Hindawi
Dermatologic Therapy
Volume 2023, Article ID 4711236, 5 pages
https://doi.org/10.1155/2023/4711236

Research Article

A Retrospective Statistical Analysis of Vitiligo Exacerbation after COVID-19 Vaccination in China

Tao Wang,[1,2] Yaojun Wang,[3] Yue Zhang,[1] Jiaoni Chi,[1] and Qiang Li[1]

[1]*Department of Dermatology, Air Force Medical Center, PLA, Beijing, China*
[2]*Department of Dermatology, West China Hospital, Sichuan University, Chengdu, China*
[3]*Handan Second Hospital, Handan, Hebei, China*

Correspondence should be addressed to Qiang Li; 16585260@qq.com

Received 2 January 2023; Revised 22 June 2023; Accepted 10 September 2023; Published 25 September 2023

Academic Editor: Nilendu Sarma

At present, COVID-19 vaccination is an effective method to stop the spread of the epidemic and reduce disease severity and mortality. It has been reported that COVID-19 vaccine can activate several autoimmune diseases. However, whether it can affect development of vitiligo remains elusive. In this study, we aimed to evaluate the possible risk factors of vitiligo disease activity or recurrence after COVID-19 vaccination. We recruited 383 vitiligo patients, of whom 126 were not vaccinated and 257 had received the COVID-19 vaccine. Vitiligo disease activity (VIDA) score was used to analyze key risk factors of vitiligo in patients who underwent COVID-19 vaccination. Multivariate logistic regression models were used to explore the risk factors associated with VIDA. Compared with patients without history of undergoing vaccination, the VIDA score of vaccinated patients increased significantly (3(2, 4) vs. 3(2, 3) scores, $P < 0.01$). Logistic regression analysis identified COVID-19 vaccination (odds ratio (OR): 3.040, 95% confidence interval (CI): 1.649–5.603) as an independent risk factor for VIDA. The data showed that COVID-19 vaccination aggravated the development of vitiligo, which is a key risk factor for recurrence.

1. Introduction

COVID-19 vaccination is an effective method to stop the spread of the epidemic and reduce disease severity and mortality [1]. It has been reported that COVID-19 vaccine can activate several autoimmune diseases, such as psoriasis, autoimmune thyroid diseases (AITDs), systemic lupus erythematosus (SLE), immune-mediated thrombotic thrombocytopenic purpura (iTTP), IgA vasculitis (IgAV), and autoimmune hepatitis [2–7]. However, whether the vaccination can trigger the autoimmune reactivity of stable vitiligo remains unclear. Previous case reports showed that vitiligo as an immune disease may also be affected by COVID-19 vaccine. However, there are no clinical studies with large sample sizes to investigate this phenomenon and cytokine profiles involved in the Th1 type immune response. In this study, we aimed to evaluate the possible risk factors of vitiligo disease activity or recurrence after COVID-19 vaccination.

2. Methods

This was a single-center, retrospective, and longitudinal study, conducted from November 2020 to October 17, 2021. The vitiligo disease activity (VIDA) score was used to analyze key risk factors of vitiligo patients after COVID-19 vaccination [8] (Figure 1). The VIDA scores of vitiligo patients were obtained from the vitiligo epidemiological questionnaire of the Air Force Medical Center Dermatology, and vitiligo patients were followed up for at least 6 months after vaccination. Binary logistic regression models were used to explore the risk factors associated with VIDA.

Statistical analysis was performed using SPSS 26.0 software. In order to reduce the differences among participants, propensity score matching (PSM) was used to match subjects with similar clinical characteristics. The data were presented as numbers (%) for categorical variables and median (P25, P75) for continuous variables.

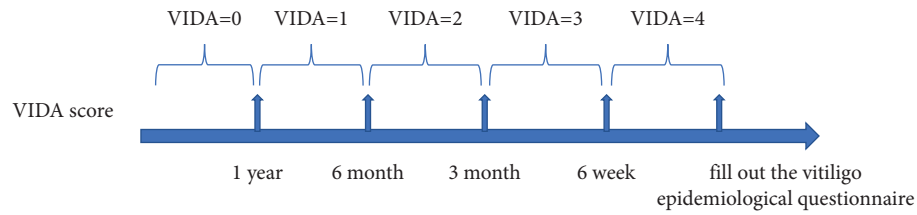

Figure 1: VIDA score criteria.

