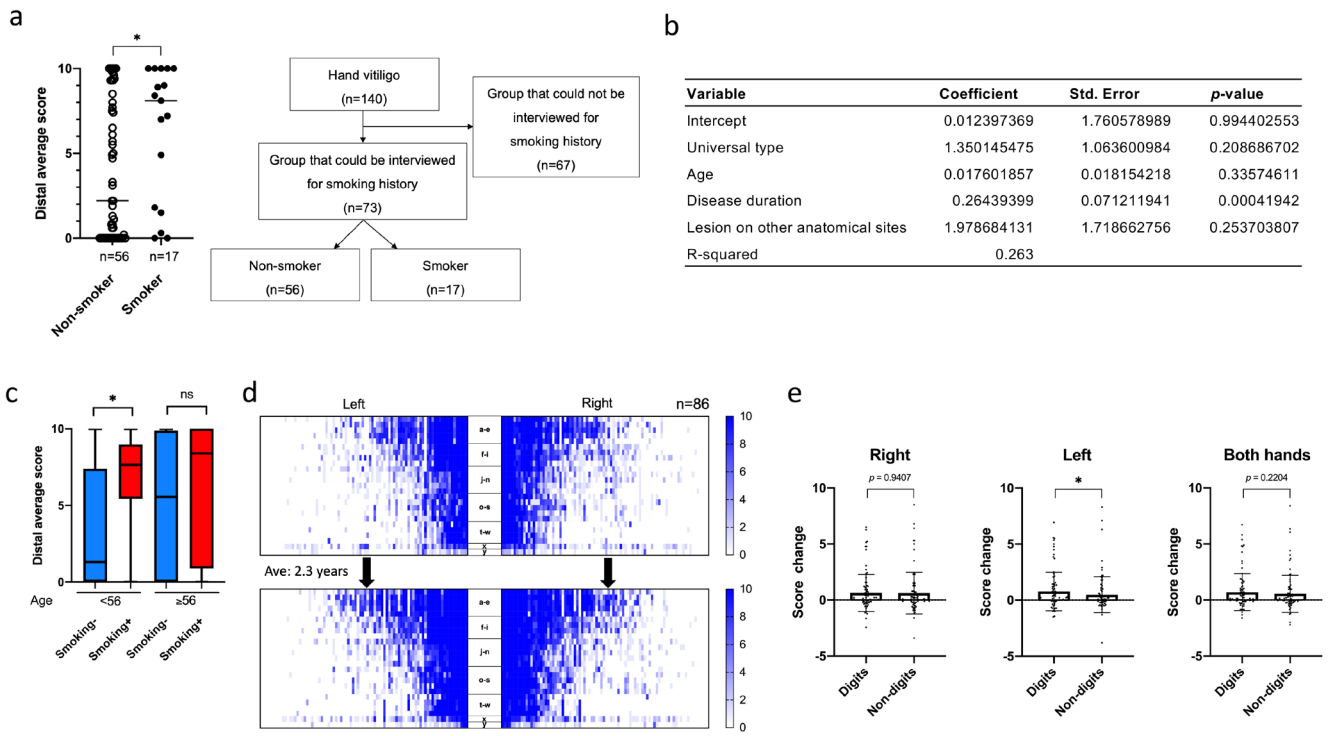


FIGURE 3 | Although the distribution of hand vitiligo was symmetric, the dominant hand was more frequently affected. (a) A strong correlation was found between the scores for the right and the left hand. ($R^2 = 0.9319$, $p < 0.0001$). (b) The scores for the right hand were significantly higher than those for the left hand ($p < 0.0001$). (c) 63.08% of cases showed higher scores in their dominant hand.



