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Increased Risk of Herpes Zoster Following Dermatomyositis and Polymyositis

A Nationwide Population-Based Cohort Study

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Abstract: This study explored the possible association between dermatomyositis or polymyositis (DM or PM) and the subsequent risk of herpes zoster (HZ).

We used data from the Taiwan National Health Insurance (NHI) system to address the research topic. The exposure cohort comprised 2023 patients with new diagnoses of DM or PM. Each patient was frequency matched according to age, sex, index year, and comorbidities including diabetes, renal disease, obesity, malignancy, rheumatoid arthritis, immunodeficiency virus infection, autoimmune disease not elsewhere classified, mixed connective tissue disease, or vasculitis with 4 participants from the general population who did not have a history of HZ (control cohort). Cox proportional hazards regression analysis was conducted to estimate the relationship between DM or PM and the risk of subsequent HZ.

The incidence of HZ in the exposure and control cohorts was 35.8 and 7.01 per 1000 person-years, respectively. The exposure cohort had a significantly higher overall risk of subsequent HZ than did the control cohort (adjusted hazard ratio [HR] = 3.90, 95% confidence interval [CI] = 3.18–4.77). The risk of HZ in patients with DM or PM in whichever stratification (including sex, age, and comorbidity) was also higher than that of the control cohort.

The findings from this population-based retrospective cohort study suggest that DM or PM is associated with an increased risk of subsequent HZ. A synergistic effect was observed between DM or PM and one of the comorbidities.

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Abbreviations: CI = confidence interval, DM = dermatomyositis, HR = hazard ratio, HZ = herpes zoster, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, NHIRD = National Health Insurance Research Database, PM = polymyositis, VZV = varicella-zoster virus.

INTRODUCTION

Dermatomyositis (DM) and polymyositis (PM), systemic autoimmune diseases with clinical features associated with inflammatory myopathies,[1] are diagnosed according to the presence of autoantibodies and intravascular complement deposition and supported by distinct immunohistopathological findings and responses to immunosuppressive therapies.[2] In addition to shared features of symmetrical weakness of the proximal skeletal muscles and evidence of myositis, DM presents with hallmark cutaneous features including a heliotrope rash, Gottron papules, a Gottron sign, and poikiloderma in photo-exposed areas (V-sign on the neck and upper chest, shawl sign on the upper back).[3] Extramuscular manifestations of DM or PM, such as malignancy, pulmonary and cardiac involvement, and infections, are the most common causes of death.[4] Epidemiological studies have demonstrated an increased susceptibility of viral infections in patients with autoimmune diseases.[5] Immunocompromised hosts are particularly vulnerable to varicella-zoster virus (VZV) dissemination, visceral involvement and reactivation, and an atypical presentation with considerable morbidity and mortality.[6] Herpes zoster (HZ) infection was reported to be associated with DM or PM and increased risk for DM or PM;[7] the correlation benefits healthcare providers to be attentive to the various indications of primary and secondary VZV infection in the patients with DM or PM and patients should be screened for HZ immunity

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and vaccinated prior to commencing immunosuppression. However, the correlation has not been verified by a nationwide population-based retrospective cohort study using the National Health Insurance Research Database. Thus, the study aim is to investigate the interaction relationship between these diseases.

In this population-based retrospective cohort study, data from the Taiwan National Health Insurance (NHI) database were used to explore the possible association of an increased subsequent HZ risk in patients with DM or PM according to demographic characteristics and comorbidities (diabetes, renal disease, obesity, cancer, other autoimmune diseases, and therapeutic drugs).

METHODS

Data Source

The Taiwan NHI program was established in 1995, and approximately 99% of Taiwan residents are enrolled and 97% of medical providers are under contract (http://www.nhi.gov.tw/english/index.aspx). The present cohort study used data obtained from the NHI Research Database (NHIRD), part of the NHI electronic records system in Taiwan that contains medical claims data from 1996 to 2011 and is maintained by the National Health Research Institutes (NHRI). The NHIRD includes comprehensive data about the clinical visits of insureds, such as outpatient visits, hospital admissions, prescriptions, disease status, and diagnostic codes in the format used in the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). Details of the NHIRD have been described in previous studies.[8,9]

The NHI program allows insureds with major diseases, such as malignancies, transplant, or autoimmune diseases, to apply for a Catastrophic Illness Certificate. Application for such a certificate requires cytological or pathological evidence supporting diagnosis. The NHI database of catastrophic illnesses integrates multiple NHI databases to provide comprehensive information on utilization and enrollment for patients with severe diseases who obtained copayment exemption from the NHI program.

