Association of Coagulation Disorder with the Severity and Mortality of Coronavirus Disease 2019 (COVID-19): A Meta-Analysis

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Abstract: Background: Coronavirus disease 2019 (COVID-19) , a significant health concern in recent years, is known for its multiple complications. Coagulation disorder is a prevalent complication among patients with COVID-19, but the association of coagulation disorder with the severity and mortality of COVID-19 is still unclear. The object of this study is to ascertain the potential association between coagulation disorder and severity and mortality of COVID-19. Methods: We conducted a systemic literature search of the CNKI, PubMed, Cochrane Library,and Web of Science databases for all relevant studies up to October 1, 2024. All the articles published were retrieved without language restriction. Meta-analysis were performed by Stata 18.0 software. The Newcastle Ottawa scale was used to assess the quality of the included studies. The funnel plot, Egger's regression asymmetry test, and Begg's test used to measure the bias of publications. Results: Eighteen studies comprising 2,577 COVID-19 patients were included. Six studies was associated with the mortality of COVID-19, indicating significant differences in DD (SMD: 0.81, 95% confidence interval [CI](0.48-1.14), P=0.02, I2=63.82%); APTT (SMD: 0.37, 95% confidence interval [CI](-0.12-0.86), P=0.14, I2=86.85%); PT (SMD: 0.74, 95% confidence interval [CI](0.34-1.15), P=0.00, I2=70.28%) . Twelve studies was associated with the severity of COVID-19, indicating significant differences in DD (SMD: 1.39, 95% confidence interval [CI](0.93-1.86), P=0.00, I2=93.49%); FIB (SMD: 0.63, 95% confidence interval [CI](0.30-0.96), P=0.00, I2=86.32%); PT (SMD: 0.43, 95% confidence interval [CI](0.12-0.74), P=0.01, I2=82.73%) . Conclusions: The findings confirm that coagulation disorder is associated with severity and mortality of COVID-19. Therefore, it is imperative to monitor blood coagulation indicator and administer treatments in COVID-19 to reduce the severity and mortality.

***Keywords*:** Coagulation disorder; COVID-19; SARS-CoV-2, Severity, Mortality

1. Introduction

Since its initial emergence in Wuhan, China in December 2019, coronavirus disease 2019 (COVID-19) has swiftly disseminated across the globe. On January 30, 2020, the World Health Organization (WHO) designated COVID-19 as a Public Health Emergency of International Concern. The relentless and swift proliferation of COVID-19 has triggered a global health crisis, profoundly affecting normal life, economy and political landscapes. Despite the implementation of preventive measures, the numbers of confirmed cases and fatalities continues to rise. As of July 2024, the WHO has reported over 775,673,955 confirmed cases of COVID-19, including 7,053,524 deaths.

COVID-19, one of the major diseases impacting human health in recent times, exhibits a spectrum of clinical symptoms that span from fever and cough to hypoxemia and acute respiratory distress syndrome (ARDS) and multiple organ failure (MOF). As a common complication of COVID-19 patients, coagulation disorder is thought to be intricately linked to the severity and mortality of COVID-19 patients. Some patients with severe COVID-19 have coagulation dysfunction, which is manifested by a marked elevation in D-dimer levels and fibrinogen degradation products[1]. However, due to the ongoing investigations into the pathogenesis of COVID-19, a unified consensus on the precise mechanism underlying coagulation disorders in these patients has not yet been established, and the corresponding treatment strategy remains elusive.

A meta-analysis conducted in 2021[2] reveled that patients with severe COVID-19 exhibited significantly elevated levels of D-dimer, fibrin degradation product (FDP) compared to those with non-severe cases. However, this meta-analysis did not offer a statistical analysis of coagulation disorder and clinical mortality in COVID-19 patients, nor did it assess all markers of coagulation function. Considering the limitations of the time and space of existing studies, the limitation of the source of cases, and the existence of other influencing factors such as gender, age, study type and research method, this study conducts a meta-analysis based on existing studies. The aim is to investigate the potential link between coagulation disorders and the severity as well as mortality in COVID-19 patients.

2. Material and Methods

2.1 Study protocol and registration

This meta-analysis was conducted in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[3]. The International Prospective Register of Systematic Reviews has reported this protocol (PROSPERO identifier: CRD42024560963).