Variable	Coefficient	Std. Error	*p*-value
Intercept	0.012397369	1.760578989	0.994402553
Universal type	1.350145475	1.063600984	0.208686702
Age	0.017601857	0.018154218	0.33574611
Disease duration	0.26439399	0.071211941	0.00041942
Lesion on other anatomical sites	1.978684131	1.718662756	0.253703807
R-squared	0.263		

FIGURE 4 | Relationship between smoking and digital vitiligo lesions and temporal progression of hand lesions. (a) The initial univariate analysis revealed that distal scores of smoking cases ($n = 17$) were significantly higher than those of non-smoking cases ($n = 56$) ($p = 0.0443$). (b) In a subsequent analysis of covariance (ANCOVA) using variables selected by the least absolute shrinkage and selection operator (LASSO), disease duration remained a statistically significant predictor of the distal digit score (coefficient = 0.264, $p = 0.00042$). Other selected variables, including age, universal type distribution pattern (identified in subsequent cluster analysis), and involvement of other anatomical sites, did not show statistically significant associations. The model explained approximately 26.3% of the variance in distal digit scores ($R^2 = 0.263$). (c) Upon stratification by age group (≥ 56 vs. < 56 years), a statistically significant association between smoking and the distal digit score was evident only in patients under 56 years of age. (d) Score changes in 86 cases during 2.3 years of average follow-up. (e) The score for the digits tended to deteriorate compared to that for others, especially found in the left hand. *$p < 0.05$.

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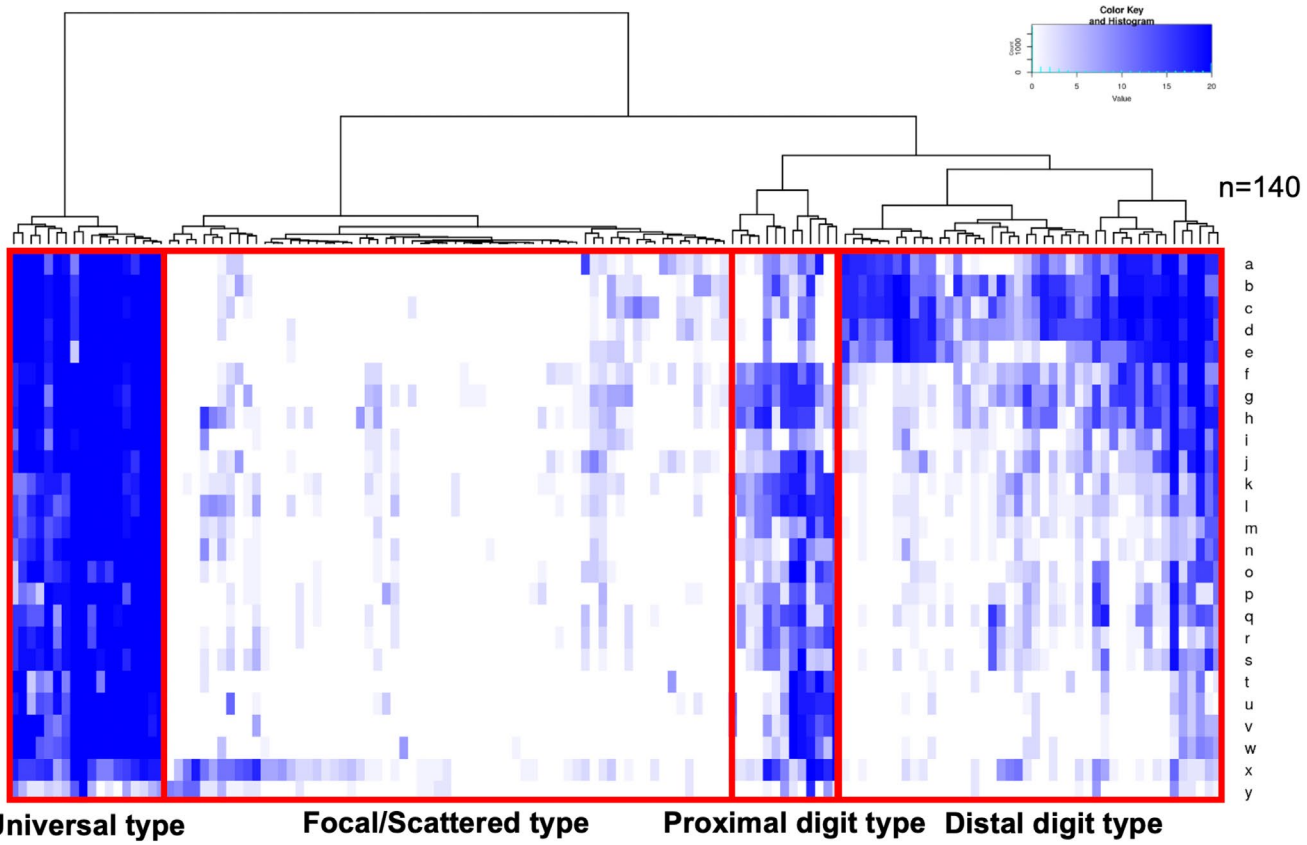

FIGURE 5 | The results of cluster analysis presented as a heat map identified four distinct distribution patterns.