Table 1: Comparison of vitiligo activity ($x \pm s$/case (%)/M (IQR)).

Variable	Total ($N = 383$)	Before PSM ($n = 383$)		P value	After PSM ($n = 300$)		P value
		Vaccinated ($n = 257$)	Unvaccinated ($n = 126$)		Vaccinated ($n = 200$)	Unvaccinated ($n = 100$)	
VIDA				0.001*			0.002*
4	121 (31.6)	98 (38.1)	23 (18.3)		73 (36.5)	16 (16.0)	
3	116 (30.3)	70 (27.2)	46 (36.5)		61 (30.5)	40 (40.0)	
2	72 (18.8)	45 (17.5)	27 (21.4)		35 (17.5)	23 (23.0)	
≤1	74 (19.3)	44 (17.1)	30 (23.8)		31 (15.5)	21 (21.0)	

*indicates statistically significant differences between groups for this variable.

The Mann–Whitney U test was used for nonnormally distributed continuous and ordered variables. Categorical variables were tested by the chi-square test and Fisher's exact probability method. Whether new lesions appeared within one month was used as a dependent variable ($Y_{\mathrm{VIDA}=4} = 1$, $Y_{\mathrm{VIDA}\neq 4} = 0$), and x^2 test was utilized for univariate analysis. Multivariable logistic regression was employed to evaluate the possible risk factors of vitiligo disease activity or recurrence after COVID-19 vaccination. Significant variables ($P < 0.2$) associated with vitiligo disease activity in univariate analysis or clinical relevance were selected for the multivariable logistic regression model. Odds ratios (ORs) with associated 95% confidence intervals (CIs) were estimated for effects of variables on each outcome. A P value ≤0.05 was considered as statistically significant.

3. Results

This study included 383 vitiligo patients, of which 126 were not vaccinated and 257 had received the COVID-19 vaccine. After PSM, the unvaccinated group had 100 and the vaccinated group had 200 patients (Supplementary Table S1). Compared to the 100 patients without vaccination, the VIDA score of vaccinated patients increased significantly (3(2, 4) vs. 3(2, 3) scores, $P < 0.01$; Table 1). The binary logistic regression model exhibited a promising calibration capability (Hosmer–Lemeshow test, $P = 0.960$). Logistic regression analysis identified COVID-19 vaccination (OR: 3.040, 95% CI: 1.649–5.603) as an independent risk factor for VIDA (Table 2). The data showed that vitiligo patients who had received the COVID-19 vaccine were 3.0 times more likely to aggravate the development of vitiligo than vitiligo patients who had not received the COVID-19 vaccine. Therefore, COVID-19 vaccination aggravated the development of vitiligo, which is a key risk factor for recurrence.

4. Discussion

Vitiligo is a chronic autoimmune disorder characterized by the destruction of melanocytes in the epidermis and hair follicles, with a prevalence of 0.5–2% in different races and geographical areas worldwide, and it is susceptible to recurrence [9, 10]. Vitiligo is the result of disturbances in systemic immune homeostasis [11, 12]. Innate and adaptive immune responses are involved in the pathogenesis of vitiligo, with T cell subsets playing a central role, cytotoxic CD8+ T cells mediating melanocyte clearance, regulatory T cells (Treg) maintaining immune homeostasis and suppressing inflammation, and skin-resident memory T cells (TRM) inducing vitiligo recurrence. Keratinocytes exacerbate the disease by secreting chemokines to recruit more cytotoxic CD8+ T cells [13, 14].

Vaccines protect the host by generating strong and long-lasting memory T and B cells through a complex interaction between innate, humoral, and cellular immunity [15, 16]. Moreover, cytokines play a protective role in humans by stimulating innate immune responses, shaping adaptive immunity, and inducing immune memory [17]. However, these immune cells and cytokines also have an equally crucial role in the pathogenesis of vitiligo.

