

The prevalence and risk factors for serositis in patients with systemic lupus erythematosus: a cross-sectional study

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Abstract This study aims to estimate the prevalence of serositis and identify risk factors for serositis in a large cohort of systemic lupus erythematosus (SLE) patients. A cross-sectional study was conducted based on the medical records of patients hospitalized with SLE at the First Affiliated Hospital of Anhui Medical University and Anhui Provincial Hospital. Patients were diagnosed with serositis when they presented with symptoms and signs of pleuritis or/and pericarditis. We explored factors associated with the generation and quantity of serositis by using binary and ordinal logistic regression analysis. Among the 1668 lupus patients, 298 have serositis. Active lupus disease, fever (≥ 38 °C) and high D-dimer were all significantly associated with the generation and quantity of serositis. Male gender was independent significant risk factor for pleuritis but not for pericarditis, while low complement C4 and high erythrocyte sedimentation rate (ESR) were risk factors for pericarditis rather than for pleuritis. The possible prevalence of serositis in patients with SLE was 17.9%. The significant associations of active lupus disease, fever (≥ 38 °C) and high D-dimer with serositis suggest that higher disease activity and hypercoagulability may both contribute to the generation and development of serositis in SLE. The risk factors for pleuritis and pericarditis in SLE are similar but not identical.

Keywords Serositis · Pleuritis · Pericarditis · Systemic lupus erythematosus · Risk factor

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Introduction

Systemic lupus erythematosus (SLE) is one of the common autoimmune diseases that can affect almost all organs of the body. Predominant manifestations include arthritis, rash, renal and nervous system involvement [1]. Serositis, which refers to inflammation of serous membranes, does occur in SLE and may be a significant cause of morbidity. In light of the 1997 revised American College of Rheumatology (ACR) criteria, serositis refers either to pleuritis or to pericarditis [2].

The prevalence of serositis in SLE varies depending on definitions of disease used, the different diagnostic approaches, the patient's selection criteria and number of patients involved. A study including 50 SLE patients and 50 age- and sex-matched control subjects found that 54% patients had pericardial effusion and this prevalence was significantly higher than that in control subjects [3]. Another study of 2104 SLE patients reported 16% patients with serositis as a component, which was found to have significant association with the presence of nephropathy, interstitial lung diseases, pulmonary hypertension, hypocomplementemia, leucopenia, thrombocytopenia, elevated anti-double-stranded DNA (anti-dsDNA) antibodies and active disease [4].

An important aim in clinical evaluation of patients is to recognize those at risk to develop disease manifestations, with the goal of precluding irreversible organ and tissue damage before they occur. The symptom of lupus serositis ranges from pleuritic pain and/or pericardial friction murmur to the life-threatening consequences of massive pleural effusion and/or congestive heart failure [5–7]. In this study, we set out to (1) determine the prevalence of serositis in a SLE patient cohort; (2) find the risk factors for occurrence

of serositis; and (3) test whether the common risk factors for occurrence of pleuritis and pericarditis were associated with the quantity of serositis.

Patients and methods

Study's design

A cross-sectional study.

Patient recruitment

The protocol for our study was consistent with the provisions of the World Medical Association Declaration of Helsinki, and informed consent was obtained from each subject before enrollment. This study was conducted with the approval of the ethics committee of Anhui Medical University. We collected the medical records of patients hospitalized with SLE at the First Affiliated Hospital of Anhui Medical University and Anhui Provincial Hospital. All patients fulfilled at least 4 of the SLE classification criteria of the ACR [8]. Collection of data was carried out from January 2011 to December 2015.

Definition of pleuritis, pericarditis and serositis

Patients were diagnosed with serositis when they presented with symptoms and signs of pleuritis or/and pericarditis. Pleuritis was diagnosed when any of the following symptoms were present: typical pleuritic chest pain, pleural rub, radiological evidence (such as chest X-ray or CT scan) or pleurocentesis and laboratory examinations of pleural effusion. Pericarditis was diagnosed when any of the following were detected: typical precordial sharp pain, pericardial rub, electrocardiographic abnormalities, evidence of pericardial effusion on echocardiographic examination or pericardiocentesis and laboratory examinations of pericardial effusion. The diagnosis of lupus-associated serositis was made by exclusion of malignant, thromboembolic and transudative causes such as hypoalbuminemia and heart failure [9]. Moreover, to be considered as non-infectious lupus-related serositis, the clinical records were further reviewed to exclude cases due to tuberculosis, viral and bacterial infections [10]. With these criteria, a retrospective cohort of 1766 SLE patients was recruited. Ninety-eight patients were excluded for missing or incomplete case notes. A final sample of 1668 SLE patients contributed to the analyses.