3.5 | Lesional Spreading to the Distal Digits and Interdigital Areas Was Noticeable During the Clinical Course

Visualization of the clinical changes in 86 cases indicated that the distal digits and interdigital areas were frequently affected during the clinical course, with an average duration of 2.3 years (Figure 4d). The score for the digits tended to deteriorate more than that for the non-digital dorsal part of the hand, especially for the left hand (Figure 4e).

3.6 | Hand Vitiligo Lesions Were Clustered Into Four Types

The cluster analysis classified distribution patterns of hand vitiligo into four distinct subtypes ($n = 140$) (Figure 5, Table 2): focal/scattered (46.4%), distal digit (31.4%), universal (12.9%), and proximal digit (9.2%). The focal/scattered type was the most frequent subtype, defined by the presence of a single localized lesion or small multiple scattered lesions. More than two-thirds (68.8%) of the hand vitiligo cases in individuals under 12 years of age fell into this subtype. The distal digit type, in which vitiligo lesions are mainly distributed on the distal digits, was the second most common subtype. A distinguishing feature of this type is the distribution of lesions around the periungual region, particularly on the distal portions of the digits. The universal type (12.9%) was a distinct subtype characterized by extensive depigmentation, the highest age of onset, the poorest treatment response, and the highest prevalence of cases exhibiting activity signs. Lesions in this subtype typically involve more than 80%–90% of the dorsal hands. The proximal digit type is the rarest subtype, with onset at a younger age. In addition to lesions on the proximal digits, this subtype frequently involves the dorsal hands as well. No marked differences were observed in the female-to-male ratio for any subtype.

4 | Discussion

As mentioned in the introduction, hand vitiligo lesions are a major physiological burden for patients because they are extremely unresponsive to treatment, even though they greatly impair quality of life. However, clinical studies specifically focusing on hand lesions are limited. In particular, very few studies have divided the hand area into detailed anatomical regions.

NSV lesions are well known to show symmetrical distribution (Ezzedine et al. 2015) which was consistent with the strong correlation between those of the right and left hands in this study ($R^2 = 0.9319$, $p < 0.0001$) (Figure 3a). While showing a strong correlation between the right and left sides, the scores for the right hand were significantly higher than those for the left hand (Figure 3b). Among the patients enrolled in this study, 65 were interviewed about their dominant hand, and 92.3% were right-handed. In this study, 63.1% of patients had higher scores on their dominant hand. Moreover, we found that lesions were more frequently distributed on the digital areas than on the dorsal hands (Figure 2a) because the Koebner phenomenon might have a certain effect on this distribution pattern. The contribution of the Koebner phenomenon to the

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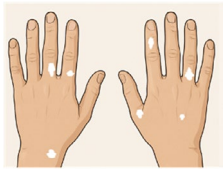
TABLE 2 | Clinical characteristics of the four subtypes of hand vitiligo.

						
***n* (%)**	**Focal/Scattered type**	**Distal digit type**	**Universal type**	**Proximal digit type**	**Total**	***p*-value (group comparison)**
	65 (46.4)	44 (31.4)	18 (12.9)	13 (9.2)	140 (100.0)	
Gender, *n* (%)						
Male	36 (55.4)	23 (52.3)	9 (50)	7 (53.8)	75 (53.5)	0.976
Female	29 (44.6)	21 (47.7)	9 (50)	6 (46.2)	65 (46.4)	
Age of onset, year [range]	41.7 [0–81]	37.9 [3–84]	44.8 [6–82]	34.8 [5–69]	40.3 [0–84]	0.397
Disease duration, year [range]	6.41 [0.1–37]	6.55 [0.05–29]	6.14 [0.3–15]	8.65 [0.5–30]	6.60 [0.05–37]	0.824
Activity signs[a], *n* (%)	9/65 (13.8)	5/44 (11.4)	3/18 (16.7)	2/13 (15.4)	19/140 (13.6)	0.946
Improved cases, *n* (%)	13/40 (32.5)	12/31 (38.7)	2/13 (15.4)	1/2 (50.0)	28/86 (32.6)	0.465
Exacerbated cases, *n* (%)	21/40 (52.5)	16/31 (51.6)	8/13 (61.5)	1/2 (50.0)	46/86 (53.5)	0.939
Remarks	Most common ·2/3 of < 12 years old hand vitiligo cases	Smoking	Poor treatment response	Less common		

[a]Activity signs are including confetti-like depigmentation, Koebner phenomenon, and hypochromic areas/borders.