For research purposes, the NHRI released the NHIRD in electronic format, encrypted patient personal information for privacy protection, and provided researchers with anonymous identification numbers associated with relevant claims information including sex, date of birth, registry of medical services, and medication prescriptions. Patient consent is not required for accessing the NHIRD or the Longitudinal Health Insurance Database, so the study was approved to exempt from patient consent by the Institutional Review Board of China Medical University in Central Taiwan (CMU-REC-101-012).

Participants

Figure 1 shows the selection process of the participants in the 2 study cohorts. From the Catastrophic Illness and NHI databases, we identified patients with newly diagnosed with DM or PM (ICD-9-CM 710.3 and 710.4) between January 1, 1998 and December 31, 2011 (exposure cohort). The date of diagnosis for DM or PM was defined as the index date. Patients with HZ before the index date were excluded.

The control cohort used same exclusion criteria and was frequency matched with the exposure cohort at an approximately 4:1 ratio for sex, age (every 5 years) and comorbidities of diabetes, renal disease, obesity, malignancy, rheumatoid arthritis, immunodeficiency virus infection, autoimmune disease not elsewhere classified, mixed connective tissue disease, or vasculitis, and index year.

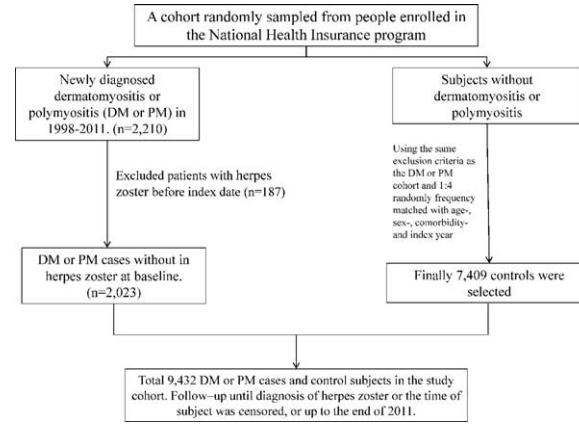

FIGURE 1. The selection process of the participants in the 2 study cohort.

Finally, we recruited 2023 patients with DM or PM and 7409 unexposed participants in this study.

Outcome Measurement and Comorbidities

Every participant in both cohorts was followed up until a diagnosis of HZ (ICD-9-CM 053) was made, or until the patients were censored because of loss to follow-up, death, withdrawal from the database, or December 31, 2011.

For other baseline comorbid conditions, we searched for diagnoses of diabetes (ICD-9-CM 250), renal disease (ICD-9-CM 580–589), obesity (ICD-9-CM 278.0), malignancy (ICD-9-CM 140–208, 230–235), rheumatoid arthritis (ICD-9-CM 714.0–714.3), immunodeficiency virus infection (ICD-9-CM 041–044), autoimmune disease not elsewhere classified (ICD-9-CM 279.4), mixed connective tissue disease (ICD-9-CM 710.0–710.2, 710.8, 710.9), or vasculitis (ICD-9-CM 446, 447.6). Medication included immunosuppressants and corticosteroids, the primary medications use in treating DM and PM.

Statistical Analysis

The distribution of categorical sociodemographic characteristics and comorbidities were compared between the 2 cohorts, and the differences were examined using the Chi-square test. Follow-up person-years were used to estimate the incidence rate of each variable. Cox proportional hazards regression analysis was applied to assess the risk of HZ with DM or PM and the interaction of DM or PM with the comorbidities associated with the relative risk of HZ. The cohort-specific survival curves were plotted after adjusting for age, sex, and comorbidities in the Cox model. A $P < 0.05$ was considered statistically significant. All statistical analyses were performed using the SAS statistical software (Version 9.3 for Windows; SAS Institute, Inc., Cary, NC).