Study variables

Clinical manifestations of SLE patients, including lupus nephritis, skin rash, alopecia, oral ulcers, neuropsychiatric

symptoms, arthritis, myositis, fever (≥ 38 °C) and vasculitis, were obtained from the medical records. Laboratory abnormalities, including thrombocytopenia ($<100 \times 10^9/L$), leukopenia ($<4.0 \times 10^9/L$), anti-Sm, anti-SSA/Ro, anti-SSB/La, anti-RNP, anti-ribosomal RNP (anti-Rib P), anti-dsDNA, low C3 (<0.85 mg/mL), low C4 (<0.12 mg/mL), high erythrocyte sedimentation rate (ESR) (>20 mm/h), high D-dimer (>0.5 ug/mL) and high fibrinogen (>4.0 mg/ml), were also retrieved. SLE disease activity was evaluated by SLE Disease Activity Index (SLEDAI) score [11]. Active lupus disease was defined as SLEDAI score >8 . Additionally, data on use of corticosteroids or immunosuppressive drugs (use in the past month or not) were obtained by medical record review.

Statistical analysis

A case-control approach was used to compare parameters between disease and non-disease groups. Age and disease duration were dichotomized at the median value. Categorical variables were summarized as frequency (percentage). Comparison of each variable between different groups was evaluated using the Chi-square test or Fisher's exact test. Factors with p values <0.05 in the univariate analyses were investigated further using binary logistic regression analysis; results are presented as odds ratio (OR) along with their 95% confidence intervals (CI).

Next, we investigated the association between the variables, which were the common risk factors for occurrence of pleuritis and pericarditis, with the quantity of serositis. For this analysis, we categorized outcome as (1) 'A' (if the patients have neither pleuritis nor pericarditis); (2) 'B' (if the patients have either pleuritis or pericarditis) and (3) 'C' (if the patients have both pleuritis and pericarditis). Ordinal logistic regression models tested the relation of the risk factors with the odds of having multi-symptom disease.

To test the robustness of our findings, ordinal logistic regression models were further adjusted for demographic variables, including age, sex and disease duration. However, because this did not change the results appreciably, only the results of analyses without adjusting these variables were described below. p value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS 13.0 (Chicago, Illinois, USA).

Results

Serositis

The majority of the cohort was female ($n = 1526$; 91.5%). The median age was 36 years. The median disease duration for SLE was 1.5 years. Among the 1668 lupus patients in

Table 1 Comparison of demographic data between systemic lupus erythematosus patients with pleuritis/pericarditis/serositis and without these features

Variables	Pleuritis			Pericarditis			Serositis		
	Non-disease (n = 1435)	Disease (n = 233)	p value	Non-disease (n = 1507)	Disease (n = 161)	p value	Non-disease (n = 1370)	Disease (n = 298)	p value
Age, \geq 36 years, n (%)	739 (51)	127 (55)	0.394	795 (53)	71 (44)	0.037	709 (52)	157 (53)	0.770
Disease dura- tion, \geq 1.5 years, n (%)	731 (51)	105 (45)	0.094	771 (51)	65 (40)	0.009	707 (52)	129 (43)	0.009
Sex, male, n (%)	113 (8)	29 (12)	0.020	129 (9)	13 (8)	0.834	109 (8)	33 (11)	0.081

Table 2 Comparison of clinical manifestations between systemic lupus erythematosus patients with pleuritis/pericarditis/serositis and without these features

