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De-novo development of fragmented QRS during a six-month follow-up period in patients with COVID-19 disease and its cardiac effects

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ABSTRACT

Objective: The aim of this study is to examine the probability of de-novo fQRS in patients with mild COVID-19 disease, as an indicator of cardiac injury.
Methods: Data of 256 patients with normal admission electrocardiography and no comorbidities between 1.12.2020–31.12.2021, were examined retrospectively 6-month after mild COVID-19 disease. Patients were divided into two groups: fQRS+ group ($n = 102$) and non-fQRS group ($n = 154$). Relation between fQRS and other electrocardiography, echocardiographic and laboratory findings were investigated.
Results: No significant difference was found between the groups among age and gender. Troponin-I and creatine kinase myocardial band values (retrospectively 9.10 ± 1.76 vs 0.74 ± 1.43, 34.05 ± 82.20 vs. 14.68 ± 4.42), COVID-19 IgG levels (45.78 ± 14.82 vs. 36.49 ± 17.68), diastolic dysfunction (39.21% vs. 15.07%), EF value (58.02 ± 1.95 vs. 64.27 ± 3.07), dyspnea (41.17% vs. 6.84%), post-COVID-19 tachycardia syndrome (19.6% vs. 2.74) were more frequent in fQRS+ group compared to non-fQRS group. The EF value was lower in the presence of fQRS in the high lateral leads (57.12 ± 1.99, 58.47 ± 1.79, p:0.018). There was a positive correlation between IgG value and endsystolic diameter, septum thickness and left atrium diameter. In multivariate analysis de-novo fQRS, dyspnea, high troponin and IgG values, diastolic dysfunction, low EF value and left atrial diameter were determined as independent risk factors for post-COVID-19 tachycardia syndrome in follow-up.
Conclusion: In COVID-19 disease de-novo fQRS, dyspnea, high IgG and troponin value, left atrial diameter, lower EF value, diastolic dysfunction were associated with post-COVID-19 tachycardia syndrome. The de-novo fQRS in SARS-COV-2 may be a predictor of future more important adverse cardiovascular outcomes and this should alert clinicians.

Introduction

Coronavirus disease 2019 (COVID-19) is an important health problem since 2019. Angiotensin converting enzyme 2 (ACE2) has a strong binding affinity to the spike protein of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [1]. ACE2 is found in the heart and vessels as well as in the lung tissue. It is assumed that the virus causes heart damage through ACE2 [1]. Acute cardiac injury, defined as serum troponin elevation is detected extensively among patients hospitalized due to COVID-19 in Wuhan and is linked with higher mortality rates in hospitalized patients [2]. Cardiac injury occurs in approximately 8–12% of all hospitalized patients [3]. Direct myocardial injury and systemic inflammation due to viral involvement of cardiomyocytes are the most common mechanisms responsible for cardiac injury [1,4,5]. As we know, no study published so far has examined the development of de-novo fragmented QRS (fQRS) in follow-up in COVID-19 patients. Our study will be the first study in the literature. QRS fragmentation is defined as: the presence of an additional wave like RSR' pattern in <120 ms duration of QRS complex, or the existence of notched S or R waves without any bundle branch block [6]. fQRS is an electrocardiographic sign of myocardial scar tissue, that explain the nonhomogeneous ventricular conduction delay of injured and/or ischemic ventricular myocardium [7]. fQRS has been associated with coronary artery disease severity, mortality, development of heart failure and arrhythmias.[8,9] fQRS development in COVID-19 patients was taken as an indicator of cardiac injury. In our study, the possibility of occurrence of de-novo fQRS in outpatients without any comorbidities, the relationship between fQRS and SARS-CoV-2 immunoglobulin G (IgG) and other laboratory, electrocardiography and echocardiographic findings were

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investigated. The aim of this study is to examine the probability of de-novo fQRS in patients with mild COVID-19 disease, as an indicator of cardiac injury.

Method

The data of 256 patients who were admitted to the outpatient clinic of our hospital between December 1, 2020 and December 31, 2021 and had SARS-CoV-2 real-time RT-PCR method (PCR) positive with mild symptoms, not hospitalized, with normal admission electrocardiography (ECG) and no comorbidities were examined retrospectively six months after COVID-19 disease. The history and physical examination information of the patients were recorded. Patients symptoms: cough, fever, dyspnea, chest pain, weakness, loss of taste, loss of smell were recorded. All patients were screened consecutively for post-COVID-19 tachycardia sendrom. Inclusion criteria for the study: Outpatient treatment with COVID-19 PCR positive test results, between the ages of 18–60, without any comorbidity, no previous drug use, without any pathology in admission ECG. Patients laboratory, ECG and echocardiographic data were examined six months after the diagnosis of COVID-19 disease. Exclusion criteria for the study: patients who were hospitalized with a diagnosis of moderate-to-severe viral pneumonia with COVID-19 PCR positive test results, patients with any comorbidities, patients with fQRS or any pathological findings in their admission ECG.

