

# Increased Risk of Chronic Fatigue Syndrome Following Atopy

## A Population-Based Study

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**Abstract:** Several hypotheses have been proposed to explain the etiopathogenesis of chronic fatigue syndrome (CFS), including immune dysregulation. However, few population-based prospective cohort studies have been conducted on CFS and atopy. We investigated the relationship between atopy and CFS by using a population-based cohort study.

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In this prospective, population-based cohort study of the National Health Insurance Research Database, we identified 42,558 patients with atopy and 170,232 patients without atopy from 2005 to 2007 with follow-up to 2011. The incidence rates and risks for CFS were estimated using Cox proportion hazards regression.

The overall incidence rate of CFS was higher in the atopy cohort compared with the nonatopy cohort (1.37 versus 0.87 per 1000 person-year), with an adjusted hazard ratio of 1.48 (95% confidence interval 1.30–1.69). The risk of CFS in the atopy cohort increased 1.47- to 1.50-fold for each nonexisting comorbidity. Patients with numerous atopic symptoms exhibited a biological gradient of increasing risk for CFS, and the risk changed significantly after adjustment for age, sex, and comorbidities, increasing from 1.46- to 2.59-fold.

We revealed that atopy is associated with CFS, particularly in patients with numerous atopic syndromes. The actual mechanism for CFS development in patients with atopy remains unclear and requires further investigation. We recommend researching the subsequent fatigue symptom in patients with atopy, particularly those with multiple atopic syndromes.

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**Abbreviations:** aHR = adjusted hazard ratio, CFS = chronic fatigue syndrome, CI = confidence interval, NHIRD = National Health Insurance Research Database.

## INTRODUCTION

Chronic fatigue syndrome (CFS) is a complex disorder characterized by easy fatigability. Allergies have been identified as one predisposing risk factor of CFS, though this risk factor was deemed inadequate by the U.S. Centers for Disease Control and Prevention.<sup>1</sup> A previous study that summarized the validity of atopic complaints in CFS cases investigated percutaneous skin testing and demonstrated a high correlation between CFS and history of atopy.<sup>2</sup> Several immunological abnormalities of CFS have been reported, such as eosinophil-related protein and histamine allergies.<sup>3,4</sup> Another study discussed whether eosinophil activation plays a pathogenic role in CFS, is associated with allergic conditions, or whether a common immunological background exists for more atopic syndromes and CFS.<sup>5</sup>

CFS has been documented as having uncertain pathogenesis. Allergies have been suggested as one possible predisposing factors.<sup>6,7</sup> Furthermore, the symptoms of allergies and CFS are very similar, the previous study mentioned there were over 50% prevalence rate of atopy in CFS.<sup>8</sup> Therefore, clarifying the relationship between atopy and CFS is difficult. The etiology of CFS might be related to complexity predisposing factor, such as immune system dysfunction, physical deconditioning, exercise avoidance, and childhood illness, etc. Continuing to be

active despite increasing fatigue might be a crucial step in CFS development.<sup>9</sup> One study demonstrated that autoimmune, fatigue, and atopic syndromes were more prevalent in female patients with endometriosis than in those without endometriosis.<sup>10</sup> These findings prompted us to hypothesize an association between atopy and CFS, even the correlation between amounts of atopic syndromes and CFS. Moreover, atopic syndromes, such as idiopathic nonallergic rhinitis, might be associated with the autonomic dysfunction of CFS.<sup>11</sup> Considering these findings, we proposed that atopic syndromes might be associated with subsequent CFS development, and that this relationship might be revealed by a survey of a nationwide health insurance database. Furthermore, this hypothesis of atopic syndromes being associated with an increased risk of CFS lacks evidence from a study with a large sample size; therefore, we tested this hypothesis by using a population-based prospective cohort study and provide the additional evidence for the clarification of atopy and CFS link.

## MATERIALS AND METHODS

### Study Design

We performed a prospective population-based cohort study of 1 million health insurance beneficiaries randomly sampled from the National Health Insurance Research Database (NHIRD) of claims data. All personal identification data in the NHIRD had been encrypted by the National Health Research Institutes (NHRI). The study design was approved by the Institutional Review Board of China Medical University Hospital, China Medical University (CMU-REC-101-012). Previous studies have examined the NHIRD and demonstrated its diagnostic accuracy and validity.<sup>12–15</sup> The claims data collected from the Taiwan National Health Insurance (NHI) program is sorted into data files, including registration files and original claims data. These data files are deidentified by scrambling the identification codes of the patients and medical facilities and then sent to the NHRI, which compiles them into the NHIRD.

