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Increased Risk of Stroke in Patients With Fibromyalgia

A Population-BASED Cohort Study

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Abstract: Neuropsychiatric diseases might enhance stroke development, possibly through inflammation and atherosclerosis. Approximately 25% to 40% of patients with stroke, largely younger patients, are not associated with any conventional stroke risk factors. In this research, we explored whether fibromyalgia (FM), a neuropsychosomatic disorder, increases stroke risk.

From a claims dataset with one million enrollees sourced of the Taiwan National Health Insurance database, we selected 47,279 patients with FM and randomly selected 189,112 age- and sex-matched controls within a 3-year period from January 1, 2000 to December 31, 2002. Stroke risk was assessed using Cox proportional hazards regression.

Comorbidities associated with increased stroke risk, such as hypertension, diabetes, hyperlipidemia, coronary heart disease, irritable bowel syndrome, and interstitial cystitis, were more prevalent in patients with FM and high stroke risk than in the controls. The overall stroke risk was 1.25-fold (95% confidence interval [CI]: 1.21–1.30) higher in the FM group than in the non-FM group. Even without comorbidities, stroke risk was higher in patients with FM than in the controls (adjusted hazard ratio [aHR] = 1.44, 95% CI: 1.35–1.53, $P < 0.001$). The relative risk of stroke was 2.26-fold between FM and non-FM groups in younger patients (age <35 years, 95% CI: 1.86–2.75).

This is the first investigation associating FM with an increased risk of stroke development. The outcomes imply that FM is a significant risk factor for stroke and that patients with FM, particularly younger patients, require close attention and rigorous measures for preventing stroke.

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Abbreviations: CI = confidence interval, FM = fibromyalgia, HR = hazard ratio, ICD-9 = the International Classification of Diseases Ninth Revision, NHIRD = the National Health Insurance Research Database.

INTRODUCTION

Stroke is a leading cause of disability and death in adults.[1–3] To reduce stroke-related socioeconomic and health care costs, early recognition of risk factors has become a priority in stroke prevention.[1–3] However, despite expansive trials, no conventional stroke risk factors have been identified for approximately 25% to 40% of patients with stroke,[4,5] particularly for the younger patients.[6,7] Therefore, identifying other stroke risk factors is necessary to supplement the widely documented cardiovascular risk factors for stroke—including hypertension,[1–7] diabetes,[1–6] hyperlipidemia,[1–4,6] coronary artery disease (CAD),[2,5,6] and atrial fibrillation (AF)[1,2,5–7]—and neuropsychosomatic comorbidities for stroke, such as irritable bowel syndrome (IBS)[8,9] and interstitial cystitis (IC).[10,11]

Possibly through inflammation and atherosclerosis, some psychoemotional disorders (eg, depression[12,13] and anxiety[12,13]) and neuropsychiatric diseases (eg, migraine[14,15] and sleep disorders[16,17]) have been linked to stroke development. Fibromyalgia (FM) is a neuropsychosomatic disorder characterized by several neurosomatic symptoms, such as widespread musculoskeletal pain and chronic fatigue,[18] and certain neuropsychiatric manifestations, including emotional distresses[13] and sleep disturbance.[19] FM is substantially more prevalent among women than among men. Except symptom relief medications,[20] no effective FM therapies have been reported. To the best of our knowledge, no studies have linked FM and stroke development. In the present population-based study, we used the Taiwan National Health Insurance (NHI) claims database to investigate the relationship between FM and stroke development in a cohort containing more than one million enrollees for a 3-year period from January 1, 2000, to December 31, 2002. The selected patients and controls were followed-up from 2000 to 2011.

METHODS AND MATERIALS

Data Source

The NHI program was established by the Bureau of National Health Insurance of Taiwan in March 1995 for

centralizing the disbursement of healthcare funds in Taiwan. This insurance program offers nearly full medical services to over 99% of the approximately 23 million residents of Taiwan.[21,22] In this population-based cohort study, we used the Longitudinal Health Insurance Database (LHID 2000), a subset of the National Health Insurance Research Database (NHIRD). The LHID 2000 contains claims data of one million randomly selected insurants from the 23 million NHI enrollees between 1996 and 2011. It comprises information of the insurants, including age, sex, diagnoses of hospitalizations, and dates of outpatient visits, and admissions. We used International Classification of Diseases, Ninth Revision, Clinical Modification (*ICD-9-CM*) codes to classify diseases.