The study complies with the Declaration of Helsinki. We confirm that all methods were carried out in accordance with relevant guidelines and regulations. This retrospective study was approved by Ministry of Health (No. 2021–01-14T12_55_03) as well as Non-Interventional Clinical Research Ethics Committee (No. 2021/47–03).

Laboratory processes

2 ml of venous blood from patients were collected between December 1, 2020 and December 31, 2021. We used an immunofluorescence assay (IFA), using COVID-19 IgG antibody IFA fast test kits (IF2084 for Getein 1600, Getein Biotech, Inc. Nanjing, China), to evaluate the presence of serum IgG antibody against SARS-CoV-2. The test result is displayed numerically in terms of cut-off index (COI) value. Test result is negative if COI is <1.0 and positive if COI is ≥1.0.

Electrocardiographic evaluation

A 12 lead admission ECG was obtained from each patient before any treatment was started. Also six months later ECGs were obtained. ECGs were analyzed by two independent cardiologists according to the modified Minnesota criteria [8]. Presence of fQRS, length of QTc, QT dispersion and PR dispersion were measured. Myocardial regions on ECG was named as; anterioseptum (V1–4), anterolateral (V4–6), high lateral (DI, aVL), inferior (DII, DIII, aVF).

Echocardiographic data

Left ventricular ejection fraction (EF) determined with Simpson's method, diastolic dysfunction, left ventricular end-systolic diameter, left ventricular end-diastolic diameter, left atrial diameter, back wall and septum thickness were measured.

Definitions

Post-COVID-19 tachycardia syndrome include postural orthostatic tachycardia syndrome or inappropriate sinus tachycardia. A 30 bpm increase in heart rate within the first ten minutes of head-up TILT test or active standing test, without concomitant blood pressure drop and with aggravation of symptoms, is defined as postural orthostatic tachycardia syndrome [9]. Inappropriate sinus tachycardia is defined as on 24-h ECG monitoring average heart rate exceeding 90 bpm or resting heart rate > 100 bpm [9]. The presence of additional wave like RSR' pattern in <120 ms duration of fQRS complex, or the existence of notched S or R waves without any bundle branch block (Figure 1.) has been defined as QRS fragmentation [6]. According to WHO interim guidance, the definitive diagnosis of COVID-19 is based on real-time RT-PCR test.

Statistical analysis

Kolmogorov–Smirnov method was used to analyze all data and fit to a normal distribution.

Chi-square test method was used to analyze categorical variables that are presented as percentages. *t*-test method was used to analyze continues variables in two-way groups, presented as mean ± standard deviation. Pearson's correlation was used for the numerical data. Statistically significant variables were selected into the multivariate logistic regression analysis using the stepwise method. The results of multivariate regression analyses were presented as odd ratio (OR) with 95% confidence interval (CI). SPSS 20.0 (SPSS, Chicago, IL, USA) software was used, and $p < 0.05$ were considered as statistically significant.

Results

Table 1. shows the demographic characteristics and symptom findings of our study. There was no significant difference in mean age between groups with and without fQRS (respectively 36.47 ± 8.72, 33.64 ± 9.22, p: 0.085). Also, there was no statistical difference between the groups in terms of gender (p:0.583). Smoking rate was higher in the fQRS+ group (p: 0.006). When we looked at the symptoms of COVID-19 disease, it was found that the possibility of occurrence of fQRS was statistically higher in patients with dyspnea and fatigue (respectively $p < 0.001$ and p: 0.033). There was no statistical significance between the two groups in terms of other disease symptoms. When we look at the localization of fQRS in ECG, it was observed that it most frequently occurs in inferior leads. Possibility of occurrence of fQRS in the anterior leads is 29.4% $p < 0.001$, in the anterolateral leads is 2% p:0.398, in the high lateral leads is 33.3% $p < 0.001$, in inferior leads is 54.9% $p < 0.001$.