### Study Population

Efficient treatments and reliable diagnostic tools for CFS are unavailable. The CFS diagnostic guidance of Taiwan have followed that the Fukuda et al (1994) definition of CFS which ignores other possible causes of fatigue such as malignancy or other identifiable chronic diseases. The definition of atopic dermatitis that is used by the NHI of Taiwan was obtained from the Hannifin and Rajka diagnostic criteria, which involve pruritus, typical eczema, chronically relapsing dermatitis, and a history of atopy. Allergic rhinitis, asthma, and allergic conjunctivitis are diagnosed using general physical examination and other tests.

We used International Classification of Diseases Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes to identify patients. From the registry of ambulatory and inpatient claims data between 2005 and 2007, we identified 42,558 patients with newly diagnosed atopic syndromes (atopic dermatitis, code 691.8; allergic rhinitis, code 477; asthma, code 493; and allergic conjunctivitis, codes 372.14, 372.05, and 372.10) and 170,232 patients without atopy. The atopy diagnosis date was defined as the index date. We excluded patients with a history of CFS (code 780.71) or missing information. For each patient with an atopic syndrome, 4 control patients were selected and frequency-matched by age (in 5-year bands), sex,

and index year. The follow-up for each patient was from 2007 to the date of CFS diagnosis, end of 2011, loss to follow-up, or withdrawal from the NHI system, whichever came first.

### Comorbidity Variables

Numerous diseases were considered as confounders. The history of comorbidities recorded at baseline for each patient included cancer (codes 140–208, from the registry for patients with catastrophic illness), rheumatoid arthritis (code 714, from the registry for patients with catastrophic illness), psoriasis (code 696), hyperthyroidism (code 242), diabetes (code 250), renal disease (codes 582–583.7, 585, 586, and 588), chronic hepatitis (codes 571, 572.2, 572.3, 572.8, 573.1–573.3, 573.8, and 573.9), and depression (codes 296.2–296.9).

### Statistical Analysis

We compared the age, sex, and comorbidities of the case and control groups at baseline by using a  $\chi^2$  test. The incidence rates of CFS were calculated from the follow-up time until the end of 2011, date of CFS diagnosis, death, or loss to follow-up. The Kaplan–Meier (K–M) method was used to delineate the cumulative incidence curves of CFS in the atopy and nonatopy cohorts, and a *P* value was calculated using log-rank test to determine whether the K–M curves differed statistically. Cox proportional hazards regression was performed to measure the effects of atopy on the risk of CFS and calculate hazard ratios (HRs) and 95% confidence intervals (95% CIs). All statistical analyses were executed using the SAS statistical package Version 9.4 for Windows (SAS Institute, Inc., Cary, NC). We set statistical significance at  $\alpha = 0.05$  and plotted the survival curves using the R program Version 2.14.1 for Windows (R Development CT, Vienna, Austria).

## RESULTS

From the 2005 to 2007 claims data, 42,558 patients with atopy and 170,232 people without atopy who met the eligibility criteria were identified (Table 1). These 2 groups were similar in sex and age distributions, with a mean age of 47 years. However, the proportions of patients with cancer, hyperthyroidism, diabetes, renal disease, chronic hepatitis, and depression were larger in the atopy group than in the nonatopy group.