2.2 Search strategy

To discern high-quality evidence, we conducted a comprehensive search in a wide spectrum of databases, namely the CNKI, Wanfang patent database, PubMed, Cochrane Library and Web of Science databases for all relevant studies up to October 1, 2024. The search terms were as follows: “coronavirus disease 2019” or “COVID-19” or “2019 novel coronavirus” or “SARS-CoV-2” or “nCoV-2019” or “new coronavirus pneumonia” and “coagulation disorder” or “blood coagulation” or “D-dimer” or “fibrinogen” or “Activated partial thromboplastin time (APTT)” or “clinical characteristics” or “risk factors” and “cohort” or “case control” . The retrieved studies were also manually searched to ensure other related studies. We entered all the articles into EndNote X9.3.1 reference manager software for review, and then deleted duplicate articles.

2.3 Selection criteria

The included studies were characterized as follows: (1) study design: case–control study or cohort study; (2) COVID-19 cases: all COVID-19 cases were throat swab positive and COVID-19 patients ≥18 years old; (3) Clearly define "severe"; For the identification of severe patients, one of the conditions should be met in the Guidelines on the treatment with integrated traditional Chinese medicine and western medicine for severe coronavirus disease 2019[4]: ① shortness of breath, RR≥30 times /min; ② at rest, SpO2≤0.93 when inhaling air; ③ oxygenation index (arterial blood oxygen partial pressure (PaO2)/ oxygen concentration (fractional concentration of inspired oxygen, FiO2), PaO2/FiO2] ≤300mmHg (1mmHg≈0.133kPa); ④ the clinical symptoms worsened progressively, and the lung imaging showed that the lesions progressed significantly more than 50% within 24 to 48 hours; ⑤ respiratory failure and the need for mechanical ventilation; ⑥ shock occurs; ⑦ combined with other organ failure requires ICU monitoring and treatment; (4) clinical outcomes: provide clear outcome indicators; (5) study sample size: at least 10 cases; (6) provide the values of the coagulation indicators relevant to the study: hemoglobin level (Hb), platelet level (PLT), prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (FIB), thrombin time (TT), and D-dimer (DD) level.

2.4 Outcomes of interest

The primary outcome focused on the correlation between coagulation disorder and the severity of COVID-19. The secondary outcome examined the link between coagulation disorder and mortality in COVID-19 patients.

2.5 Data extraction

In this process, two researchers initially extract literature data independently. Subsequently, they will cross-check the literature they have each gathered. Should any discrepancies emerge throughout this process, the two researchers are expected to deliberate and resolve them through discussion. If necessary, a third researcher may be consulted to help resolve the differences.

2.6 Quality assessment

The quality of the articles was independently assessed separately by two reviewers using the Newcastle Ottawa Scale (NOS). The evaluation criteria in this study encompassed the selection of the COVID-19 study population (awarding up to 4 points), the comparability between groups (up to 2 points), and outcome of disease severity or mortality (up to 3 points). The studies included in this meta-analysis were all high quality.

2.7 Data synthesis and analysis

This meta-analysis was performed using statistical analysis software Stata18.0. Forest plots were used to illustrate the association between cocoagulation disorder and the severity and mortality of COVID-19 patients. Mean value, standard deviation (SD), standardized mean difference (SMD), and 95% confidence interval (CI) were used to describe statistical significance, and the association between coagulation disorder and severity and mortality of COVID-19 was quantitatively assessed. The statistical heterogeneity of the included studies was evaluated comprehensively using the I^2 and Q tests. If $I^2<50\%$ and $P>0.10$ of the Q test, it indicates that there is no significant heterogeneity between studies, and the fixed-effect model is used; otherwise, the random-effect model is combined. The P-value of the effect was derived from the fixed or random effect models, and the outcome was considered statistically significant at $P<0.05$.

3. Results

3.1 Search results

A total of 515 studies were retrieved, 121 duplicates were excluded after preliminary screening. Subsequently 326 studies were excluded after reviewing the titles and abstracts. Following a thorough examination of the full texts. 50 were dismissed due to inconsistencies in primary and secondary outcome. Ultimately, 18 studies were included, involving 2,577 patients with COVID-19. Of these, 6 studies focused on mortality risk associated with COVID-19, while 12 studies addressed the severity of the disease. The process of literature screening are illustrated in Figure 1. Sample sizes ranged from 33 to 420 people.

