

# Impact of treatment delays on vitiligo during the COVID-19 pandemic: A retrospective study

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## Abstract

*Due to the COVID-19 pandemic, routine treatments are delayed to some extent and their negative impacts have been widely reported. However, virtually nothing is known about vitiligo in the context of COVID-19. Therefore, we analyzed treatment delays and its impact on vitiligo, aiming to provide suggestions on vitiligo management within this special period. We performed a retrospective cohort study on 322 patients who visited our clinics at least 2 times from January to December 2020, and their medical records and photographs were reviewed. Patients were divided into normal ( $n = 155$ ) and late group ( $n = 167$ ) based on whether experienced treatment delays. As for the active cases, the late group showed higher progression rate than normal group (35 of 86 [40.7%] vs. 10 of 81 [12.3%];  $p = 0.002$ ). Moreover, we observed higher recurrence rate in delay group than those of normal group (26 of 81[32.1%] vs. 9 of 74 [12.2%];  $p = 0.018$ ) among stable cases. Further univariate and multivariate analysis determined treatment delays as the most important independent risk factor for disease progression and recurrence, and maintenance therapy (>2 years) as a protective factor against recurrence. This study, for the first time, revealed the independent adverse impact of treatment delays on the progression and recurrence of vitiligo and indicated the significance of continuous treatment for halting progression and long-term maintenance therapy for preventing recurrence for vitiligo, which should be highly valued in the management of vitiligo during the COVID-19 pandemic.*

## KEYWORDS

COVID-19, progression, recurrence, treatment delays, vitiligo

## 1 | INTRODUCTION

The COVID-19 pandemic is currently sweeping across the world and has contributed to 108,153,741 confirmed cases and 2,381,295 deaths globally by 14 February 2021.<sup>1</sup> The global healthcare system are under unprecedented pressure. Moreover, a series of interventions such as social distancing measures and mobility restrictions are implemented to contain the spreading of COVID-19.<sup>2,3</sup> Under the influence of multiple COVID-19 associated factors, health-seeking behaviors in the patients with non-COVID-19 related disease have

also been influenced and delayed to some extent, imposing a huge burden on the management of chronic disease for physicians during this special period.<sup>4-6</sup> In response, the corresponding recommendations have been made based on available data to guide clinician judgments balancing the risks of potential COVID-19 transmission and treatment delays in patients.<sup>7,8</sup>

In the context of COVID-19 dermatology practice has also been inevitably compromised as reported by studies from various countries.<sup>9-11</sup> However, virtually nothing is known about vitiligo, a common chronic autoimmune cutaneous depigmenting disorder, requiring active treatment to halt progression,<sup>12</sup> maintenance therapy to prevent recurrence.<sup>13</sup> These clinical characteristics of vitiligo may confer

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greater risk of adverse outcomes in disease condition under the influence of treatment delays. Yet, there is no relevant literature assessing how treatment delays affect vitiligo outcomes before or during the COVID-19 pandemic. We therefore sought to investigate the impact of treatment delays on the disease condition of vitiligo, aiming to provide useful evidence and suggestions for better management of vitiligo in response to the current pandemic wave.

## 2 | MATERIALS AND METHODS

This retrospective cohort study was carried out at Department of Dermatology, Huashan Hospital, Shanghai, which reviewed the available medical records and photographs of patients with vitiligo visited our outpatient at least 2 times from January to December 2020, during the COVID-19 pandemic. The study was approved by the Ethics Committee of Huashan Hospital, Fudan University. Written informed consent to publish images was obtained from the patients.

The included patients were categorized into two groups according to whether experienced the treatment delays (late group) or not (normal group). A discontinuation of original treatments (>1 month) was considered as treatment delays, while changes due to improved condition were excluded. Clinical data, including demographics, vitiligo characteristics, previously therapies and clinical outcomes were extracted from medical records of patients. Clinical outcomes were also evaluated based on clinical photographs taken at each visit. Patients who exhibited a blurry boundary of lesions under Wood light or had a VETF spreading score of +1 to +5 were considered as active, and as stable otherwise.<sup>14</sup> Progression was considered in the patients with active vitiligo if they exhibited larger affected body surface area (BSA) than last follow-up.<sup>15</sup> Recurrence was defined as depigmentation in previously repigmented lesions or appearance of new lesions in patients with stable vitiligo.<sup>16</sup>

Although this study was performed in retrospective fashion, patients were treated according to a unified protocol: systemic corticosteroid therapy for patients with active vitiligo, topical therapy with calcineurin inhibitors on the lesions twice daily for all patients, and narrowband ultraviolet B (NB-UVB) therapy twice weekly for the patients with stable vitiligo.