The NHIRD encrypts patients' personal information to protect privacy and provides researchers anonymous data containing relevant claims information, including sex, date of birth, medical services received, and prescriptions. Therefore, patient consent is not required to access the NHIRD. This study was approved to fulfill the condition for exemption by the Institutional Review Board (IRB) of China Medical University (CMUH-104-REC2–115). The IRB also specifically waived the consent requirement.

Study Participants

In this retrospective cohort study, we selected patients diagnosed with FM (*ICD-9-CM 729.0, 729.1*) between 2000 and 2002 as the study group (FM group).[22] The FM group comprised 47,279 patients newly diagnosed with FM. FM diagnosis dates were defined as the index dates. By frequency matching according to age (in 5-year bands), sex, and index year, 4 patients without FM were randomly selected for each FM patient from the LHID 2000 to form the non-FM group (n = 189,112). The study objective was to estimate the risk of different types of stroke (*ICD-9-CM 430–438*), including hemorrhagic stroke (intracerebral hemorrhage + subarachnoid hemorrhage) and ischemic stroke (transient ischemic attack + cerebral infarction), in the FM and non-FM groups.

Patients with missing demographic information or with stroke diagnoses before the index dates were excluded from this study. The potential stroke risk factors considered for amendment were diabetes (*ICD-9-CM 250*), hypertension (*ICD-9-CM 401–405*), hyperlipidemia (*ICD-9-CM 272*), CAD (*ICD-9-CM 410–413, 414.01–414.05, 414.8, 414.9*), AF (*ICD-9-CM 4273, 427.31, 427.32*), IBS (*ICD-9-CM 564.1*), and IC (*ICD-9-CM 595.1*). The follow-up duration was calculated from the index date to the date of stroke diagnosis, withdrawal from the NHI, or December 31, 2011.

Statistical Analysis

The SAS 9.3 statistical package (SAS Institute Inc, NC, USA) was used for the statistical analyses. A 2-tailed $P < 0.05$ was considered significant. The baseline distribution of demographic variables and potential risk factors in the FM and non-FM groups were analyzed using a χ^2 test for categorical variables and a Student *t* test for continuous variables, respectively. The incidence rates of stroke in both groups were calculated after stratifying each variable. The crude hazard ratios and 95% confidence intervals (CI) of stroke were presented using Cox proportional hazard regression. After adjusting confounding factors (age, sex, diabetes, hypertension, hyperlipidemia, CAD, IBS, IC, and AF), the association between FM and stroke was evaluated using a multivariate Cox proportional hazard model to estimate the adjusted hazard

ratio (aHR) and 95% CI. To analyze the association between FM severity and stroke development, we stratified the FM patients into subgroups of having been (severe FM group) and having not been hospitalized because of FM (mild FM group) during the study period. In addition, we conducted a Kaplan–Meier analysis of the cumulative incidence of stoke in the 2 groups by using R software (R Foundation for Statistical Computing, Vienna, Austria) and estimated the difference between the 2 cumulative incidence curves by using a log-rank test.

RESULTS

The baseline demographic characteristics of the FM group and non-FM group are listed in Table 1. The mean ages were 44.6 years (standard deviation [SD] 16.4) and 44.7 years (SD 16.3) in the non-FM and FM groups, respectively. The 2 groups did not significantly differ in age ($P = 0.40$). Most participants were women (59.5%) and in the age group of 35 to 65 years (59.0%). Most stroke comorbidities, including diabetes (9.58% [FM] vs 6.98% [non-FM]), hypertension (22.3% vs 16.5%), hyperlipidemia (15.5% vs 9.12%), CAD (6.08% vs 3.71%), IBS (6.98% vs 3.50%), and IC (0.15% vs 0.05%) were more prevalent in the FM group than in the non-FM group (Table 1).