Variables	Pleuritis			Pericarditis			Serositis		
	Non-disease (n = 1435)	Disease (n = 233)	p value	Non-disease (n = 1507)	Disease (n = 161)	p value	Non-disease (n = 1370)	Disease (n = 298)	p value
Lupus nephri- tis, n (%)	641 (45)	135 (58)	<0.001	693 (46)	83 (52)	0.178	611 (45)	165 (55)	0.001
Skin rash, n (%)	548 (38)	74 (32)	0.059	555 (37)	57 (35)	0.235	517 (38)	105 (35)	0.413
Alopecia, n (%)	126 (9)	30 (13)	0.047	131 (9)	25 (16)	0.005	120 (9)	36 (12)	0.075
Oral ulcers, n (%)	109 (8)	19 (8)	0.766	114 (8)	14 (9)	0.608	102 (7)	26 (9)	0.452
Neuropsychiat- ric manifes- tations, n (%)	99 (7)	21 (9)	0.247	103 (7)	17 (11)	0.082	95 (7)	25 (8)	0.378
Arthritis, n (%)	217 (15)	31 (13)	0.470	227 (15)	21 (13)	0.494	205 (15)	43 (14)	0.814
Myositis, n (%)	37 (3)	6 (3)	0.998	33 (2)	10 (6)	0.005	32 (2)	11 (4)	0.181
Vasculitis, n (%)	152 (11)	15 (6)	0.050	148 (10)	19 (12)	0.426	142 (10)	25 (8)	0.303
Fever (\geq 38 °C), n (%)	167 (12)	51 (22)	<0.001	182 (12)	36 (22)	<0.001	156 (11)	62 (21)	<0.001

this study, 298 have serositis; the prevalence was 17.9%. As shown in Table 1, patients with disease duration <1.5 years were more likely to have serositis than those with a longer disease course ($p = 0.009$), while there was no significant difference in age or gender between SLE patients with serositis versus those without serositis.

Clinical characteristics and laboratory findings are compared between patients with serositis and patients without this feature. The results indicated that lupus nephritis and fever (\geq 38 °C) were significantly associated with serositis (all $p < 0.050$). Moreover, rates of anti-Sm, anti-dsDNA, thrombocytopenia, low C3, low C4, high ESR, high D-dimer and high fibrinogen were significantly higher in the patients with serositis (all $p < 0.050$). However, rates of other clinical manifestations and laboratory findings were

not significantly different between the groups (Tables 2, 3). Associations of lupus activity and drug use with serositis were also analyzed. As shown in Table 4, the presence of active lupus disease was significantly higher in the patients with serositis ($p < 0.001$); in contrast, rate of use of corticosteroids or immunosuppressive drugs was significantly lower ($p = 0.002$). Finally, binary logistic regression analysis revealed that fever (\geq 38 °C), active lupus disease, high D-dimer, low C4 and high ESR were independent significant risk factors for serositis (all $p < 0.050$) (Table 5).

Pleuritis

Among the 1668 lupus patients, 233 patients have pleuritis; the prevalence was 14.0%. Compared with female, male

Table 3 Comparison of laboratory data between systemic lupus erythematosus patients with pleuritis/pericarditis/serositis and without these features