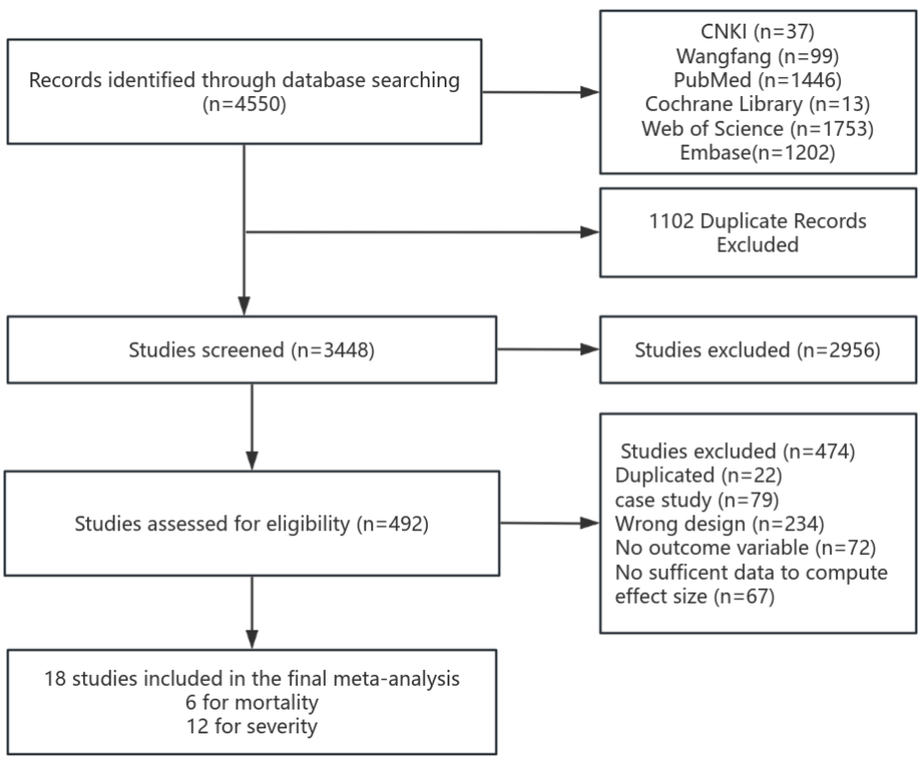

Figure 1. Flow chart showing the study selection

3.2 Patients characteristics

The included studies included the following information: (1) name of the first author; (2) publication year, type of study design, sample size and severity criteria; (3) general characteristics of participants (sample size of non-severe cases, severe cases, deaths, and survival cases); (4) Data level of relevant coagulation indicators, if reported.(Table 1)

Table 1. Patients characteristics based on COVID-19; Data are expressed as mean± standard deviation; median [interquartile range]; median (range)

First author	Year	Local	Study period	Study design	Diagnose criteria	Number of patients (severe/non-severe; non-survival/survival)	Age	Gender(male)
Qiu[5]	2022	Changde	2020.1.20-2020.3.9	Retrospective analysis	RT-PCR	22/60	56.5 ±14.43/ 43.25 ±10.62	12(54.55)/ 29(48.33)
Guo[6]	2022	Yangzhou	2021.1-2021.9	Retrospective analysis	RT-PCR	50/15	60.51 ±15.72/ 58.41 ±14.09	11(73.33)/ 17(34.00)
Ke[7]	2023	Fujian	2022.12.1-2023.2.1	Retrospective analysis	RT-PCR	30/20	22~85	29
Zhong[8]	2021	Chongqing	2020.1.20-2020.3.1	Retrospective analysis	RT-PCR	33/33	60.5 ±14.8/ 43.2 ±7.7	19/20
Duan[9]	2022	Henan	2020.1.21-2020.3.1	Retrospective analysis	RT-PCR	18/35	59.8 ±10.7/ 44.3 ±16.4	10/10
Wang[10]	2021	Fuyang	2020.1-2020.2	Retrospective analysis	RT-PCR	17/103	/	/