Some studies noted a significant increase in IFN-γ, CXCL10, IL-15, TNF-α, and IL-17 after COVID-19 vaccination [17–19]. Bergamaschi et al. showed that the levels of IFN-γ and CXCL10 were significantly higher in humans after the first dose of vaccine, and the levels of IFN-γ, IL-15, and CXCL10 were significantly higher after the second dose of vaccine than the first dose, indicating that the second dose of vaccine induced a stronger immune response [17]. This phenomenon was confirmed in the case report of a vitiligo patient who developed white patches after the first dose of vaccine, and the vitiligo worsened after the second dose of vaccine [20]. This study noted the synergistic effects of IL-15 and IFN-γ, IL-15 and CXCL10, and IFN-γ and CXCL10

Table 2: Analysis of factors influencing vitiligo activity (*t*-test, chi-square test, and binary logistic regression).

Variable	Single factor analysis			Multiple factor analysis		
	VIDA = 4 ($n = 90$)	VIDA ≠ 4 ($n = 210$)	*P* value	OR	95% CI	*P* value
Age (years)	26 (16, 36.25)	23 (11, 37)	0.371			
Sex, *n* (%)			0.417			
Male	53 (58.9)	113 (53.8)				
Female	37 (41.1)	97 (46.2)				
Distribution			0.181			
Head and neck	65 (72.2)	135 (64.3)				
Others	25 (27.8)	75 (35.7)				
Bilateral distribution			0.562			
Yes	50 (55.6)	109 (51.9)				
No	40 (44.4)	101 (48.1)				
Extent of lesion			0.807			
Focal	39 (43.3)	99 (47.1)				
Sporadic	47 (52.2)	101 (48.1)				
Universal	4 (4.5)	10 (4.8)				
Disease duration (year)			0.884			
≤3	68 (75.6)	157 (74.8)				
>3	22 (24.4)	53 (25.2)				
Age of onset (year)			0.510			
<40	74 (82.2)	179 (85.2)				
≥40	16 (17.8)	31 (14.8)				
Skin lesion symptom[a]			0.499			
Yes	17 (18.9)	33 (15.7)				
No	73 (81.1)	177 (84.3)				
Body surface area (%), *n* (%)			0.421			
≤1%	61 (67.8)	152 (72.4)				
>1%	29 (32.2)	58 (27.6)				
Family history			0.315			
Yes	17 (18.9)	30 (14.3)				
No	73 (81.1)	180 (85.7)				
Mental factors[b]			0.048*	1.557	0.930–2.607	0.092
Yes	48 (53.3)	86 (41.0)				
No	42 (46.7)	124 (59.0)				
History of trauma[c]			0.772			
Yes	10 (11.1)	21 (10.0)				
No	80 (88.9)	189 (90.0)				
History of sun exposure[d]			0.217	1.595	0.551–4.619	0.389
Yes	7 (7.8)	9 (4.3)				
No	83 (92.2)	201 (95.7)				
Associated autoimmune disease[e]			0.403	1.245	0.528–2.938	0.616
Yes	10 (11.1)	17 (8.1)				
No	80 (88.9)	193 (91.9)				
Clinical type			0.250	1.106	0.800–1.528	0.543
Sporadic type	42 (46.7)	96 (45.7)				
Segmental	24 (26.7)	73 (34.8)				
Other	24 (26.6)	41 (19.5)				
COVID-19 vaccination			<0.001*	3.040	1.649–5.603	<0.001*
Yes	74 (82.2)	126 (60.0)				
No	16 (17.8)	84 (40.0)				

[a]Skin lesion symptom refers to itching and burning at the beginning of the white spot; [b]mental factors refer to depression, stress, prolonged late night, shock, overwork, and overexertion leading to onset; [c]history of trauma refers to frostbite, burns, trauma, and repeated rubbing leading to onset; [d]sun exposure refers to outdoor stay for 2 h at noon; [e]associated autoimmune disease includes hyperthyroidism, hypothyroidism diabetes mellitus, dermatomyositis, scleroderma, discoid erythema, systemic lupus erythematosus, pemphigus, psoriasis, atopic dermatitis/eczema, and rheumatoid arthritis. *indicates statistically significant differences between groups for this variable.

during the immune response and the existence of synergistic effects of these cytokines in the pathogenesis of vitiligo [17]. IFN-γ plays a central role in inflammation and autoimmunity, inducing the local accumulation of specific CD8+ T cells targeting melanocytes in the skin, and induces production of CXCL9 and CXCL10 by keratinocytes to recruit more T cells, which induce apoptosis of melanocytes through a synergistic effect [9, 21]. TNF-α reduces melanin content through dendrite shedding, downregulation of MITF-M and TYR, and upregulation of TNFR, IL6, and ICAM 1 expression [22, 23].