Variables	Pleuritis			Pericarditis			Serositis		
	Non-disease (n = 1435)	Disease (n = 233)	p value	Non-disease (n = 1507)	Disease (n = 161)	p value	Non-disease (n = 1370)	Disease (n = 298)	p value
Anti-Sm, n (%)	451 (31)	85 (36)	0.126	467 (31)	69 (43)	0.002	420 (31)	116 (39)	0.006
Anti-SSA/Ro, n (%)	865 (60)	138 (59)	0.761	898 (60)	105 (65)	0.166	825 (60)	178 (60)	0.876
Anti-SSB/La, n (%)	184 (13)	33 (14)	0.573	191 (13)	26 (16)	0.213	176 (13)	41 (14)	0.672
Anti-RNP, n (%)	417 (29)	66 (28)	0.819	423 (28)	60 (37)	0.014	390 (28)	93 (31)	0.344
Anti-Rib P, n (%)	325 (23)	43 (18)	0.152	337 (22)	31 (19)	0.366	314 (23)	54 (18)	0.070
Anti-dsDNA, n (%)	563 (39)	108 (46)	0.040	578 (38)	93 (58)	<0.001	523 (38)	148 (50)	<0.001
Thrombocyto- penia, n (%)	312 (22)	66 (28)	0.026	327 (22)	51 (32)	0.004	297 (22)	81 (27)	0.040
Leukopenia, n (%)	435 (30)	74 (32)	0.657	451 (30)	58 (36)	0.110	410 (30)	99 (33)	0.263
Low C3, n (%)	950 (66)	185 (79)	<0.001	1005 (67)	130 (81)	<0.001	903 (66)	232 (78)	<0.001
Low C4, n (%)	684 (48)	145 (62)	<0.001	715 (47)	114 (71)	<0.001	641 (47)	188 (63)	<0.001
High ESR, n (%)	1000 (70)	193 (83)	<0.001	1053 (70)	140 (87)	<0.001	943 (69)	250 (84)	<0.001
High D-dimer, n (%)	1056 (74)	218 (94)	<0.001	1124 (75)	150 (93)	<0.001	997 (73)	277 (93)	<0.001
High fibrino- gen, n (%)	486 (34)	100 (43)	0.007	515 (34)	71 (44)	0.012	458 (33)	128 (43)	0.002

anti-Sm anti-Smith, *anti-RNP*, anti-ribonucleoprotein, *anti-Rib P* anti-ribosomal RNP, *anti-dsDNA* anti-double-stranded DNA, *ESR* erythrocyte sedimentation rate

Table 4 Comparison of disease activity and drug use between systemic lupus erythematosus patients with pleuritis/pericarditis/serositis and without these features

Variables	Pleuritis			Pericarditis			Serositis		
	Non-disease (n = 1435)	Disease (n = 233)	p value	Non-disease (n = 1507)	Disease (n = 161)	p value	Non-disease (n = 1370)	Disease (n = 298)	p value
Active lupus disease, n (%)	767 (53)	182 (78)	<0.001	809 (54)	140 (87)	<0.001	713 (52)	236 (79)	<0.001
Drug use, n (%) ^a	958 (67)	138 (59)	0.025	1008 (67)	88 (55)	0.002	923 (67)	173 (58)	0.002

^a Use of corticosteroids or immunosuppressive drugs in the past month

patients were more likely to have pleuritis ($p = 0.020$). In contrast, there was no significant difference in age or disease duration between SLE patients with pleuritis versus those without pleuritis (Table 1).

Clinical characteristics and laboratory findings are compared between patients with pleuritis and patients without this feature. The results indicated that lupus nephritis, fever (≥ 38 °C) and alopecia were significantly associated with pleuritis (all $p < 0.050$). Moreover, rates

of anti-dsDNA, thrombocytopenia, low C3, low C4, high ESR, high D-dimer and high fibrinogen were significantly higher in the patients with pleuritis (all $p < 0.050$). However, rates of other clinical manifestations and laboratory findings were not significantly different between the groups (Tables 2, 3). Associations of lupus activity and drug use with pleuritis were also analyzed. As shown in Table 4, the presence of active lupus disease was significantly higher in the patients with pleuritis ($p < 0.001$); in

Table 5 Binary logistic regression analysis on risk factors for pleuritis/pericarditis/serositis in patients with systemic lupus erythematosus

Variables	Pleuritis			Pericarditis			Serositis		
	<i>p</i> value	OR	95% CI	<i>p</i> value	OR	95% CI	<i>p</i> value	OR	95% CI
Fever (≥ 38 °C)	0.006	1.658	1.157–2.377	0.048	1.525	1.005–2.315	0.013	1.534	1.093–2.153
Active lupus disease	<0.001	2.422	1.731–3.388	<0.001	3.735	2.282–6.115	<0.001	2.454	1.781–3.381
High D-dimer	<0.001	3.922	2.268–6.781	0.008	2.422	1.263–4.645	<0.001	3.146	1.951–5.072
Male	0.018	1.725	1.097–2.713	–	–	–	–	–	–
Low C4	–	–	–	0.005	1.709	1.177–2.482	0.049	1.321	1.000–1.743
High ESR	–	–	–	0.024	1.765	1.078–2.893	0.022	1.502	1.060–2.129

OR odds ratio, CI confidence intervals, ESR erythrocyte sedimentation rate

contrast, rate of use of corticosteroids or immunosuppressive drugs was significantly lower ($p = 0.025$). Finally, binary logistic regression analysis revealed that fever (≥ 38 °C), active lupus disease and high D-dimer and male gender were independent significant risk factors for pleuritis (all $p < 0.050$) (Table 5).