RESULTS

Table 1 summarizes the baseline characteristics of the 2023 patients with DM or PM and the 7409 matched controls. Women accounted for 67.2% of the study population. The mean age of the study participants was 45.9 ± 17.9 years for the control cohort and 45.9 ± 18.0 years for the exposure cohort; 30.2% of the participants were aged between 35 and 49 years.

The baseline comorbidities of the cohorts are shown in Table 1. The exposure cohort was more likely to have rheumatoid arthritis (1.52% versus 2.17%, $P = 0.04$), autoimmune

TABLE 1. Demographic Characteristics and Comorbidity in Patient With and Without Dermatomyositis or Polymyositis

	Dermatomyositis or Polymyositis		
Variable	**No N = 7409**	**Yes N = 2023**	***P*-Value**
Sex	n (%)	n (%)	0.99
Female	5053 (67.5)	1359 (67.2)	
Male	2437 (32.5)	664 (32.8)	
Age, mean (SD)[#]	45.9 (17.9)	45.9 (18.0)	0.94
Stratify age			0.99
≤34	1882 (25.1)	513 (25.4)	
35–49	2281 (30.5)	611 (30.2)	
50–64	2205 (29.4)	599 (29.6)	
≥65	1122 (15.0)	300 (14.8)	
Comorbidity			
Diabetes	491 (6.56)	152 (7.51)	0.13
Renal disease	602 (8.04)	186 (9.19)	0.09
Obesity	92 (1.23)	35 (1.73)	0.08
Cancer	1161 (15.5)	342 (16.9)	0.12
Rhematoid arthritis	114 (1.52)	44 (2.17)	0.04
Autoimmune disease not elsewhere classified	255 (3.40)	124 (6.13)	0.001
Mixed connective tissue disease	2416 (32.3)	713 (35.2)	0.01
Vasculitis	170 (2.27)	73 (3.61)	0.001
Medicine treatment in the 6 months before the index date			
Immunosuppressant[*]	125 (1.67)	1018 (50.3)	<0.0001
Corticosteroids	1730 (23.1)	1518 (75.0)	<0.0001

Chi-square test: 2 sample *t*-test.
[#] Two sample *t*-test.
[*] Included Azathioprine, mycophenolate mofetil, tacrolimus, cyclosporine, and immunoglobulin.

disease not elsewhere classified (3.40% versus 6.13%, $P = 0.0001$), mixed connective tissue disease (32.3% versus 35.2%, $P = 0.01$), and vasculitis (2.27% versus 3.61%, $P = 0.001$) than was the control cohort. Medication use was more prevalent in the exposure cohort than in the control cohort at baseline ($P < 0.0001$).

Table 2 shows the HZ incidence densities in both cohorts and the HRs for the HZ. During the follow-up period, 324 patients in the control cohort (incidence rate = 7.01 per 1000 person-years) and 338 patients in the exposure cohort (incidence rate = 35.8 per 1000 person-years) developed an HZ infection. The exposure cohort had a significantly higher risk of HZ than did the control cohort (crude hazard ratio [HR] = 4.96, 95% confidence interval [CI] = 4.26–5.78; adjusted HR = 3.90, 95% CI = 3.18–4.77) (Table 2). The results of the cumulative incidence curve for the HZ (Figure 2) indicate a significantly higher risk of HZ in patients with DM or PM.

Patients with DM or PM was significantly associated with increased risk of HZ than the subjects without DM or PM for both women and men (HR = 4.32, 95% CI = 3.41–5.47; HR = 2.88, 95% CI = 1.93–4.28). The age-specific exposure cohort to control cohort relative risk for HZ was significant for all age group. Stratified by comorbidity, the relative risk of HZ was higher in the exposure cohort than in the control cohort for both without or with comorbidity (HR = 4.74, 95% CI = 3.33–6.74; HR = 3.55, 95% CI = 2.77–4.54).