The sixth month laboratory values are summarized in Table 2. The troponin and creatine kinase myocardial band (CK-MB) value was found to be significantly higher in the fQRS+ group (respectively

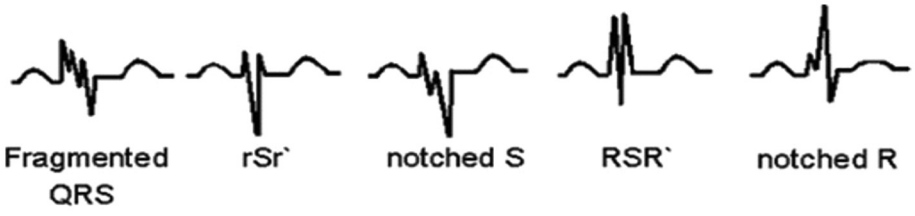

Fig. 1. Fragmented QRS morphology.

Table 1
Relation between demographic characteristics, symptoms and de-novo fQRS of the study population.

Demographic characteristics and symptoms	All patients (n: 248, %)	fQRS (+) (n: 102, %)	non - fQRS (n: 146, %)	P
Age (years)	35.05 ± 8.97	36.47 ± 8.72	33.64 ± 9.22	0.085
Gender (female)	154 (62.09)	58 (56.86)	96 (65.75)	0.583
Smoking	62 (25)	38 (37.3)	24 (16.43)	0.006
Cough	18 (7.25)	4 (3.92)	14 (9.58)	0.315
Fever	46 (19.35)	16 (15.68)	30 (20.54)	0.645
Joint Pain	76 (30.64)	28 (27.45)	48 (32.87)	0.697
Fatigue	78 (31.45)	20 (19.6)	58 (39.72)	0.033
Chest pain	24 (9.67)	14 (13.72)	10 (6.8)	0.219
Dyspnea	52 (20.96)	42 (41.17)	10 (6.84)	<0.001
Taste abnormalities	74 (29.83)	36 (35.29)	38 (26.02)	0.234
Smell abnormalities	66 (26.61)	36 (35.29)	30 (20.54)	0.063

9.10 ± 1.76 vs. 0.74 ± 1.43, p:0.001, 34.05 ± 82.20 vs. 14.68 ± 4.42, p:0.041). In addition, as an indicator of disease severity, it was observed that COVID-19 IgG antibody level was statistically significant higher in the fQRS+ group (respectively 45.78 ± 14.82, 36.49 ± 17.68, p:0.004). D-dimer value was higher in fQRS+ group, but it was not statistically significant. There was no significant difference between the two groups in terms of other laboratory data.

Table 3. shows the echocardiographic and electrocardiographic findings among the groups in the sixth month. The EF value was statistically significant lower in the fQRS+ group compared to the non-fQRS group (respectively 58.02 ± 1.95, 64.27 ± 3.07, $p < 0.001$). Also the diastolic dysfunction was more frequent in fQRS+ group (39.21% vs. 15.07%, p:0.01). Presence of fQRS was related also with wider: end-diastolic diameter (46.21 ± 3.73, 44.13 ± 3.18, p:0.039), end-systolic diameter (31.32 ± 3.32, 29.39 ± 2.70, p:0.03), septum thickness (9.82 ± 0.863, 9.04 ± 1.26, 0.012), and left atrium diameter (35.07 ± 2.61 vs 32.22 ± 2.64, $p < 0.001$). The prevalence of post-COVID-19 tachycardia syndrome in the sixth month was 9.67% (in fQRS+ group 19.6%, in non-fQRS group 2.74%, $p < 0.001$). There was no significant difference between the groups for other parameters.

When we look at the fQRS localization, the EF value was found to be significantly lower in the presence of fQRS in the high lateral ECG leads (57.12 ± 1.99, 58.47 ± 1.79, p: 0.018). There was no significant relationship between the presence of fQRS in other derivations and the EF value.

Table 2
Relationship between sixth month laboratory values and de-novo fQRS.

Laboratory values	fQRS (+)	non - fQRS	P
Troponin (pg/mL)	9.10 ± 1.76	0.74 ± 1.43	0.001
CK* (U/L)	222.57 ± 668.64	89.96 ± 121.48	0.091
CK-MB# (U/L)	34.05 ± 82.20	14.68 ± 4.42	0.041
Covid-19 IgG antibody† (CO/I)	45.78 ± 14.82	36.49 ± 17.68	0.004
CRP‡ (mg/L)	2.24 ± 0.905	2.21 ± 0.57	0.843
Ferritin (ng/mL)	76.25 ± 58.16	67.34 ± 159.55	0.367
Urea (ng/dL)	24.25 ± 9.53	23.17 ± 5.60	0.400
Creatinine (mg/dL)	0.72 ± 0.09	0.73 ± 0.11	0.409
AST§ (U/L)	19.94 ± 11.19	20.34 ± 8.16	0.818
ALT** (U/L)	23.57 ± 15.38	22.43 ± 13.29	0.656
LDH## (U/L)	170.65 ± 37.06	168.92 ± 28.84	0.768
Leukocyte (K/uL)	35.25 ± 9.32	36.68 ± 7.88	0.351
Neutrophil (%)	53.60 ± 10.84	52.02 ± 8.48	0.368
Haematocrite (%)	49.38 ± 58.92	41.85 ± 2.88	0.264
Haemoglobin (g/dL)	16.09 ± 14.60	13.55 ± 1.20	0.131
D-dimer (ng/mL)	95.77 ± 125.03	65.69 ± 97.54	0.130