The overall incidence rate for CFS in the atopy cohort (1.37 per 1000 person-year) was higher than in the nonatopy cohort (0.87 per 1000 person-year), as shown in Table 2. The adjusted hazard ratio (aHR) in the atopy cohort indicated a 1.48-fold increased risk of CFS compared with the nonatopy cohort after adjustment for age, sex, and comorbidities. After we stratified the data according to sex, the crude HR for CFS indicated that the atopy cohort exhibited a significantly higher risk of CFS for both men (1.44, 95% CI = 1.17–1.77,  $P < 0.01$ ) and women (1.52, 95% CI = 1.28–1.80,  $P < 0.001$ ) compared with the nonatopy cohort. The stratified age groups  $\geq 65$  years and 20 to 39 years exhibited higher crude HRs, with an approximately 1.56- to 1.80-fold increased risk of CFS, and higher aHRs, with an approximately 1.49- to 1.69-fold increased risk of CFS. Patients with atopy but without cancer, rheumatoid arthritis, hyperthyroidism, diabetes, renal disease, chronic hepatitis, or depression were more likely to exhibit a higher risk of CFS compared with the nonatopy patients (HR = 1.48, 95% CI = 1.30–1.69 for those without cancer; HR = 1.49, 95% CI = 1.30–1.70 for those without rheumatoid arthritis; HR = 1.47, 95% CI = 1.29–1.68 for those without

**TABLE 1.** Demographic Factors and Comorbidity of Study Participants According to Atopic Syndrome

Variable	Nonatopy N = 170,232		Atopy N = 42,558		P-Value
	N	%	N	%	
Gender					0.99
Female	96,128	56.47	24,032	56.47	
Male	74,104	43.53	18,526	43.53	
Age, years					0.99
20–39	66,556	39.10	16,639	39.10	
40–64	73,460	43.15	18,365	43.15	
≥65	30,216	17.75	7554	17.75	
Means ± SD	46.86 ± 17.03		46.95 ± 17.00		0.34
Follow-up time, years, means ± SD	5.25 ± 1.22		5.37 ± 1.14		<0.001
Comorbidity					
Psoriasis	1005	0.59	376	0.88	<0.001
Cancers	3588	2.11	974	2.29	0.02
RA	258	0.15	78	0.18	0.16
Hyperthyroidism	2230	1.31	770	1.81	<0.001
DM	13,035	7.66	4492	10.56	<0.001
Renal disease	3872	2.27	1289	3.03	<0.001
Chronic hepatitis	20,758	12.19	7626	17.92	<0.001
Depression	2515	1.48	954	2.24	<0.001

DM = diabetes, RA = rheumatoid arthritis.

hyperthyroidism; HR = 1.49, 95% CI = 1.29–1.72 for those without diabetes; HR = 1.45, 95% CI = 1.27–1.66 for those without renal disease; HR = 1.43, 95% CI = 1.22–1.68 for those without chronic hepatitis; and HR = 1.50, 95% CI = 1.31–1.71 for those without depression). However, patients with atopy and renal disease (HR = 2.57, 95% CI = 1.33–4.97) and chronic hepatitis (HR = 1.60, 95% CI = 1.26–2.03) exhibited a higher risk of CFS than did patients with renal disease in the nonatopy cohort.

Table 3 shows that patients with more than 1 atopic syndrome exhibited a 1.46- to 2.59-fold higher risk of developing CFS compared with the nonatopic group. The amounts of atopic syndromes were revealed using a biological gradient versus the risk of developing CFS ( $P < 0.001$ ). The cumulative incidence rate of the atopy cohort correlated with a higher risk of CFS than that of the nonatopy group (log-rank test,  $P < 0.001$ ), as shown in Figure 1.

### DISCUSSION

A previous study yielded inconsistent evidence of atopy-related CFS.<sup>16</sup> Patients with CFS are not more likely to have experienced childhood illness or atopy; however, increased levels of exercise throughout childhood and early adult life and a lower body mass index have been associated with an increased risk of CFS later in life.<sup>17,18</sup> Small sample size has been a problem for these studies; therefore, we used a national database to investigate the association.

This study used claims data collected from the NHIRD and thus had a well-defined population. However, several limitations of our study must be mentioned. For example, the data lacked certain information such as laboratory examination and exposure factor data. Most diagnoses recorded in the NHI database are used to request insurance benefits and the reliability is not verified. Furthermore, despite our meticulous

study design, in which confounding factors were adequately controlled, data derived from a retrospective cohort study are generally of lower statistical quality than those derived from randomized trials, because of potential biases.