We analyzed the association between comorbidities and DM or PM with the risk of HZ (Table 3). Relative to the control cohort without comorbidity, the DM or PM patients with comorbidity were at a higher risk of HZ (HR = 6.03, 95% CI = 4.60–7.91; interaction $P < 0.001$). Table 4 shows the effects of medications on the risk of HZ. Compared with patients without DM or PM and who received no corticosteroid and immunosuppressant treatment, the patients with DM or PM receiving corticosteroid and immunosuppressant therapy had a significantly higher risk of HZ (HR = 7.43, 95% CI = 6.02–9.18), followed by patients with DM or PM receiving inhaled corticosteroid or immunosuppressant treatment (HR = 5.89, 95% CI = 4.68–7.43), patients with DM or PM who received no corticosteroid or immunosuppressant treatment (HR = 4.98, 95% CI = 3.62–6.84), and patients with no DM or PM receiving corticosteroid or immunosuppressant treatment (HR = 1.68, 95% CI = 1.35–2.10). Compared with patients with DM or PM and who received no corticosteroid and immunosuppressant treatment, the patients with DM or PM receiving corticosteroid and immunosuppressant therapy had a significantly higher risk of HZ (HR = 1.45, 95% CI = 1.05–1.99).

DISCUSSION

This study presents conclusive evidence supporting the association of DM or PM with a greater risk of subsequent HZ. In the study population, a higher incidence of HZ was observed in patients with DM or PM who were predominantly female, aged older than 50 years, and had one or more comorbidities, including diabetes,[10] renal disease,[11] obesity,[12] cancer,[13] other autoimmune diseases,[14] mixed connective tissue disease,[15] vasculitis,[16] or those who underwent medical treatment with immunosuppressants or corticosteroids.[17]

The Taiwan NHI database provides complete and valid information on the demographic characteristics of patients with DM or PM because of the distinctive diagnosis of DM or PM and HZ. The incidence of HZ was significantly higher in patients with DM or PM than in those without DM or PM. The findings of our study corresponded with previous epidemiological data:[18,19]

TABLE 2. Comparison of Incidence and Hazard ratio of Herpes Zoster Viral Infection Stratified by Sex, Age, and Comorbidity Between With and Without Dermatomyositis or Polymyositis Patients

	Dermatomyositis or Polymyositis							
	No			Yes				
Variables	Event	PY	Rate†	Event	PY	Rate†	Crude HR (95% CI)‡	Adjusted HR (95% CI)§
All	324	46,209	7.01	338	9455	35.8	4.96 (4.26, 5.78)***	3.90 (3.18, 4.77)***
Sex								
Female	222	31,746	6.99	258	6438	40.1	5.57 (4.66, 6.67)***	4.32 (3.41, 5.47)***
Male	102	14,463	7.05	80	3017	26.5	3.65 (2.72, 4.90)***	2.88 (1.93, 4.28)***
Stratify age								
≤ 49	122	28,281	4.31	167	6379	26.2	5.99 (4.74, 7.56)***	3.65 (2.68, 4.97)***
≥50	202	17,928	11.3	171	3076	55.6	4.72 (3.85, 5.80)***	4.00 (3.07, 5.22)***
Comorbidity‖								
No	105	22,388	4.69	127	4344	29.2	6.03 (4.65, 7.81)***	4.74 (3.33, 6.74)***
Yes	219	23,821	9.19	211	5110	41.3	4.40 (3.64, 5.31)***	3.55 (2.77, 4.54)***

*** $P < 0.001$.

† Incidence rate, per 1000 person-years.

‡ Relative hazard ratio.

§ Multivariable analysis including age, sex, diabetes, renal disease, obesity, cancer, rhematoid arthritis, autoimmune disease not elsewhere classified, mixed connective tissue disease, vasculitis, immunosuppressant and corticosteroids.

‖ Only to have one of comorbidities (including diabetes, renal disease, obesity, cancer, rhematoid arthritis, autoimmune disease not elsewhere classified, mixed connective tissue disease, and vasculitis) classified as the comorbidity group.

more women were diagnosed with DM or PM (67.2%) and the adjusted HR was greatest in a female population with DM or PM. Moreover, VZV-specific cellular immunity declines with an increasing age.[20] Our findings were consistent with a retrospective review conducted by Chen et al,[21] who identified late DM or PM onset (at 52.3 years of age) as a predictor of infectious complications. Patients aged 50 years or older had a high HZ incidence in our study. The mean age of patients with DM or PM in our study was 45.9 ± 18.0 years, reflecting a peak incidence of DM or PM at 40 to 50 years.[22] The adjusted HR appeared to be higher in the older age group and the exposure cohort was more likely to have coexisting comorbidities and a higher HZ incidence than was the control cohort.