All statistical testing in our study was performed with the SPSS version 21.0 (IBM, Armonk, NY). For comparison of quantitative variables, Kruskal-Wallis test or Student's *t* test was used. Categorical variables were compared with  $\chi^2$  test or Fishers exact test. The independent factors associated with disease aggravation or recurrence were analyzed using univariable logistic regression, followed by multivariable logistic regression (variables with *p*-value < 0.1). For all analysis, differences were considered significant if *p* < 0.05.

## 3 | RESULTS

In total, 322 patients were finally included in the present study, consisting of 167 (51.9%) experienced treatment delays (late group) and

155 (48.1%) received normal treatment (normal group) (Table 1). The patients experienced treatment delays with a mean duration of  $4.46 \pm 2.02$  months, which mainly occurred at February–April (Figure 1). Among treatment modalities, systemic corticosteroid therapy (38.9%) was the most frequently delayed, followed by combination therapy (two or more therapies, 25.7%) and phototherapy (12.6%; Figure 2). Patients in the two groups did not significantly differ with regard to demographic and vitiligo characteristics (all *p* > 0.05; Table 1).

Representative photographs of disease progression and recurrence were shown in Figure 3(A)–(B). Comparison of progression rate were conducted in the 167 active cases (late, *n* = 86; normal, *n* = 81) and disease progression was more commonly observed in the late group (40.7% vs. 12.3%, *p* = 0.002; Figure 4). In addition, disease recurrence was analyzed in the 155 stable cases (late, *n* = 81; normal, *n* = 74). The late group also showed higher rate of recurrence than those of normal group (32.1% vs. 12.2%, *p* = 0.018; Figure 4).

To further investigate whether treatment delays was the independent factor for disease progression and recurrence, univariate, and multivariate analyses were performed (Table 2). On univariate analysis, we found that treatment delays was associated with both disease progression (all *p* < 0.05) and recurrence (all *p* < 0.05 except for delays less than 3 months; Table 2). Treatment delays, along with other significant variables in univariate analysis were entered in the final multivariate analysis. The results revealed that treatment delays, large affected body surface area (BSA, >10%),<sup>17</sup> emotional dysregulation and fatigue as independent risk factors for progression (all *p* < 0.05; Table 2). As for recurrence, treatment delays (>3 months), large affected BSA, long disease duration (>5 years), emotional dysregulation and fatigue were the independent risk factors (all *p* < 0.05), whereas maintenance therapy (>2 years) was protective (*p* = 0.016; OR: 0.21; CI 95%: 0.06–0.75) (Table 2). Strikingly, treatment delays were the most important risk factor associated with both progression and recurrence. The longer duration of treatment delays, the higher risk for progression and recurrence.

## 4 | DISCUSSION

Treatment delays caused by the COVID-19 pandemic and its related restrictions are serious challenges for the management of chronic disease faced by clinicians currently.<sup>6</sup> Considering the importance of long-term active treatment for vitiligo and its high global incidence (0.5%–1%),<sup>12,18</sup> there is an urgency to develop a clear recommendation for vitiligo management during pandemics based on fully understanding the impact of treatment delays on vitiligo. To date, however, the data is limited. Therefore, the impact of treatment delays on disease condition of vitiligo during the COVID-19 pandemic was investigated for the first time in the present study.

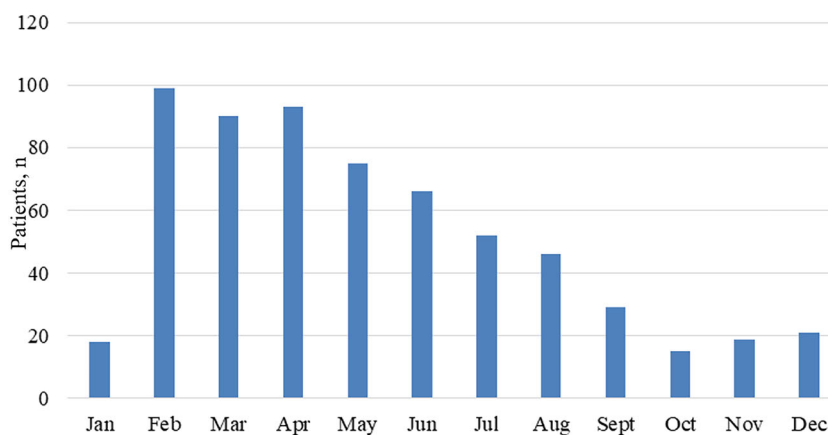
Our study revealed that the patients mainly experienced treatment delays between February 2020 and April 2020, and gradually decreased in the number since May 2020, which was basically consistent with the epidemic situation in China.<sup>19</sup> It is well-recognized that the skin-infiltration of melanocyte-specific CD8 + T cells