The Fukuda definition provides a clear description of CFS, which is required to rule out other causes before CFS diagnosis.<sup>19</sup> CFS is similar to disorders such as fibromyalgia, but no efficient treatments for CFS exist.<sup>20,21</sup> Treatment and medication for similar disorders are provided in Taiwan through the NHI program. We assumed a low degree of indiscriminate insurance benefit payment of CFS for unavailable effective biomarkers or treatments in NHI of Taiwan. In addition, self-treatment of atopy is common, particularly among patients with mild symptoms. Most patients with severe atopy are treated in hospitals or clinics. We anticipated that the population-based cohort would underestimate the prevalence or incidence of CFS, because the NHI lacks CFS-specific diagnostic tools and treatments.

Atopy-related CFS was heterogeneous which might be because of the symptom-based diagnosis interference and complexity etiology. However, possible misclassification exists in the both entire population-based cohorts. We therefore restricted patients who were not diagnosed with CFS to the comparison group at baseline and conducted follow-up until the end of 2011. Another limitation was that atopy involves heterogeneous disorders, causing symptoms to appear in different organs damage among different organisms, leading to misclassification. Therefore, we assumed that we would underestimate the risk of CFS following atopy, which could not be avoided when using the NHIRD. Future research on the constructed CFS prospective cohort that considers individual exposure levels, such as adiposity, physical activity, occupation, medication, diet, and other laboratory examination, is warranted.

Despite the prevalence, incidence of CFS would still exist controversy,<sup>22–24</sup> the Institute of Medicine (IOM) of U.S. National Academies was considered that the prevalent CFS

**TABLE 2.** Incidence Density Rates and Hazard Ratio for Chronic Fatigue Syndrome According to Atopic Syndrome Stratified by Demographic Factors and Comorbidity

Variables	Atopic Illness						Atopy to Nonatopy			
	No			Yes			Crude HR (95% CI)	Adjusted HR (95% CI)		
Case	Person-year	IR	Case	Person-year	IR					
Overall	777	893,623.58	0.87	314	228,397.46	1.37	1.59	(1.39–1.81)***	1.48	(1.30–1.69)***
Gender										
Female	450	511,079.26	0.88	183	130,463.56	1.40	1.60	(1.34–1.90)***	1.52	(1.28–1.80)***
Male	327	382,544.33	0.85	131	97,933.89	1.34	1.57	(1.28–1.92)***	1.44	(1.17–1.77)**
Age, years										
20–39	199	358,584.52	0.55	79	91,321.40	0.87	1.56	(1.20–2.03)***	1.49	(1.15–1.94)**
40–64	389	391,240.30	0.99	147	99,615.13	1.48	1.49	(1.23–1.80)***	1.38	(1.14–1.68)*
≥ 65	189	143,798.76	1.31	88	37,460.92	2.35	1.80	(1.40–2.32)***	1.69	(1.31–2.18)***
Comorbidity										
No	496	705,310.87	0.70	168	161,360.70	1.04	1.48	(1.24–1.77)***	1.50	(1.26–1.78)***
Yes	281	188,312.71	1.49	146	67,036.75	2.18	1.47	(1.20–1.80)***	1.49	(1.22–1.82)***
Comorbidity										
Psoriasis										
No	773	888,414.32	0.87	312	226,417.74	1.38	1.59	(1.39–1.81)***	1.49	(1.30–1.70)***
Yes	4	5209.26	0.77	2	1979.72	1.01	1.31	(0.24–7.17)	1.04	(0.18–5.87)
Cancers										
No	762	878,266.03	0.87	306	223,869.22	1.37	1.58	(1.38–1.81)***	1.48	(1.30–1.69)***
Yes	15	15,357.55	0.98	8	4528.24	1.77	1.81	(0.77–4.26)	1.69	(0.82–4.02)
RA										
No	776	892,377.65	0.87	314	228,000.87	1.38	1.59	(1.39–1.81)***	1.49	(1.30–1.70)***
Yes	1	1245.94	0.8	0	396.59	0.00	–	–	–	–
Hyperthyroidism										
No	769	881,762.58	0.87	307	224,207.16	1.37	1.58	(1.38–1.80)***	1.47	(1.29–1.68)***
Yes	8	11,861.00	0.67	7	4190.30	1.67	2.50	(0.91–6.90)	2.47	(0.89–6.83)
DM										
No	685	830,171.53	0.83	92	63,452.05	1.30	1.58	(1.37–1.82)***	1.49	(1.29–1.72)***
Yes	267	205,418.56	1.45	47	22,978.90	2.05	1.42	(1.00–2.02)	1.43	(1.00–2.03)
Renal disease										
No	758	876,544.13	0.86	297	222,108.32	1.34	1.55	(1.36–1.77)***	1.45	(1.27–1.66)***
Yes	19	17,079.45	1.11	17	6289.13	2.70	2.43	(1.26–4.67)*	2.57	(1.33–4.97)**
Chronic hepatitis										
No	594	787,839.53	0.75	204	188,152.96	1.08	1.44	(1.23–1.69)***	1.43	(1.22–1.68)***
Yes	183	105,784.05	1.73	110	40,244.50	2.73	1.59	(1.26–2.02)***	1.60	(1.26–2.03)***
Depression										
No	756	880,828.74	0.86	305	223,381.68	1.37	1.59	(1.40–1.82)***	1.50	(1.31–1.71)***
Yes	21	12,794.84	1.64	9	5015.77	1.79	1.10	(0.51–2.41)	1.07	(0.49–2.35)