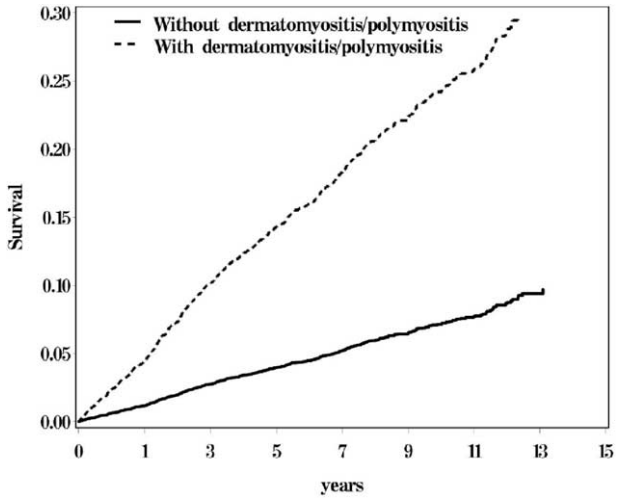

FIGURE 2. The results of the cumulative incidence curve for the HZ.

Current treatment of DM or PM is based on immunosuppression. The core therapeutic approach is daily administration of a high dose of oral corticosteroid therapy along with immunosuppressive agents.[23] In our study, the coexistence of comorbidities and concurrent treatment with immunosuppressants and corticosteroids is independently associated with an increased incidence of subsequent HZ. As documented by Schmader and Oxman,[20] an immunosuppressed patient has a 20- to 100-fold greater risk of developing HZ than does an immunocompetent individual of the same age.

HZ development is determined by factors influencing the host–virus relationship, including old age, cellular immune dysfunction, the female sex, physical trauma to the affected dermatome, and interleukin 10 (IL-10) gene polymorphisms.[24] Hassan et al[25] proposed that VZV increased tropism for activated memory T-cells, which are infiltrated in the muscles affected by DM or PM, leading to a latent HZ viral infection. Cho et al reported a cytokine imbalance, specifically higher levels of IL-10, in patients with DM or PM attributable to the presence of autoantibodies.[26] IL-10 is an immunomodulatory cytokine that suppresses cell-mediated immunity by inhibiting the functions of antigen-presenting cells and cytokine production through activated T-cells.[26] In a study conducted by Cho et al,[27] polymorphisms of the IL-10 promoter gene were reported to be possibly associated with increased susceptibility to HZ. Other nonimmune processes of DM or PM include the endoplasmic reticulum (ER) stress response.[28,29] The ER contributes to the synthesis, folding, and assembly of viral proteins, which can be provoked by a variety of conditions including ischemia in the tissue microenvironment of DM or PM.[30] The ER overload response follows a viral infection, thereby fuelling the inflammatory cascade

TABLE 3. Cox Proportional Hazard Regression Analysis for the Risk of Dermatomyositis or Polymyositis-Associated Herpes Zoster Viral Infection With Interaction of Comorbidity

Variables		N	Event n	Adjusted HR[†] (95% CI)	P-Value[‡]
Dermatomyositis or polymyositis	Comorbidity[§]				<0.001
No	No	3300	105	1 (Reference)	
No	Yes	4190	209	1.70 (1.34, 2.15)***	
Yes	No	832	127	4.80 (3.58, 6.43)***	
Yes	Yes	1191	211	6.03 (4.60, 7.91)***	

*** $P < 0.001$.

[†] Adjusted for age, sex, immunosuppressant, and corticosteroids.

[‡] *P*-value for interaction.