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distribution of vitiligo lesions has long been recognized by clinicians (Gauthier 1995). Hand lesions are thought to be related to occupational activities and/or hand washing (Taïeb and Picardo 2009). The proposed etiological mechanisms of the Koebner phenomenon in vitiligo include inflammatory signals induced by mechanical stress, deficient melanocyte adhesion, and increased oxidative stress, followed by immunological reactions, which lead to the recruitment of specific $CD8^+$T cells that attract melanocytes in patients (van Geel et al. 2011; Xie et al. 2016). Although the K-VSCOR (Koebner's phenomenon in vitiligo score) study (Diallo et al. 2013) did not identify the hands as significantly associated with the Koebner phenomenon, this could be attributed to the already high baseline prevalence of hand involvement in vitiligo patients, potentially masking additional effects. In our study, greater involvement of the dominant hand likely reflects subclinical mechanical stress consistent with the Koebner phenomenon, which is not adequately captured by existing scoring systems. This may be attributed to the notion that the dominant hand serves as a particularly sensitive anatomical site for detecting subtle mechanical triggers in vitiligo.

We also investigated the relationship between smoking and vitiligo involvement of the distal digits. In univariate analysis, smokers exhibited significantly higher distal digit scores compared to non-smokers, consistent with a previous study reporting more frequent involvement of the distal digits in smokers with hand vitiligo (Enomoto et al. 2024). However, after adjusting for covariates in multivariate ANCOVA, this association was no longer statistically significant, suggesting possible confounding effects. To avoid overfitting and identify the most relevant predictors, we performed ANCOVA using variables selected via LASSO regression. This analysis revealed that disease duration—rather than smoking, age, cluster-defined distribution patterns, or involvement of other anatomical sites—was the only statistically significant predictor of distal digit scores. These findings indicate that the extent of disease progression over time has a stronger influence on distal digit involvement than smoking alone. Interestingly, when stratified by age (≥ 56 vs. < 56 years), smoking was significantly associated with higher distal digit scores only among patients under 56. This implies greater susceptibility to environmental exposures such as tobacco smoke in younger individuals, while in older patients, factors like age-related immune modulation appear to exert a stronger influence, thereby overshadowing the impact of smoking. While our findings echo the association between smoking and distal digit involvement reported by Enomoto et al., the lack of consistent significance across all analytical models in our study highlights the complexity of lifestyle–disease interactions in vitiligo. Furthermore, limitations such as missing smoking data, reliance on clinical records for exposure classification, and the cross-sectional study design constrain the ability to draw causal conclusions. Overall, our analysis suggests that smoking is associated with distal digit involvement in younger individuals and that disease duration emerges as a more robust and consistent predictor. Longitudinal and multicenter studies incorporating comprehensive lifestyle data and biological markers are required to further clarify these associations. Moreover, the digit score tended to deteriorate more than that for the non-digital dorsal part of the hand, especially for the left hand. Although the mechanism of this distribution pattern is still unknown, plausible contributing factors include mechanical stress around the nail plates, hypoxic conditions due to deficient peripheral blood circulation, or oxidative stress substances.

Importantly, the cluster analysis identified four distinct distribution patterns of hand vitiligo. Although the focal/scattered type (46.4%) was the most prevalent subtype, followed by the distal digit type (31.4%), the latter was considered to be the most characteristic phenotype of hand vitiligo lesions because of the variability in the distribution pattern of the focal/scattered type. The universal type not only exhibits poor treatment responsiveness and a tendency for progression, but also exhibits the highest frequency of activity signs (16.7%), including confetti-like depigmentation, the Koebner phenomenon, and hypochromic areas/borders. The proximal digit type exhibited lesions on the non-digital dorsal part of the hand in 92.3% of the cases, suggesting a potential association with anatomically neighboring dorsal hand lesions.