At the end of the follow-up period, the cumulative stroke incidence was higher in the FM group than in the non-FM group (Figure 1). The incidences of stroke were 9.86 and 7.17 per 1000 person-years in the FM and non-FM groups, respectively. The overall stroke risk was 1.25-fold (95% CI: 1.21–1.30) higher in the FM group than in the non-FM group (Table 2). After adjusting for age, sex, and all comorbidities, there was no significantly difference in the risk of hemorrhagic stroke

TABLE 1. Baseline Demographic Characteristics and Comorbidities in Cohorts With or Without Fibromyalgia

Variable	Non-fibromyalgia (N = 189,112)		Fibromyalgia (N = 47,279)		P
	n	%	N	%	
Sex					0.99
Women	112,572	59.5	28,143	59.5	
Men	76,540	40.5	19,136	40.5	
Age, y					0.99
<35	53,748	28.4	13,437	28.4	
35–65	111,512	59.0	27,878	59.0	
≥65	23,852	12.6	5964	12.6	
Mean (SD)*	44.6 (16.4)		44.7 (16.3)		0.40
Comorbidity					
Diabetes	13192	6.98	4530	9.58	<0.0001
Hypertension	31212	16.5	10550	22.3	<0.0001
Hyperlipidemia	17246	9.12	7318	15.5	<0.0001
CAD	7017	3.71	2873	6.08	<0.0001
IBS	6614	3.50	3298	6.98	<0.0001
IC	104	0.05	69	0.15	<0.0001
AF	710	0.38	170	0.36	0.6123

AF = atrial fibrillation, CAD = coronary artery disease, IBS = irritable bowel syndrome, IC = interstitial cystitis, SD = standard deviation.
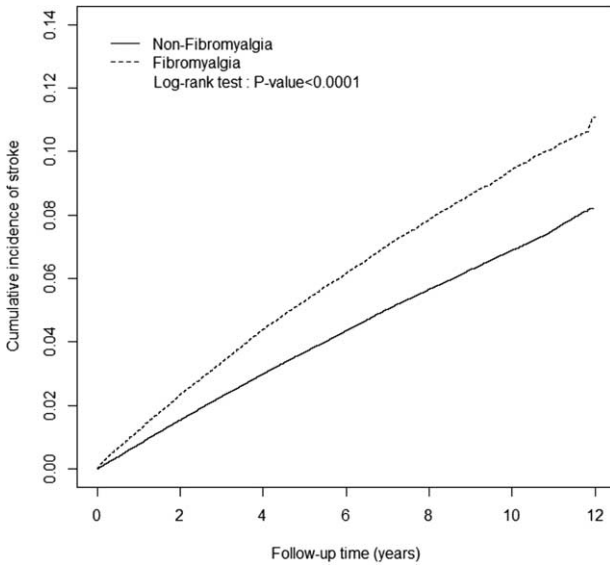Chi-square test.
* Student *t* test.

FIGURE 1. The cumulative stroke incidence between fibromyalgia group (dashed line) and non-fibromyalgia cohort (solid line).

between FM and non-FM groups (aHR = 0.92, 95% CI: 0.82–1.03). However, the risk of ischemic stroke was obviously higher in FM group than non-FM group (aHR = 1.30, 95% CI: 1.25–1.35). Stroke aHR was 1.18-fold higher in men with FM than in men without FM, and 1.32-fold higher in women with FM than in women without FM. The incidence rate of stroke increased with age in both groups. However, the risk of stroke in FM patients decreased with increasing age

(aHR = 2.26, 95% CI: 1.86–2.75 for age <35 years; aHR = 1.25, 95% CI: 1.20–1.31 for 35–65 years; aHR = 1.14, 1.14, 95% CI: 1.09–1.21 for ≥65 years). Regardless of the presence of comorbidities, patients with FM exhibited a higher risk of stroke than people in the non-FM group (Table 2).