Abbreviations: *CK: creatine kinase; #CK-MB: creatine kinase myocardial band; †Covid-19 IgG antibody: Covid-19 immunoglobulin G antibody; ‡CRP: C-reactive protein; §AST: aspartate aminotransferase; **ALT: alanine aminotransferase; ##LDH: lactate dehydrogenase.

Table 3
Echocardiographic and electrocardiographic findings in the sixth month.

	fQRS (+)	non - fQRS	P
Ejection fraction (EF) (%)	58.02 ± 1.95	64.27 ± 3.07	<0.001
Diastolic Dysfunction (n, %)	40 (39.21%)	22 (15.07%)	0.01
End-diastolic diameter (mm)	46.21 ± 3.73	44.13 ± 3.18	0.039
End-systolic diameter (mm)	31.32 ± 3.32	29.39 ± 2.70	0.03
Septum thickness (mm)	9.82 ± 0.863	9.04 ± 1.26	0.012
Back wall thickness (mm)	9.31 ± 1.06	9.36 ± 0.97	0.785
Left atrium diameter (mm)	35.07 ± 2.61	32.22 ± 2.64	<0.001
Post-COVID-19 tachycardia syndrome (n, %)	20 (19.6%)	4 (2.74%)	<0.001
QTc (s)	0.406 ± 0.023	0.402 ± 0.023	0.309
QT dispersion (s)	0.369 ± 0.027	0.360 ± 0.029	0.094
PR dispersion (s)	0.159 ± 0.144	0.142 ± 0.018	0.332

There was a positive correlation between IgG value and end-systolic diameter, septum thickness and left atrium diameter (respectively r: 0.337 and $p < 0.001$, r: 0.227 and p:0.013, r: 0.248 and p:0.007).

Predictors of post-COVID-19 tachycardia syndrome were analyzed by logistic regression analysis (Table 4). In multivariate analysis de-novo fQRS, dyspnea, high troponin and IgG values, high diastolic dysfunction, low EF value and left atrial diameter were determined as independent risk factors for post-COVID-19 tachycardia syndrome in follow-up.

Discussion

It has been found that ACE-2 receptors in human cells have a strong binding affinity to the spike protein of SARS-CoV-2 [6]. It is assumed that the cardiac injury associated with SARS-CoV-2 is caused by the high rate of ACE-2 receptors in the heart [1]. It is reasonable to assume that the heart injury caused by COVID-19 could be mediated by ACE-2. Infection of the secretory cell population in the bronchial branches is not only affected by ACE-2 expression; potential cofactors such as proteases, TMPRSS2 and furin are also known to affect this process [5]. However, it is not known how these proteases and SARS-Cov-2 affect heart cells and what kind of damage they cause.

In many studies, the high level of "high sensitivity troponin" or the occurrence of new abnormalities in electrocardiography or echocardiography have been defined as indicators of cardiac injury. Acute myocardial injury due to COVID-19 infection contributes to the development of cardiovascular complications such as acute coronary syndrome, myocarditis, cardiomyopathy, arrhythmia, cardiogenic shock or cardiac arrest. Six month after mild COVID-19 disease we examined the probability of occurrence of de-novo fQRS, as an indicator of cardiac injury, also its relationship with laboratory, electrocardiography and echocardiography data. ECG is usually used as noninvasive test for cardiovascular system disease in which fQRS can be easily detected. We observed that among the laboratory data examined six month later, patients with high troponin, CK-MB and IgG values were found to be more likely to develop fQRS. High troponin and CK-MB value

Table 4
Multivariate logistic regression analysis on risk factors associated with post-COVID-19 tachycardia syndrome.