First author	Year	Local	Study period	Study design	Diagnose criteria	Number of patients (severe/non-severe; non-survival/survival)	Age	Gender(male)
Lihong Wang[11]	2023	Shijiazhuang	2022.10-2023.2	Retrospective analysis	RT-PCR	102/55	77(68,83)/ 70(53,78)	68/32
Hend M[12]	2022	/	2021.1-2021.6	Prospective study	WHO interim guidelines	71/196	52.65 ±14.92/39.59 ±15.62	33/117
Ti Yang[13]	2023	Kunshan	2022.11-2023.1	Prospective study	SARS-CoV-2 PCR	177/243	/	122/124
Shiyan Feng[14]	2023	Shenzhen	2020.1-2020.3	Prospective study	RT-PCR	63/73	/	39/30
Xu Chen[15]	2020	Jingzhou	2020.2.1-2020.3.6	Retrospective analysis	RT-PCR	30/58	/	/
Ying Zou[16]	2020	Shanghai	2020.1.20-2020.2.24	Retrospective analysis	RT-PCR	26/277	65(63-76)/ 50(36-63)	20/138
Zheng[17]	2024	Shantou	2022.12-2023.2	Retrospective analysis	RT-PCR	13/45	74.00 ±10.17/ 65.09 ±10.67	11/33
Reyes Maria Martin-Rojas[18]	2021	Madrid	2020.4	Retrospective analysis	PCR	11/51	64.7 ±14.9/ 61.2 ±15.4	8/35
Al Rasyid[19]	2022	Indonesia	2021.6-2021.8	Retrospective analysis	PCR	11/22	63.45 ±10.66	19
Naif K Binsaleh[20]	2023	Saudi arabia	2020.4-2020.8	Retrospective analysis	RT- PCR	54/54	57.9(12.2)/ 53.5(10.8)	44/42
Huiqi Zhu[21]	2023	Zhejiang	2022.12.1-2023.1.31	Retrospective analysis	RT- PCR	69/132	/	/
Shi Wei[22]	2024	Anhui	2022.12-2023.1	Retrospective analysis	RT- PCR	36/168	80(71-83)/ 68(55-77)	28/110

3.3 Data analysis

A total of 8 indicators of abnormal coagulation function were included in the analysis. The literature included fewer than 3studies for FDP, INR and PT-INR, which were described qualitatively. Meta-analysis was performed for the remaining 6 indicators. According to the heterogeneity test results, a fixed-effect model was employed for FDP, whereas a random-effects model was utilized for the other indicators.(Table 2)

3.4 Results of qualitative analysis

4 studies examined the relationship between INR and COVID-19 outcomes; two of these studies found no significant statistical correlation with patient mortality, while the remaining two also found no significant statistical correlation with the severity of the disease in COVID-19 patients. In contrast, 3 studies focused on FDP, and all indicated a statistically significant association with the severity of COVID-19 patients.

Table 2. Meta-Analysis of some Coagulation Parameters in COVID-19 Patients

Parameters			Heterogeneity			Meta-analysis			
	No. studies	No. patients	I^2	P	T^2	Model	SMD(95%CI)	Z	P
Severe vs. Non-severe									
APTT,s	9	1453	89.94	0.00	0.31	Random	0.36	1.81	0.07
DD,mg/L	12	1807	93.49	0.00	0.61	Random	1.39	5.86	<0.001
FIB,g/L	10	1524	86.32	0.00	0.24	Random	0.63	3.72	<0.001
PT,s	9	1343	82.73	0.00	0.18	Random	0.43	2.70	0.01
TT,s	5	681	92.86	0.00	0.57	Random	0.35	0.98	0.33
FDP,μg/ml	3	510	0.00	0.56	0.00	Fixed	1.17	9.41	<0.001
None-survival vs. survival									
DD,mg/L	6	662	63.82	0.02	0.10	Random	0.81	4.85	<0.001
APTT,s	6	712	86.85	0.00	0.31	Random	0.37	1.47	0.14
Fib,g/L	5	604	69.94	0.02	0.11	Random	-0.02	-0.12	0.91
PT,s	5	511	70.28	0.01	0.14	Random	0.74	3.62	<0.001

3.5 Sensitivity analysis

The sensitivity analysis of the factors for meta-analysis was carried out by deleting literatures one by one.