The risk of stroke stratified by comorbidity for FM patients is reported in Table 3. Irrespective of the presence of hypertension, hyperlipidemia, CAD, and IBS, the FM group had a higher risk of stroke than non-FM group. The aHRs for patients with FM but without diabetes, IC, and AF were 1.31 (95% CI: 1.26–1.36), 1.25 (95% CI: 1.21–1.30), and 1.26 (95% CI: 1.21–1.30), respectively. Compared with patients without comorbidities, the risk of stroke increased in different extents with various comorbidities in both the FM and non-FM groups (Table 4). In the non-FM group, patients with only diabetes exhibited the highest risk of stroke (aHR = 2.57, 95% CI: 2.44–2.70). In the FM group, patients with only hypertension had the highest risk of stroke (aHR = 2.15, 95% CI: 1.99–2.32). With stratification of FM severity, the risk of stroke development in FM patients with different severities was illustrated in Table 5. Compared with the non-FM group, the risk of stroke was slightly higher ($P < 0.0001$) in patients with FM with hospitalization (severe FM group) (aHRs = 1.30, 95% CI: 1.05–1.62) than in patients with FM without hospitalization (mild FM group) (aHRs = 1.25, 95% CI: 1.21–1.30).

DISCUSSION

Most patients with FM were women and middle aged (Table 1), which is in agreement with the literature.[23–25] The age and sex distributions validated the FM population collected from the Taiwan NHI database. Our result suggests that FM group was correlated with a relatively high risk of stroke.

TABLE 2. Incidence and HRs of Stroke Between Fibromyalgia and Comparison Cohorts, Stratified by Demographic Characters and Comorbidities

| | Fibromyalgia | | | | | | With Compared to Without Fibromyalgia | |
| | No | | | Yes | | | | |
Variables	Event	PY	Rate	Event	PY	Rate	Crude HR (95% CI)	Adjusted HR[†] (95% CI)
Overall	12,759	1,779,084	7.17	4464	452,748	9.86	1.38 (1.33–1.42)**	1.25 (1.21–1.30)**
Hemorrhagic stroke	1519	1779083	0.85	370	452,748	0.82	0.96 (0.86–1.07)	0.92 (0.82–1.03)
Ischemic stroke	11,239	1,779,083	6.32	4094	452,748	9.04	1.43 (1.38–1.49)**	1.30 (1.25–1.35)**
Sex								
Women	6822	1,076,788	6.34	2506	273,011	9.18	1.45 (1.39–1.52)**	1.32 (1.26–1.38)**
Men	5937	702,296	8.45	1958	179,738	10.9	1.29 (1.23–1.36)**	1.18 (1.12–1.24)**
Age, y								
<35	262	526,392	0.50	169	136,094	1.24	2.48 (2.05–3.01)**	2.26 (1.86–2.75)**
35–65	6734	1,079,236	6.24	2496	271,806	9.18	1.47 (1.41–1.54)**	1.25 (1.20–1.31)**
≥65	5763	173,456	33.2	1799	44,849	40.1	1.21 (1.15–1.28)**	1.14 (1.09–1.21)**
Comorbidity								
No	4938	1,394,484	3.54	1414	308,941	4.58	1.29 (1.22–1.37)**	1.44 (1.35–1.53)**
Yes	7821	384,600	20.3	3050	143,807	21.2	1.05 (1.00–1.09)*	1.15 (1.11–1.20)**

CI = confidence interval, HR = hazard ratio, PY = person-year, Rate = incidence rate per 1000 person-years.
* $P < 0.05$.
** $P < 0.001$.
† Adjusted HR: multiple variable analysis including age, sex, and history of comorbidities including diabetes, hypertension, hyperlipidemia, coronary artery disease, irritable bowel syndrome, interstitial cystitis and atrial fibrillation.

TABLE 3. Incidence and HRs of Stroke Between Fibromyalgia and Comparison Cohorts, Stratified by Comorbidities