Hand vitiligo lesions are known to be more difficult to treat in comparison to lesions on the face, trunk, and extremities. The response rate to phototherapy is 76% for the face, 40% for the trunk and extremities, and 27% for the axillae, while it is only 4% for the hands and feet (Narayan et al. 2023). Considering the anatomical and physiological differences between the face and distal digits, peripheral blood circulation, oxidative stress, and mechanical stress may play a role in the stabilization of vitiligo lesions. Our group reported that melanocyte-specific $CD49a^+CD8^+$ T cells in vitiligo lesions have the potential to maintain their activity even during systemic corticosteroid therapy (Yokoi et al. 2023). This study indicates that skin-resident T cells recognizing melanocyte-specific antigens might contribute to the maintenance of vitiligo lesions. Differences in the activation state of $CD8^+$ T cells at different anatomical sites may account for variations in the treatment response. A recent study revealed that anatomically distinct fibroblasts are associated with the recruitment of $CD8^+$ cytotoxic T cells that express CXCL9 and CXCL10. Notably, the dorsal hand, back of the foot, and chest were reported to be typical anatomical sites where fibroblasts are activated to produce chemokines (Xu et al. 2022). Therefore, dermal fibroblast activity may influence the distribution patterns of hand vitiligo lesions. Interestingly, a previous report suggested that acral lesions are more frequently observed in patients with autoimmune diseases, including thyroid diseases (Speeckaert and van Geel 2014). This suggests that not only cytotoxic T cells but also various autoimmune reactions, including B-cell activation, might be associated with hand vitiligo lesions.

The present study was associated with several limitations. First, as this was a retrospective study, it was difficult to assess and compare treatment responses for each subtype under identical treatment regimens. Second, lesions in areas other than the dorsal digits or hands were not evaluated, preventing the analysis of potential correlations with lesions in other anatomical regions. Third, patients with a history of smoking were classified as smokers, but information on whether they were current smokers or how many cigarettes they smoked daily was unavailable. Finally, the study's sample size was limited due to its single-center design. Especially, two subgroups (universal and proximal digit types) include fewer than 30 cases. This may limit

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the statistical power and generalizability of the findings. Future studies should focus on validating the proposed classification of hand vitiligo through multicenter prospective studies to ensure its applicability across diverse populations. Additionally, investigating the treatment response of each subtype could provide valuable insights into personalized therapeutic approaches, leading to more effective management strategies. Genetic and immunological analyses are also needed to identify biomarkers associated with specific subtypes, which may help to clarify the mechanisms underlying disease progression and treatment resistance. Furthermore, long-term follow-up studies are helpful in assessing the mutual changes across each subtype and identifying the factors influencing disease stability or exacerbation.

In conclusion, we proposed a categorization of hand lesions in nonsegmental vitiligo patients and explored the relationship between their clinical characteristics and distribution patterns. Our findings suggest that these lesions might be presented not at random, but according to certain patterns. This proposed categorization not only enhances our understanding of the heterogeneity of hand vitiligo but also holds potential therapeutic relevance. In another point, lesions on the dorsal hands categorized except distal digit type relatively show better treatment response compared to those on the digits. This indicates that distribution patterns are influenced by treatment outcomes. Therefore, future therapeutic strategies such as JAK inhibitors and their combination with phototherapy may change the distribution followed by subtype in the future. A deeper recognition of these patterns could contribute to more tailored and effective therapeutic approaches for hand vitiligo.

Author Contributions

Kazunori Yokoi: conceptualization, data analysis, investigation, methodology, validation, visualization, original draft preparation, and editing. **Yosuke Ishitsuka:** methodology, data analysis, supervision. **Kanae Kusao:** data analysis, investigation. **Jing Wang:** data analysis, investigation. **Haruna Kawashima:** data analysis, investigation. **Narumi Jikihara:** data analysis, investigation. **Seitaro Nakagawa:** data analysis. **Eiji Kiyohara:** methodology, data analysis, supervision. **Noriko Arase:** methodology, data analysis, supervision. **Manabu Fujimoto:** conceptualization, project administration, supervision, editing. **Atsushi Tanemura:** conceptualization, funding acquisition, methodology, project administration, investigation, supervision, visualization, editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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