Pericarditis

Among the 1668 lupus patients, 161 have pericarditis; the prevalence was 9.7%. Patients with age <36 years were more likely to have pericarditis than those with age ≥ 36 years ($p = 0.009$). In addition, patients with disease duration <1.5 years were more prone to have pericarditis than those with a longer disease course ($p = 0.009$). In contrast, there was no significant difference in gender between SLE patients with pericarditis versus those without pericarditis (Table 1).

Clinical characteristics and laboratory findings are compared between patients with pericarditis and patients without this feature. The results indicated that fever (≥ 38 °C), alopecia and myositis were significantly associated with pericarditis (all $p < 0.05$). Moreover, rates of anti-Sm, anti-RNP, anti-dsDNA, thrombocytopenia, low C3, low C4, high ESR, high D-dimer and high fibrinogen were significantly higher in the patients with pericarditis (all $p < 0.050$). However, rates of other clinical manifestations and laboratory findings were not significantly different between the groups (Tables 2, 3). Associations of lupus activity and drug use with pericarditis were also analyzed. As shown in Table 4, the presence of active lupus disease was significantly higher in the patients with pericarditis ($p < 0.001$); in contrast, rate of use of corticosteroids or immunosuppressive drugs was significantly lower ($p = 0.002$). Finally, binary logistic regression analysis revealed that fever (≥ 38 °C), active lupus disease, high D-dimer, low C4 and high ESR were independent significant risk factors for pericarditis (all $p < 0.050$) (Table 5).

Association between fever (≥ 38 °C), active lupus disease and high D-dimer with the quantity of serositis.

For this analysis, we categorized patients as ‘A’, ‘B’ and ‘C,’ as discussed in the ‘Patients and methods’ section. Occurrence of serositis only at only one site (pleura or pericardium) was found in 202 (12.1%) patients. Simultaneously, occurrence of serositis at two sites (pleura or pericardium) was present in 96 (5.7%) patients. Ordinal logistic regression analysis found that fever (≥ 38 °C), active lupus disease and high D-dimer were all significantly associated with the quantity of serositis ($p = 0.003$ for fever, $p < 0.001$ for active lupus disease and $p < 0.001$ for high D-dimer) (Table 6).

Discussion

In our study, the point prevalence of serositis in the patients with SLE was 17.9%. This rate is in accordance with recent data from mainland Chinese SLE patients [4]. By contrast, it is lower than the prevalence reported in Hong Kong SLE patients [3]. Because of the retrospective nature of the study, we have tried to enhance the validity of the results through collecting the medical records of lupus patients who have been hospitalized in department of rheumatology, which ensured the reasons for hospital admission were related to SLE. Moreover, in general, medical records from patients in inpatient settings were more detailed than that from patients in outpatient settings. Therefore, it is likely that our study reflects the prevalence rate better than the previous studies.

Among the connective tissue diseases, SLE is the most important cause of serositis. Identifying a subgroup of patients with SLE at higher risk of serositis provides the opportunity for early intervention. We found that active lupus disease was significantly associated with serositis. In line with this result, Li et al. [12] and Zhao et al. [4] reported that the presence of serositis was significantly more frequent in active SLE than in inactive SLE.