Variables	Fibromyalgia						With Compared to Without Fibromyalgia	
	No			Yes				
	Event	PY	Rate	Event	PY	Rate	cHR (95% CI)	aHR[†] (95% CI)
Diabetes								
No	9968	1,673,338	5.96	3438	414,166	8.30	1.39 (1.34–1.45)***	1.31 (1.26–1.36)***
Yes	2791	105,746	26.4	1026	38,582	26.6	1.01 (0.94–1.09)	1.06 (0.99–1.14)
HTN								
No	6405	1,523,391	4.20	2047	362,994	5.64	1.34 (1.28–1.41)***	1.39 (1.32–1.46)***
Yes	6354	255,693	24.9	2417	89,755	26.9	1.09 (1.04–1.14)***	1.14 (1.08–1.19)***
Hyperlip								
No	9945	1,626,674	6.11	3141	386,440	8.13	1.33 (1.28–1.38)***	1.28 (1.22–1.33)***
Yes	2814	152,410	18.5	1323	66,309	20.0	1.08 (1.02–1.16)*	1.16 (1.09–1.24)***
CAD								
No	11223	1,725,269	6.51	3759	429,378	8.75	1.35 (1.30–1.40)***	1.27 (1.22–1.32)***
Yes	1536	53,814	28.5	705	23,370	30.2	1.06 (0.97–1.16)	1.14 (1.05–1.25)**
IBS								
No	12507	1,750,999	7.14	4327	440,313	9.83	1.38 (1.33–1.43)***	1.25 (1.21–1.30)***
Yes	252	28,085	8.97	137	12,436	11.0	1.23 (0.99–1.51)	1.30 (1.15–1.46)***
IC								
No	12747	1,778,118	7.17	4453	452,114	9.85	1.38 (1.33–1.42)***	1.25 (1.21–1.30)***
Yes	12	966	12.4	11	634	17.3	1.38 (0.61–3.13)	1.60 (0.67–3.84)
AF								
No	12569	1,774,744	7.08	4420	451,569	9.79	1.38 (1.34–1.43)***	1.26 (1.21–1.30)***
Yes	190	4340	43.8	44	1179	37.3	0.86 (0.62–1.20)	0.93 (0.67–1.29)

AF = atrial fibrillation, aHR = adjusted hazard ratio, CAD = coronary artery disease, cHR = crude hazard ratio, CI = confidence interval, HTN = hypertension, Hyperlip = hyperlipidemia, IBS = irritable bowel syndrome, IC = interstitial cystitis, PY = person-year, Rate = incidence rate per 1000 person-years.
* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.
[†] Adjusted hazard ratio: multiple variable analysis including age, sex, and history of comorbidities including hypertension, diabetes, hyperlipidemia, coronary artery disease, irritable bowel syndrome, interstitial cystitis and atrial fibrillation.

TABLE 4. Joint Effect of Comorbidities on Stroke Between Fibromyalgia and Comparison Cohorts

	Fibromyalgia			
	No		Yes	
Comorbidity	Event	Adjusted HR (95% CI)	Event	Adjusted HR (95% CI)
Without any comorbidity	4859	1.00	1336	1.00
With hypertension only	6354	2.32 (2.22–2.41)***	2417	2.15 (1.99–2.32)***
With hyperlipidemia only	2814	2.06 (1.97–2.17)***	1323	1.88 (1.73–2.04)***
With diabetes only	2791	2.57 (2.44–2.70)***	1026	2.14 (1.96–2.34)***
With CAD only	1536	2.05 (1.93–2.18)***	705	1.94 (1.75–2.15)***
With IBS only	684	1.63 (1.50–1.76)***	448	1.69 (1.52–1.89)***
With IC only	12	2.31 (1.31–4.07)**	11	2.02 (1.12–3.66)*
With AF only	190	2.22 (1.91–2.57)***	44	1.69 (1.24–2.30)***

Adjusted HR = hazard ratio adjusted for age and sex, AF = atrial fibrillation, CAD = coronary artery disease, CI = confidence interval, HR = hazard ratio, IBS = irritable bowel syndrome, IC = interstitial cystitis.
* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

TABLE 5. Incidence and Hazard Ratio for Stroke, Stratified by Fibromyalgia With or Without Hospitalization During the Study Period

Variables	Event	PY	Rate	Adjusted HR (95% CI)[†]
Non-fibromyalgia group	12,759	1,779,084	7.17	1.00
Fibromyalgia group				
Without Hospitalization	4382	446,249	9.82	1.25 (1.21–1.30)[**]
With Hospitalization	82	6500	12.6	1.30 (1.05–1.62)[*]
P for trend				<0.0001

CI = confidence interval, HR = hazard ratio, PY = person-year, Rate = incidence rate (per 1000 person-years).
[*] *P* < 0.05.
[**] *P* < 0.001.
[†] Adjusted HR: multiple analysis including age, sex, and history of comorbidities.

Although women were the majority in the FM group, FM increased the stroke risk in both sexes.