**TABLE 1** Demographic and clinical characteristics of both groups

	Late group (n = 167)	Normal group (n = 155)	p
<b>Demographic characteristics</b>			
Female, n (%)	79 (47.3)	88 (56.8)	0.325
Age (years), mean ± SD	29.30 ± 15.43	27.27 ± 16.40	0.244
<b>Vitiligo characteristics</b>			
<b>Onset age, n (%)</b>			0.273
≤12 years	76 (45.5)	80 (51.6)	
>12 years	91 (54.5)	75 (48.4)	
<b>Subtypes, n (%)</b>			0.432
NSV	134 (80.2)	115 (74.2)	
SV	29 (17.4)	35 (22.6)	
Mixed	4 (2.4)	5 (3.2)	
<b>Disease duration</b>			0.388
≤5 years	91 (54.5)	77 (49.7)	
>5 years	76 (45.5)	78 (50.3)	
<b>Affected BSA</b>			0.616
≤10%	88 (52.7)	86 (55.5)	
>10%	79 (47.3)	69 (44.5)	
<b>Disease stage, n (%)</b>			0.891
Active stage	86 (51.5)	81 (52.3)	
Stable stage	81 (48.5)	74 (47.7)	
<b>Autoimmune comorbidities, n (%)</b>	15 (9.0)	19 (12.3)	0.339
<b>Family history, n (%)</b>	14 (8.4)	9 (5.8)	0.370

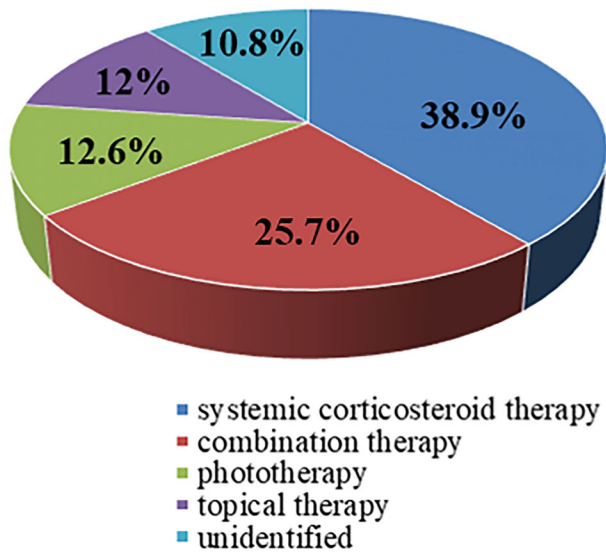
Note:  $p < 0.05$  was considered statistical significantly.

Abbreviations: BSA, body surface area; Mixed, mixed vitiligo; NSV, nonsegmental vitiligo; SV, segmental vitiligo.

**FIGURE 1** Timeline of treatment delays. The blue bar chart represented the number of patients experienced treatment delays in each month during the COVID-19 pandemic

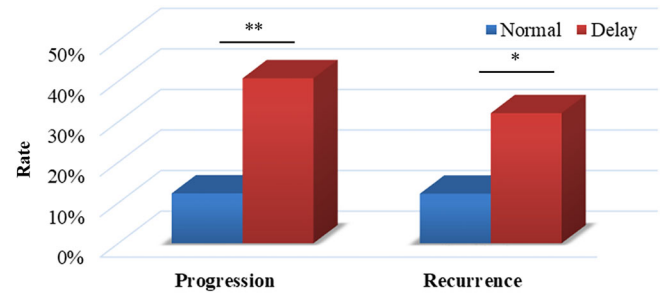
mediate the progressive destruction of melanocytes and play the key role in the progression of vitiligo.<sup>12</sup> Hence, halting the progressive depigmentation is the foremost step in the treatment of active vitiligo. Currently, systemic corticosteroid therapy combined with other therapies are widely utilized to promote disease stabilization through its immunomodulatory effects.<sup>20</sup> However, systemic corticosteroid therapy and combination therapy were mainly delayed during the pandemic as showed in the present study. Different from active vitiligo, maintenance therapy such as topical tacrolimus ointment is

emphasized in stable vitiligo to maintain achieved repigmentation and prevent disease recurrence,<sup>13</sup> which was also found to be delayed in our study. In this study, we compared the progression and recurrence rate between the two groups and detected the higher rates in late group, preliminarily indicating the adverse impact of treatment delays on the condition of vitiligo. Furthermore, we showed in the univariate and multivariate analysis that treatment delays was the most important independent risk factor for both disease progression and recurrence.