IFN-γ and TNF-α act together to induce keratinocytes to produce the protease MMP-9 to induce the cleavage of melanocyte E-calcineurin, leading to melanocyte shedding [24]. IL-15 and IL-17 stimulate CD8+ TRM cells, causing upregulation of the expression of signaling pathway molecules such as JAK-STAT in CD8+ TRM cells, increasing interferon-γ, perforin, and granzyme B production, which leads to melanocyte destruction [23, 25]. These cytokines appear to increase after vaccination and correlate with each other, which illustrates that vaccination may trigger immune mechanisms that contribute to the development of vitiligo.

The limitations of this study included it being a single-center, small-sample, and retrospective study, and the relationship between vaccine type and vitiligo disease activity was not analyzed. Further clinical studies with large number of participants and multicenter prospect, assessing the impact of different vaccines on vitiligo, are needed.

This study showed an association between COVID-19 vaccine and vitiligo, and physicians should be aware of this adverse effect, especially while treating genetically susceptible patients.

Data Availability

Data are available upon reasonable request to the corresponding author.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

TW and QL were responsible for conceptualization and methodology. TW was responsible for investigation, formal analysis, and original draft preparation. QL was responsible for validation. YZ, JC, and YW were responsible for data curation. QL, YZ, and YW were responsible for review and editing. All authors have read and agreed to the published version of the manuscript.

Supplementary Materials

Table S1: comparison of baseline information before and after propensity score matching (PSM) (case (%)/M (IQR)). (*Supplementary Materials*)

References

[1] L. Frederiksen, Y. Zhang, C. Foged, and A. Thakur, "The long road toward COVID-19 herd immunity: vaccine platform technologies and mass immunization strategies," *Frontiers in Immunology*, vol. 11, p. 1817, 2020.

[2] R. M. Ruggeri, L. Giovanellla, and A. Campenni, "SARS-CoV-2 vaccine may trigger thyroid autoimmunity: real-life experience and review of the literature," *Journal of Endocrinological Investigation*, vol. 45, no. 12, pp. 2283–2289, 2022.

[3] Y. Huang and T. Tsai, "Exacerbation of psoriasis following COVID-19 vaccination: report from a single center," *Frontiers of Medicine*, vol. 8, Article ID 812010, 2021.

[4] I. Sagy, L. Zeller, Y. Raviv, T. Porges, A. Bieber, and M. Abu-Shakra, "New-onset systemic lupus erythematosus following BNT162b2 mRNA COVID-19 vaccine: a case series and literature review," *Rheumatology International*, vol. 42, no. 12, pp. 2261–2266, 2022.

[5] G. Giuffrida, U. Markovic, A. Condorelli et al., "Relapse of immune-mediated thrombotic thrombocytopenic purpura following mRNA COVID-19 vaccination: a prospective cohort study," *Haematologica*, vol. 107, no. 11, pp. 2661–2666, 2022.

[6] Y. Ramdani, T. Bettuzzi, A. Bouznad et al., "IgA vasculitis following COVID-19 vaccination: a French multicenter case series including 12 patients," *Journal of Rheumatology*, vol. 50, no. 2, pp. 252–257, 2022.

[7] M. Mathew, S. B. John, J. Sebastian, and M. D. Ravi, "COVID-19 vaccine triggered autoimmune hepatitis: case report," *European Journal of Hospital Pharmacy*, vol. 30, no. 5, p. 27, 2023.

[8] M. D. Njoo, P. K. Das, J. D. Bos, and W. Westerhof, "Association of the Kobner phenomenon with disease activity and therapeutic responsiveness in vitiligo vulgaris," *Archives of Dermatology*, vol. 135, no. 4, pp. 407–413, 1999.

[9] M. L. Frisoli, K. Essien, and J. E. Harris, "Vitiligo: mechanisms of pathogenesis and treatment," *Annual Review of Immunology*, vol. 38, no. 1, pp. 621–648, 2020.

[10] M. Bertolani, E. Rodighiero, M. B. de Felici Del Giudice, T. Lotti, C. Feliciani, and F. Satolli, "Vitiligo: what's old, what's new," *Dermatology Reports*, vol. 13, no. 2, p. 9142, 2021.