Table 6 Ordinal logistic regression analysis association between fever (≥ 38 °C), active lupus disease and high D-dimer with the quantity of serositis

Variables	A ^a (n = 1370) N (%)	B ^b (n = 202) N (%)	C ^c (n = 96) N (%)	Ordinal logistic regression		
				p value	OR	95% CI
Fever (≥ 38 °C)						
No	1214 (89)	165 (82)	71 (74)	–	1.000	–
Yes	156 (11)	37 (18)	25 (26)	0.003	1.639	1.178–2.277
Active lupus disease						
No	657 (48)	52 (26)	10 (10)	–	1.000	–
Yes	713 (52)	150 (74)	86 (90)	<0.001	2.869	2.113–3.900
High D-dimer						
No	373 (27)	16 (8)	5 (5)	–	1.000	–
Yes	997 (73)	186 (92)	91 (95)	<0.001	3.547	2.219–5.669

OR odds ratio, CI confidence intervals

^a The patients have neither pleuritis nor pericarditis

^b The patients have either pleuritis or pericarditis

^c The patients have both pleuritis and pericarditis

In addition, hypocomplementemia and increased ESR, which are two well-recognized markers for disease activity, were associated with serositis in the present study. Taken together, all of these findings support that active SLE is an indicator of serositis.

In addition to the reported active lupus disease, we note that high D-dimer was related to risk of serositis. This finding indicates the role of hypercoagulability as a mechanism in the pathogenesis of serositis in SLE. This is in keeping with results from previous studies involving experimental as well as clinical interventions. For example, blockade of pleural hypercoagulability by administration of intrapleural heparin in rabbits with tetracycline (TCN)-induced pleuritis alleviates severity of disease, which associated with reduced visceral-parietal adhesions [13, 14]. In addition, the clinical efficacy of fibrinolytic agents demonstrates fibrin deposition in the human pleural compartment [15, 16]. Thus, we suggest that lupus patients experiencing a disease flare should be screened for serositis, especially if they also have high D-dimer.

We proved that the fever was an independent risk factor. This is in line with another study, which has reported the case of SLE pericarditis presenting as fevers of unknown origin in an adult [17]. Future investigations are required to determine the exact mechanism of fever in the pathogenesis of SLE-associated serositis.

One interesting finding from this study was the fact that male gender was found to be a risk factor for pleuritis, but not for pericarditis, while low C4 and high ESR were independent risk factors for pericarditis rather than for pleuritis. Although serositis refers either to pleuritis or to pericarditis in SLE patients, significant differences between the two diseases should not be ignored.

Another intrigued finding was that the presence of fever, active lupus activity and high D-dimer were proved as indicators of the quantity of the SLE-associated serositis. It is well known that the symptom of SLE-associated serositis ranges from pleuritic pain and/or pericardial friction murmur to the life-threatening consequences of massive pleural effusion and/or congestive heart failure. Although treatment with nonsteroidal anti-inflammatory drugs (NSAID) may be effective in mild cases [5], we suggest that more aggressive immunosuppressive therapies combined with anticoagulant drugs might be considered in complex multi-symptom cases.

The present findings must be interpreted within the context of their potential limitations. First, the cross-sectional design of our study provides insights into associations, but cannot determine causality. Establishing time sequence is requisite to hypothesize causality. Second, in the course of collecting medical records, we found that only about 50% of SLE patients have data on C-reactive protein (CRP). The rest of SLE patients have data on hypersensitive CRP (hsCRP) rather than on CRP. HsCRP and CRP, while similar to each other, they are biologically different. Thus, we could not examine the relationship between CRP and serositis in this study. Third, serositis is one item that contributes to the SLEDAI score of disease activity. When including the SLEDAI score of disease activity among the tested risk factors for serositis, this can pose a problem of circularity. However, when we subtracted the SLEDAI score of serositis from each of the SLEDAI score of the SLE patients with serositis and then tested risk factors for serositis, the results also indicated active lupus disease was significantly associated with serositis. Fourth, for the patients who were diagnosed without serositis in our study, the diagnosis partly comes from clinical practice. Further

researches are required to demonstrate our findings. Finally, the generalizability of the findings in the present study may be limited given that all lupus patients are Chinese.

In summary, serositis is not uncommon in SLE patients. Risk factors, including fever, active lupus disease and high D-dimer, were associated with the generation and quantity of SLE-associated serositis. The risk factors for pleuritis and pericarditis in SLE are similar but not identical.

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Author contribution All authors contributed to: (1) conception and design or acquisition of data or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published.

Compliance with ethical standards

Conflict of interest The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Ethical approval This study was conducted with the approval of the ethics committee of Anhui Medical University and according to the Declaration of Helsinki principles.

Humans rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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