[§] Only to have one of comorbidities (including diabetes, renal disease, obesity, cancer, rhematoid arthritis, autoimmune disease not elsewhere classified, mixed connective tissue disease, and vasculitis) classified as the comorbidity group.

observed in patients with DM or PM.[31] The DM or PM tissue microenvironment including endomysial hypoperfusion, proinflammatory cascade, and the production of a variety of antibodies against immune or stressor molecules contributes to a complex yet efficiently regulated infectious process that plays a crucial role in HZ pathogenesis.[7]

Several limitations exist in this study. First, because of the retrospective nature of this study, the database analysis did not include addressing information such as disease severity and history. However, the NHI database of Taiwan provides complete and valid information regarding the demographic characteristics of patients in both the case and control groups. Despite the shortfall which database analysis did not address information such as HZ severity and history, due to the distinctive diagnoses of DM or PM and HZ, recorded data should be comparable and representative of HZ severity requiring medical attention in both case and control groups. Nevertheless, a study reported that HZ prevalence was independent of disease status and clinical features.[5] Second, unavailable patient information such as smoking or personal habits was replaced with coexisting comorbidities. Our retrospective cohort study revealed a positive association between DM or PM and subsequent HZ viral infection. A prospective cohort study including individual information obtained from chart review may enable to determine a causal relationship between the 2 distinct disease processes. Third, the actual HZ incidence possibly was underestimated because of an underreporting bias. Fourth, the study was limited by the lack of knowledge on whether HZ is a pathogenic or an opportunistic infection in patients with DM or PM. Patients with DM or PM may be susceptible to viral infections other than HZ;[7] therefore, further studies may identify potentially threatening pathogens.

HZ treatment can be effectively provided in the form of antiviral agents and reimbursed by the NHI in Australia. Community-based data have supported the success of zoster vaccination.[32] According to the statistical results of this study, prophylaxis in the form of a live attenuated vaccine should be considered for immunocompetent older adults who have higher incident rate of HZ infection and come in contact with female patients with DM or PM and have at least 1 condition of comorbidities to reduce the risk of transmitting HZ and wild-type VZV to susceptible immunosuppressed contacts.[20] Live attenuated VZV vaccines are effective in healthy individuals; however, vaccine delivery is debatable in immunocompromised patients because of a potential risk of viremia.[33] Furthermore, the involvement of cytokine imbalance in DM or PM and HZ should be considered in future therapy development.

Controlling DM or PM disease activity with immunosuppressive therapy and preventing opportunistic infections are challenging. Currently, identifying potential individuals with high incidence is essential for reducing the incidence of HZ among patients with DM or PM. These patients should be advised to seek prompt medical attention if clinical symptoms associated with HZ develop.[34] Physicians should anticipate

TABLE 4. Incidence and Hazard Ratio for Herpes Zoster Virus and Dermatomyositis or Polymyositis-Associated Medical Treatment

Medicine Treatment	N	Event no.	Rate[†]	Crude HR[‡] (95% CI)	Adjusted HR[§] (95% CI)	Adjusted HR[§] (95% CI)
Comparison						
Without corticosteroids and immunosuppressant	5700	182	5.75	1.00	1.00	
With corticosteroids or immunosuppressant	1790	142	9.76	1.79 (1.44, 2.24)***	1.68 (1.35, 2.10)***	
Dermatomyositis or polymyositis						
Without corticosteroids and immunosuppressant	339	49	28.7	4.97 (3.63, 6.82)***	4.98 (3.62, 6.84)***	1.00
With corticosteroids or immunosuppressant	832	121	33.9	5.80 (4.61, 7.30)***	5.89 (4.68, 7.43)***	1.18 (0.84, 1.64)
Corticosteroids and immunosuppressant	852	168	40.3	6.93 (5.62, 8.55)***	7.43 (6.02, 9.18)***	1.45 (1.05, 1.99)

*** $P < 0.001$.

[†] Incidence rate, per 1000 person-years.

[‡] Relative hazard ratio.

[§] Multivariable analysis including age, sex, diabetes, renal disease, obesity, cancer, rheumatoid arthritis, autoimmune disease not elsewhere classified, mixed connective tissue disease, and vasculitis.

diverse clinical manifestations and be prepared to start early treatment if necessary after understanding the atypical presentations of HZ in immunocompromised hosts. The study finding is crucial to provide insights for identifying high-risk patients likely to suffer from HZ infection, and to open a new avenue of research on the intrinsic defects in DM or PM patients which precipitate HZ infection. Therefore, the health policy to reduce incidence of HZ infection and consequently to improve the patients' quality of life is worth promoting.

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