[11] A. Hadi, J. F. Wang, P. Uppal, L. A. Penn, and N. Elbuluk, "Comorbid diseases of vitiligo: a 10-year cross-sectional retrospective study of an urban US population," *Journal of the American Academy of Dermatology*, vol. 82, no. 3, pp. 628–633, 2020.

[12] F. Han, H. Ren, M. Tang, Y. Zhu, and H. Guan, "Clinical Reasoning: a 47-year-old man with rapidly progressive ataxia and vitiligo," *Neurology*, vol. 94, no. 15, pp. e1664–e1669, 2020.

[13] Y. Wang, S. Li, and C. Li, "Clinical features, immunopathogenesis, and therapeutic strategies in vitiligo," *Clinical Reviews in Allergy and Immunology*, vol. 61, no. 3, pp. 299–323, 2021.

[14] L. Macca, L. Peterle, M. Ceccarelli, Y. Ingrasciotta, G. Nunnari, and C. Guarneri, "Vitiligo-like lesions and COVID-19: case report and review of vaccination- and infection-associated vitiligo," *Vaccines*, vol. 10, no. 10, p. 1647, 2022.

[15] S. K. Mahil, K. Bechman, A. Raharja et al., "The effect of methotrexate and targeted immunosuppression on humoral and cellular immune responses to the COVID-19 vaccine BNT162b2: a cohort study," *The Lancet Rheumatology*, vol. 3, no. 9, pp. e627–e637, 2021.

[16] N. N. Jarjour, D. Masopust, and S. C. Jameson, "T cell memory: understanding COVID-19," *Immunity*, vol. 54, no. 1, pp. 14–18, 2021.

[17] C. Bergamaschi, E. Terpos, M. Rosati et al., "Systemic IL-15, IFN-gamma, and IP-10/CXCL10 signature associated with effective immune response to SARS-CoV-2 in BNT162b2 mRNA vaccine recipients," *Cell Reports*, vol. 36, no. 6, Article ID 109504, 2021.

[18] K. E. Lineburg, M. A. Neller, G. R. Ambalathingal et al., "Rapid whole-blood assay to detect SARS-CoV-2-specific memory T-cell immunity following a single dose of AstraZeneca ChAdOx1-S COVID-19 vaccine," *Clinical & Translational Immunology*, vol. 10, no. 8, p. 1326, 2021.

[19] N. P. Kumar, V. V. Banurekha, A. Nancy et al., "Prime-boost vaccination with covaxin/BBV152 induces heightened systemic cytokine and chemokine responses," *Frontiers in Immunology*, vol. 12, Article ID 752397, 2021.

[20] J. Kaminetsky and D. Rudikoff, "New-onset vitiligo following mRNA-1273 (Moderna) COVID-19 vaccination," *Clinical Case Reports*, vol. 9, no. 9, Article ID 4865, 2021.

[21] J. E. Harris, T. H. Harris, W. Weninger, E. John Wherry, C. A. Hunter, and L. A. Turka, "A mouse model of vitiligo with focused epidermal depigmentation requires IFN-gamma for autoreactive CD8(+) T-cell accumulation in the skin," *Journal of Investigative Dermatology*, vol. 132, no. 7, pp. 1869–1876, 2012.

[22] M. Singh, M. S. Mansuri, A. Kadam et al., "Tumor Necrosis Factor-alpha affects melanocyte survival and melanin synthesis via multiple pathways in vitiligo," *Cytokine*, vol. 140, Article ID 155432, 2021.

[23] F. Shah, S. Patel, R. Begum, and M. Dwivedi, "Emerging role of Tissue Resident Memory T cells in vitiligo: from pathogenesis to therapeutics," *Autoimmunity Reviews*, vol. 20, no. 8, Article ID 102868, 2021.

[24] N. Boukhedouni, C. Martins, A. S. Darrigade et al., "Type-1 cytokines regulate MMP-9 production and E-cadherin disruption to promote melanocyte loss in vitiligo," *JCI Insight*, vol. 5, no. 11, Article ID 133772, 2020.

[25] S. Cheuk, H. Schlums, I. Gallais Sérézal et al., "CD49a expression defines tissue-resident CD8(+) T cells poised for cytotoxic function in human skin," *Immunity*, vol. 46, no. 2, pp. 287–300, 2017.