CI = confidence interval, DM = diabetes, HR = hazard ratio, IR = incidence density rates, per 1000 person-years, RA = rheumatoid arthritis. Adjusted HR: mutually adjusted for age, gender, and comorbidity in Cox proportional hazards regression.

\*  $P < 0.05$ .  
 \*\*  $P < 0.01$ .  
 \*\*\*  $P < 0.001$ .

patients would be 836,000 to 2.5 million in the United States.<sup>25</sup> The previous viewpoint of CFS was demonstrated that previous approaches contributed to inconclusive observation results and lack of definitive epidemiological evidence, such as incidence and prevalence of CFS in clinic.<sup>26</sup>

In the present study, the incidence of CFS in Taiwan is conservatively estimated because of the low accuracy of CFS diagnosis, matched-pair study design, and presence of other diseases with similar symptoms. Therefore, we conducted a random matched-pair analysis to examine the variation in the risk of developing CFS between patients with and without atopy in the nationwide health insurance database.

Furthermore, we underestimated the risk for CFS despite adjusting for CFS- and atopy-related comorbidities such as rheumatoid arthritis, hyperthyroidism, diabetes, renal disease, chronic hepatitis, and depression. Recent studies suggested that in clinical diagnosis, CFS might overlap with cancer-related fatigue, which has similar mechanisms such as immunologic responses.<sup>27,28</sup> We attempted to adjust for all cancer types to avoid cancer-related fatigue as much as possible. Among the cancer-free patients, the difference of CFS risk between the atopy and nonatopy cohorts was statistically significant. In addition, we identified atopy as a possible risk factor for developing CFS after adjusting for cancer and other comorbidities.

**TABLE 3.** Hazard Ratio of Chronic Fatigue Syndrome Among Number of Atopic Syndrome

Atopic Syndrome	N	Case	Crude HR (95% CI)	Adjusted HR (95% CI)
0	170,232	777	1.00 (Reference)	1.00 (Reference)
1	36,519	259	1.53 (1.33–1.77) <sup>***</sup>	1.46 (1.26–1.68) <sup>***</sup>
2	5546	47	1.76 (1.31–2.36) <sup>***</sup>	1.55 (1.15–2.08) <sup>**</sup>
3+	493	8	3.28 (1.63–6.57) <sup>**</sup>	2.59 (1.29–5.20) <sup>*</sup>
<i>P</i> for trend			<0.001	<0.001

CI = confidence interval, HR = hazard ratio. Adjusted HR: mutually adjusted for age, gender, and comorbidity in Cox proportional hazards regression.