Severe vs. Non-severe

The meta-analysis results of DD, FIB, PT and TT were robust. However, the analysis results of APTT (Figure 2) are not robust.

None-survival vs. Survival

The meta-analysis results of DD, FIB and PT were robust, while the analysis results of APTT (Figure 2) were not robust.

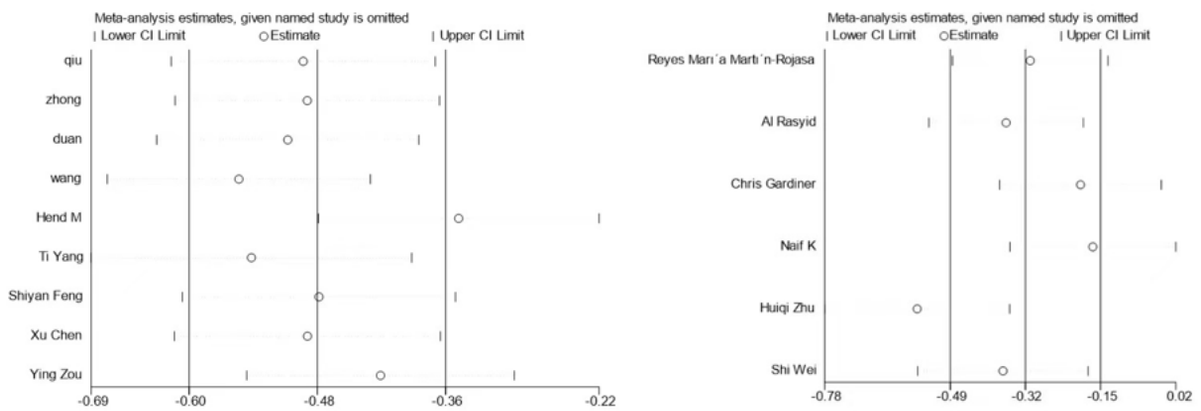

Figure 2. Sensitivity analysis of the APTT levels between COVID-19 patients with or without the severe disease. (Left); Sensitivity analysis of the APTT levels between COVID-19 patients with or without the survival disease. (Right)

3.6 Publications' Bias

Egger's test (Table 3) showed that publication bias existed in DD factors only in the severe and non-severe groups ($P<0.05$), and the combined effect P value was >0.05 after modified by scissor compensation method, indicating that publication bias had a certain impact on the results. To investigate publication bias in DD, funnel plots were drawn between patients in the severe and non-severe groups (Figure 3), and no significant bias was observed in publications.

Table 3. Assessment of Publications' Bias by the Egger's and the Begg's Test

Severe vs. Non-severe	DD	FIB	APTT	PT	TT
Begg't	0.244	0.592	0.348	0.602	0.806
Egger't	0.002	0.677	0.129	0.623	0.983
None-survival vs. survival	APTT	DD	FIB	PT	
Begg't	0.452	0.707	0.221	0.806	
Egger't	0.571	0.658	0.358	0.200	

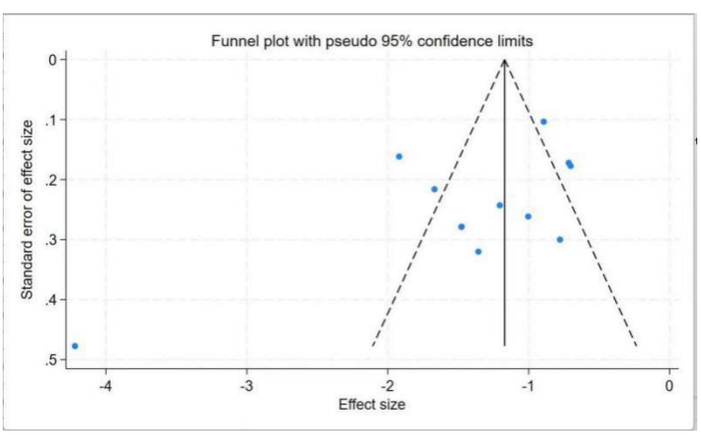

Figure 3. Funnel plot comparing the DD levels indicators among patients with COVID-19