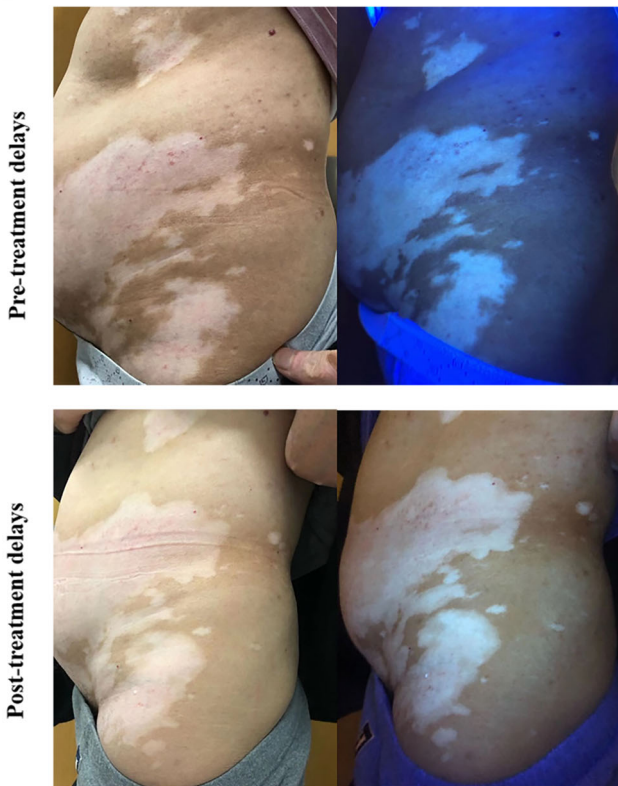
**FIGURE 2** Treatment modalities delayed during the COVID-19 pandemic. The pie charts showed the proportion of various treatment modalities for vitiligo delayed during the COVID-19 pandemic

The treatment duration of vitiligo is a major concern for both dermatologists and patients. However, there is *no consensus* exists regarding the optimal course of treatment for vitiligo and the clinical practice varies widely between dermatologists. Generally, 3–6 months of systemic corticosteroid therapy is recommended to halt the disease



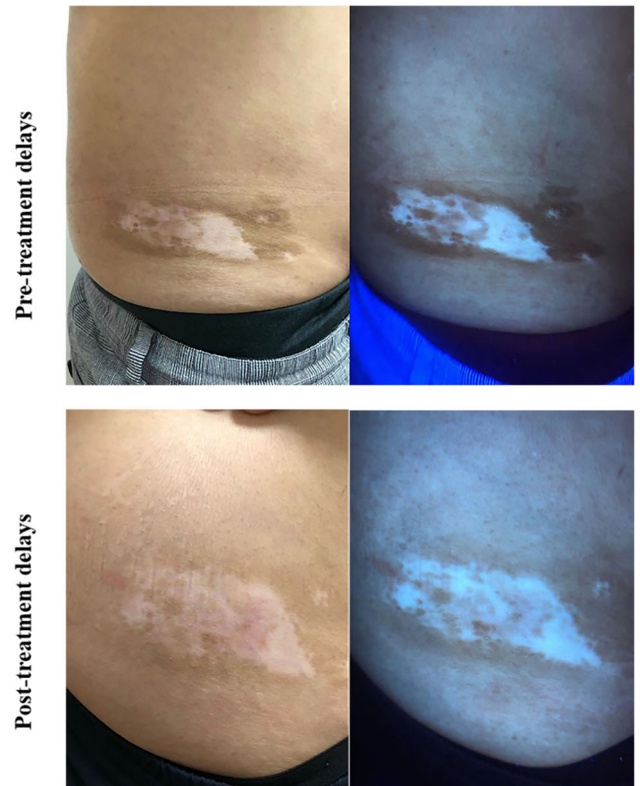
**FIGURE 4** Comparison of disease progression and recurrence between two groups. The rates of aggravation and recurrence were compared between late and normal group, respectively. \* $p < 0.05$ ; \*\* $p < 0.01$