Age is the most critical stroke risk factor.[1–3] With continuously expanding incidence rates of stroke with advancing age, most stroke patients were older than 65 years in both FM and non-FM groups. However, the weight of stroke increase was relatively higher in the younger population. Because stroke-related comorbidities were less prevalent in the younger population, the effect of FM per se was more pronounced in younger patients than in elders. Compared with the controls, Table 5 revealed a slightly higher stroke risk in FM patients with hospitalization owing to FM than in those without. These results demonstrated a dose–response effect among FM severity and stroke, and this further strengthened the association of FM with stroke development.

Stroke Comorbidities

Among the several risk factors identified for stroke,[1–11] age,[1–3] male sex,[1–3] hypertension,[1–7] diabetes,[1–6] hyperlipidemia,[1–4,6] CAD,[2,5,6] AF,[1,2,5–7] IBS,[8,9] and IC[10,11] have been demonstrated to show different weights. With and without superimposition of individual comorbidities, stroke risk increased to varying extents in both the FM and non-FM groups (Table 3). Thus, this validated the NHI database as a resource for identifying supplemental stroke risk factors, such as FM, in addition to the conventional factors. FM patients without any conventional stroke comorbidities exhibited higher risk of stroke (aHR = 1.44, 95% CI: 135–1.53) than its counterpart did (Table 2). This suggested that FM is an independent risk factor for stroke with higher weights in the younger people (Table 2).

Strengths and Limitations

This retrospective cohort study has several strengths. First, FM patients and the sex- and age-matched controls were extracted from a dataset of over one million enrollees in a national insurance program covering >98% of all Taiwanese residents. Insurance claims for reimbursement for both outpatient and inpatient services are rigorously inspected by the Taiwan Bureau of National Health Insurance for preventing healthcare fraud; such strict validation increases the reliability of diagnoses. The demographic characteristics, revealing the predominance of women and the age distributions, are consistent with the previous investigations.[23–25] Moreover, the association of widely documented stroke risk factors with increased stroke incidences in both groups affirms the validity of this study. Second, the large sample size yielded sufficient power for subgroup stratifications for further statistical analyses, which enabled the verification of the influence of FM on stroke development, particularly in the younger population, in which the stroke cause is generally unknown. The time- and severity-related effects of FM revealed in our analyses further validate FM as a risk factor for stroke.

However, this report has a few limitations. First, we could not completely eliminate the possibility of other confounding cardiovascular risk factors, such as immunity alternations, physical inactivity, and FM medication, influencing patients' stroke susceptibility. Thus, the risks obtained from the present research may contain unknown confounding impacts on FM. Second, personal health habits, such as alcohol consumption and cigarette smoking, cannot be obtained from the NHI dataset; thus, in FM group, the influence of these habits on stroke risk could not be estimated. Nevertheless, FM increased the stroke risk in both sexes, and the considerably low smoking rate (<4.5%) among Taiwanese women[26] implies that, in FM population, cigarette smoking is unlikely to be a confounder for a pronounced increase in stroke risks. Furthermore, higher risk for stroke in younger FM patients (Table 2), who have lower cumulative exposure to smoking and alcohol than older patients do, further indicates that, in FM patients, cigarette smoking and alcohol consumption are not critical in stroke development. Third, comorbidities relevant to stroke were more prevalent among FM patients than in the controls (Table 1), which might enhance the direct influence of FM on stroke development. However, even without stroke-relevant comorbidities, patients with FM exhibited higher risk for stroke development. This reinforces the strong role of FM in stroke development. Forth, in the present study, in clinical circumstances, we cannot avoid the potential bias due to the difficulties in distinguishing FM from other conditions such as myofascial pain syndrome and chronic fatigue syndrome.

CONCLUSIONS

This investigation elucidates, for the first time, that FM presented a higher risk for stroke development, with a more pronouncement in the younger patients. Although FM might share common causes, such as cardiovascular diseases, for stroke, the time- and severity-dependent effect of FM on stroke risk implies a possible causal relationship of FM and stroke development. Patients with FM must be adequately monitored and measurements should be implemented earlier for stroke prevention, particularly for those with traditional stroke risk factors. Because of relatively higher stroke risk found in this study, younger FM population is recommended to undergo rigorous follow-up for stroke prevention.

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