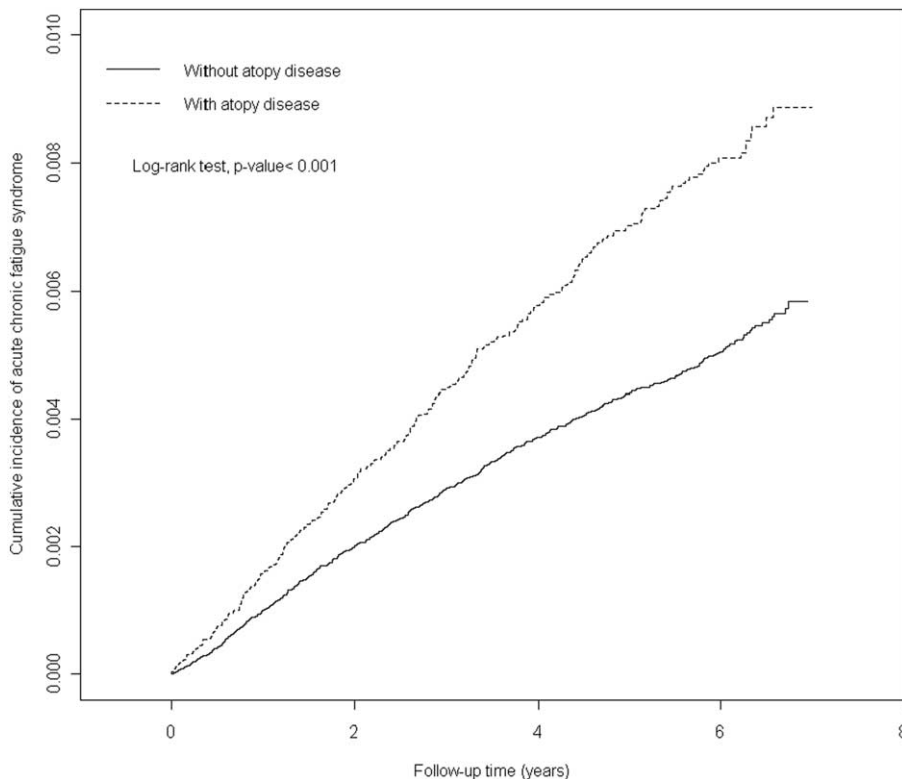
<sup>\*</sup>*P* < 0.05.  
<sup>\*\*</sup>*P* < 0.01.  
<sup>\*\*\*</sup>*P* < 0.001.

International consensus criteria (ICC) for CFS was developed in 2011 by experts from several areas<sup>29</sup> and was based on the 2003 “Canadian definition.”<sup>30</sup> Psychiatric disorders were excluded from the Canadian definition but included in the 2011 ICC definition. However, the current study also considered the atopy-related CFS risks cited as high-risk factors in the Fukuda definition. This population-based prospective cohort study demonstrated that atopy-related CFS risk was significantly higher in patients without depression. This demonstrates the value of the 2011 ICC definition; however, further study is required to demonstrate that the 2011 ICC definition is preferable to the Fukuda definition.

The actual etiology of atopy-related CFS remains unclear. Further research can improve the understanding of the etiology

of CFS, particularly in immune response dysregulation. The previous study discussed the coexistence of immunity dysregulation-associated diseases in women and suggested an underlying role of the immune system in CFS.<sup>31</sup> We considered that the relationship between CFS and atopy could be confirmed using a population-based cohort with individual information and completed specimen for a long-term follow-up, and that the national biobank can play a pivotal role in further CFS research.

Further study must improve the connection between biospecimens and insurance claims data to determine the relationship between atopy and CFS. A previous study reported that modern biobanks possess huge specimen sample sizes and detailed personal data such as medical and socioeconomic data.<sup>32</sup>



**FIGURE 1.** Cumulative incidence curves of chronic fatigue syndrome for atopic syndrome and control groups.

The results of this study demonstrated that atopy might be associated with an increased subsequent risk of CFS. Previous biomarker studies seek to have suggested an association between cytokines levels and CFS. Despite numerous studies seeking evidence to support this hypothesis, the definitive demonstration of biomarkers, such as cytokine<sup>33–38</sup> and lymphocyte activation,<sup>39</sup> such studies with large sample sizes have been limited. Until now, CFS cannot be diagnosed by a valid biomarker before the disease has progressed. We considered that the amounts of atopic syndrome would become a valuable surrogate marker in risk assessment of CFS, especially in the subpopulation existing atopic syndromes. In this study, we demonstrated that the number of atopic syndromes is associated with the risk of atopy-related CFS, but the evidence was insufficient for improving the symptom-based diagnostic criteria of CFS. However, we suggest that physicians note that patients with amounts of atopic syndromes face a higher risk of CFS, regardless of diagnostic criteria.

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