(A)



**Disease progression**

(B)



**Disease recurrence**

**FIGURE 3** Representative photographs of disease progression and recurrence. (A) Photographs of a patients with disease progression taken at pre- and post-treatment delays; (B) Photographs of a patients with disease recurrence taken at pre- and post-treatment delays

**TABLE 2** Univariate and multivariate analysis of factors associated with disease progression and recurrence

	Progression						Recurrence					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	No n (%)	Yes n (%)	p	OR	p	OR	No n (%)	Yes n (%)	p	OR	p	OR
<b>Gender</b>												
Male	59 (71.1)	24 (28.9)	0.167	1.64 (0.81–3.31)			52 (72.2)	20 (27.8)	0.149	1.74 (0.82–3.73)		
Female	63 (75)	21 (25)	Reference	Reference			68 (81.9)	15 (18.1)	Reference	Reference		
<b>Age, y</b>												
≤12	37 (74)	13 (26)	Reference	Reference			29 (80.6)	7 (19.4)	Reference	Reference		
>12	85 (72.6)	32 (27.4)	0.857	1.07 (0.51–2.27)			91 (76.5)	28 (23.5)	0.608	1.28 (0.50–3.19)		
<b>Onset age, y</b>												
≤12	57 (68.7)	26 (31.3)	0.205	1.56 (0.78–3.11)			54 (74.0)	19 (26.0)	0.333	1.45 (0.68–3.09)		
>12	65 (77.4)	19 (22.6)	Reference	Reference			66 (80.5)	16 (19.5)	Reference	Reference		
<b>Duration, y</b>												
≤5	56 (68.3)	26 (31.7)	0.173	1.61 (0.81–3.22)			72 (83.7)	14 (16.3)	Reference	Reference		
>5	66 (77.6)	19 (22.4)	Reference	Reference			48 (69.6)	21 (30.4)	0.036	2.25 (1.04–4.85)		0.045
<b>Affected BSA</b>												
≤10%	71 (83.5)	14 (16.5)	Reference	Reference			76 (85.4)	13 (14.6)	Reference	Reference		
>10%	51 (62.2)	31 (37.8)	0.002	3.08 (1.49–6.37)			44 (66.7)	22 (33.3)	0.006	2.92 (1.34–6.38)		0.038
<b>Subtype</b>												
SV	28 (77.8)	8 (22.2)	Reference	Reference			23 (82.1)	5 (17.9)	Reference	Reference		
NSV	90 (71.4)	36 (28.5)	0.450	1.40 (0.58–3.36)			94 (76.4)	29 (23.6)	0.513	1.42 (0.50–4.07)		
Mix	4 (80)	1 (20)	0.910	1.14 (0.11–11.72)			3 (75)	1 (25)	0.732	1.53 (0.13–17.97)		
<b>Treatment delays, mo</b>												
No	71 (87.7)	10 (12.3)	Reference	Reference			65 (87.8)	9 (12.2)	Reference	Reference		
1–3	20 (64.5)	11 (35.5)	0.005	3.91 (1.45–10.51)			22 (88)	3 (12)	0.983	0.99 (0.25–3.97)		0.745
3–6	21 (58.3)	15 (41.6)	<0.001	5.07 (1.99–12.94)			21 (63.6)	12 (36.4)	0.004	4.13 (1.53–11.16)		0.023
>6	10 (52.6)	9 (47.4)	<0.001	6.39 (2.09–19.54)			12 (52.2)	11 (47.8)	<0.001	6.62 (2.26–19.39)		0.006
<b>Upfront therapy, mo</b>												
<3	53 (67.9)	25 (32.1)	Reference	Reference								
3–6	41 (75.9)	13 (24.1)	0.320	0.67 (0.31–1.47)								
6–12	28 (80)	7 (20)	0.189	0.53 (0.20–1.38)								
<b>Maintenance therapy, mo</b>												
<6							13 (59.1)	9 (40.9)	Reference	Reference		
6–12							38 (77.6)	11 (22.4)	0.110	0.42 (0.14–1.24)		0.368
12–24							37 (77.1)	11 (22.9)	0.122	0.43 (0.15–1.27)		0.377
>24							32 (88.9)	4 (11.1)	0.008	0.18 (0.05–0.69)		0.016
<b>Emotional dysregulation</b>												
No	67 (82.7)	14 (17.3)	Reference	Reference			46 (68.7)	21 (31.3)	Reference	Reference		
Yes	55 (64.0)	31 (36.0)	0.006	2.70 (1.31–5.57)			74 (84.1)	14 (15.9)	0.023	2.41 (1.12–5.21)		0.038
<b>Fatigue</b>												
No	75 (82.4)	16 (17.6)	Reference	Reference			39 (67.2)	19 (32.8)	Reference	Reference		
Yes	47 (61.8)	29 (38.2)	0.003	2.89 (1.42–5.89)			81 (83.5)	16 (16.5)	0.019	2.47 (1.15–5.31)		0.035
<b>Autoimmune comorbidities</b>												
No	110 (74.3)	38 (25.7)	Reference	Reference			109 (77.9)	31 (22.1)	Reference	Reference		
Yes	12 (63.2)	7 (36.8)	0.302	1.69 (0.62–4.60)			11 (73.3)	4 (26.7)	0.690	1.28 (0.38–4.30)		
<b>Family history</b>												
No	115 (73.7)	41 (26.3)	Reference	Reference			111 (77.6)	32 (22.4)	Reference	Reference		
Yes	7 (63.6)	4 (36.4)	0.466	1.60 (0.45–5.76)			9 (75)	3 (25)	0.835	1.16 (0.30–4.53)		