4. Discussion

COVID-19 exhibits a high prevalence, incidence and fatality rate globally. The detrimental effects on the human body are intreicate and multifaceted, the physiological and pathological mechanisms are still unclear. Current studies indicates that a variety of factors can cause severe symptoms in infected patients. Beyond its impact on the respiratory system, COVID-19 can also lead to a range of complications, including thrombosis, myocardial dysfunction, liver cell damage, acute coronary syndrome, gastrointestinal symptoms, acute kidney injury, hyperglycemia and ketoacidosis, and neurological diseases[23]. As our comprehension of COVID-19 advances, it has become evident that coagulation disorders are common among patients, including hypercoagulability, widespread microthrombosis, wasting thrombocytopenia, and hyperfibrinolysis. These conditions are associated with the severity and in-hospital mortality of COVID-19 patients. Some studies have revealed that coagulation disorder in COVID-19 patients possess unique characteristics and mechanisms, which can be summarized as the following reasons: endothelial cell dysfunction, inflammatory cascade, autoimmune disorders, patients-specific factors, and therapeutic interventions. Furthermore, the primary role of endothelial cells is to ensure unobstructed blood flow. The lung lesions caused by the infection of the new coronavirus can induce different degrees of hypoxia. Under such low-oxygen conditions, the rate of fibrin deposition in the blood vessels will be accelerated, thereby disrupting the normal anticoagulant function of endothelial cells and resulting in coagulation disorders.

This meta-analysis revealed that DD, FIB, APTT, and PT were the most significant changes in coagulation function indicators in predicting clinical severity and mortality of COVID-19 patients. DD is a degradation product of cross-linked fibrin clots, resulting from the action of plasmin. Elevated levels of DD indicates the activation of coagulation system and fibrinolytic system in the body, and the body shows a hypercoagulable state[24]. In a way, COVID-19 can be considered a thrombotic disease induced by an immune disorder that may lead to an increase in DD. Regression analysis[25] results indicated that COVID-19 patients often exhibit DD levels exceeding 1.0μg/ml, which are closely related to advanced age, abnormal liver function, and low SpO2. FIB, originating from liver cells, is a glycoprotein that facilitates blood clotting. The pulmonary inflammation in severe COVID-19 patients can impede oxygen exchange in the alveoli, leading to hypoxia and triggering the fibrinolytic system, thereby increasing FIB levels. Research has found that[26] patients with severe COVID-19 tend to have notably elevated FIB levels. APTT reflects the status of endogenous coagulation system, and PT shows the status of exogenous coagulation system, both indicating the possibility of clotting risk. The study by Fu Zhongxiao et al.[27] demonstrated that APTT and PT levels in the severe group were significantly higher than those in the mild group.

Furthermore, this meta-analysis shows that DD, FIB, APTT, and PT are crucial markers for predicting the severity and mortality of COVID-19 patients. Consistent monitoring of these markers' fluctuations can assist clinicians devising strategies for prevention and treatment. Numerous studies have revealed that current clinical treatment guidelines and clinical studies on COVID-19 patients recommend that special attention should be paid to the monitoring of coagulopathy markers and treatment plans should be adjusted except for routine basic treatment. A pivotal aspect of treating COVID-19 involves addressing coagulation abnormalities, as explicitly stated in A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version)[28]: "Anticoagulant therapy should be administered in moderate cases with severe risk factors and rapid disease progression, as well as in severe and critically severe cases, and therapeutic doses of low molecular weight heparin or ordinary heparin can be given without contraindication". The clinical application of heparin is not only limited to anticoagulation, but also has anti-inflammatory and potential antiviral effects, and may improve endothelial function. Considering the various mechanisms of coagulopathy caused by COVID-19, preventive anticoagulation therapy[29], thrombolytic therapy, combined drug use, combined treatment of traditional Chinese[30] and Western medicine, have therapeutic effect on coagulation disorders in COVID-19 patients[31]. The meta-analysis itself has certain limitations. There may be potential factors that have not been clearly identified as confounding variables which could influence the current conclusions. It is also possible that additional factors have been omitted from our consideration, or that the existing literature fails to provide clear indicators or contexts. Consequently, discussing this meta-analysis presents challenges.

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