Note:  $p < 0.05$  was considered statistically significant.  
Abbreviations: BSA, body surface area; Mix, mix vitiligo; NSV, nonsegmental vitiligo; SV, segmental vitiligo.

progression for active vitiligo.<sup>18,20</sup> However, no protective effect of upfront therapy against disease progression was found in our study even if the time of upfront therapy exceeded 6 months. These findings may be explained by the still existing low-grade immune reaction against melanocytes, which need low-dose immunosuppression treatment instead of abrupt withdrawal. Therefore, continuous treatment including subsequent low-dose immunosuppression treatment should be stressed for halting progression in the active vitiligo. Limited data are available for the course of maintenance therapy in stable vitiligo. Interestingly, we noted that maintenance therapy for more than 2 years was an independent protective factor for recurrence, suggesting the relative stability of treatment cessation after 2-year maintenance therapy for the patients with stable vitiligo.

Moreover, large BSA, emotional dysregulation and fatigue were also identified as independent factors for both progression and recurrence. Large BSA has been confirmed to be correlated with active immune status, which is strongly implicated in the progression and recurrence of vitiligo.<sup>12,21,22</sup> As reported previously, emotional dysregulation and fatigue exert adverse effects on autoimmune disease and the mechanisms linking them have been well-established.<sup>23–25</sup> In the current study, we confirmed and *extended the associations to vitiligo*. Similar with psoriatic arthritis,<sup>26</sup> long disease duration was found to be another independent risk factor for recurrence in our study, further strengthening the significance of early intervention for vitiligo.

Several limitations existed in this study, including the retrospective design, small sample size and patients selection bias. In addition, our study was limited by our reliance on the self-reported emotional dysregulation and fatigue without any formally assessment. Accordingly, large prospective cohort studies with objective scoring systems for assessing emotional dysregulation and fatigue are warrant to validate our observations in the future.

In conclusion, our findings revealed the independent adverse impact of treatment delays on the progression and recurrence of vitiligo and protective effect of maintenance therapy (>2 years) against recurrence, indicating the significance of continuous treatment for halting progression and long-term maintenance therapy for preventing recurrence. Therefore, teledermatology<sup>27</sup> and home phototherapy<sup>28</sup> would be recommended, especially for the patients with risk factors. Additionally, keeping emotional stability and avoiding excessive fatigue are equally important. Hopefully, our data and suggestions will provide reference for dermatologists worldwide on the management of vitiligo in response to current pandemic wave.

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## CONFLICT OF INTEREST

The authors declared no conflict of interest.

## AUTHOR CONTRIBUTION

Xinya Xu, Chengfeng Zhang performed the study and collected the data; Xinya Xu and Min Jiang analyzed the data; Leihong Flora Xiang

and Xinya Xu conceived and designed the study; Leihong Flora Xiang obtained funding and provided overall supervision for the study; all authors *participated in writing, data interpretation and final approval* of the manuscript.

## DATA AVAILABILITY STATEMENT

Data used in this study is available with the 1st author and corresponding author.

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