	OR	95% C·I for OR		p
		Lower	Upper	
De-novo fQRS	0.999	0.998	1.000	0.007
Dyspnea	2.244	1.192	4.234	0.048
Troponin	1.041	1.009	1.074	0.022
COVID-19 IgG levels	1.957	1.122	4.525	0.001
Diastolic Dysfunction	1.766	1.109	2.917	0.009
Ejection Fraction	0.831	0.754	0.914	0.003
Left atrial diameter	1.875	1.099	2.657	0.023

Abbreviations: C·I: Confidence interval.

shows cardiac injury. There was a positive correlation between IgG value and end-systolic diameter, septum thickness and left atrium diameter. When we scan the literature information, the relationship between IgG and fQRS is emphasized for the first time in our study. In our study, the presence of fQRS, which is an indicator of myocardial fibrosis, and enlargement in the heart cavities, besides high troponin and CK-MB values was determined as an indicator of cardiac injury in patients with high IgG values, which is an indicator that the COVID-19 disease was more severe. To detecting myocardial fibrosis, we can use expensive methods such as biochemical, echocardiographic and radiological [10]. A recent study showed that fQRS was useful in predicting scar areas detected by magnetic resonance imaging [11]. fQRS can be easily detected from routine ECG recordings and shows myocardial fibrosis. In coronary artery disease and acute coronary syndromes, fQRS was found to be associated with high mortality and arrhythmic events [12]. In fQRS group mortality rate was related with larger infarcts areas and left ventricular dysfunction [12]. In another study with COVID-19 patients, fQRS was found to be more frequently in sever group, especially in inferior leads [13]. The presence of fQRS was found to be more frequently in patients with myocardial injury [13].

There was no significant difference found between the groups with and without fQRS between age and gender in our study. When we look at the symptoms, the possibility of occurrence of fQRS was found to be higher in patients with dyspnea and fatigue. Similar to our study the presence of narrow fQRS was associated with worsening New York Heart Association (NYHA) symptom status [14]. Also the relation between fQRS and NYHA symptom status was examined in mitral stenosis, and fQRS was found to be correlated with poor functional NYHA symptom status [15].

In our study, diastolic dysfunction, lower EF value, enlargement in heart cavity was found to be significant in fQRS+ group. LVEF was slightly lower in fQRS group but still in normal range. It was thouth to be due to the low scar burden. But percentage of scar tissue in patients with tachicardia coud not be determined clearly, since we did not have any patients who accepted to have cardiac MRI. As we know fQRS is an electrocardiographic sign of myocardial scar tissue, that explain the nonhomogeneous ventricular conduction delay [7]. In ischemic heard disease (IHD), the presence of fQRS was found to be an independent predictor of left ventricular (LV) dilatation, decreased ejection fraction and myocardial perfusion [16–18]. In patients with non-ischemic or ischemic cardiomyopathy fQRS was also able to predict arrhythmic events [19,20]. In patients with ischemic cardiomyopathy (ICM) fQRS was demonstrated to be an independent predictor of sudden cardiac death (SCD) risk [21]. In another study, fQRS was found to have a predictive value for ventricular arrhythmias and all-cause mortality in patients with dilated cardiomyopathy (DCM) (EF ≤40%) [22].

We found that in COVID-19 patients the probability of occurrence of de-novo fQRS was higher in inferior leads. Especially the presence of fQRS in the high lateral leads was associated with lower EF. In other study, presence of fQRS in inferior leads was found to be an independent predictor for SCD in patients with ischemic and dilated cardiomyopathy [21].

Patients with post-acute COVID-19 syndrome have a wide variety of symptoms such as fatigue, chest pain, decreased exercise tolerance, cognitive impairment, shortness of breath, fever, headache, loss of smell and taste, but rapid heartbeat and palpitations are typical and common complaints [23]. The persistence of these symptoms 4–12 or more then 12 weeks is defined as post-acute COVID-19 syndrome [24]. Approximately 25–50% of post-acute COVID-19 syndrome patients report tachycardia and/or palpitations 12 weeks or longer. In post-acute COVID-19 syndrome, tachycardia may occur as postural orthostatic tachycardia syndrome or inappropriate sinus tachycardia. The authors suggest labeling this condition as “Post-COVID-19 tachycardia syndrome” [25]. In our study we observed that post-COVID-19 tachycardia syndrome occurs 9.67% after 6 months, mostly in fQRS+ group (19.6%). Similar to out study, systematic studies show that 9% of patients with post-acute COVID-19 syndrome report palpitations at six months [23]. Postural orthostatic tachycardia syndrome is characterized by autonomic dysfunction that causes various symptoms such as tachycardia following postural change [9]. It has been previously documented that viral infections can trigger postural orthostatic tachycardia syndrome [26]. The pathophysiological mechanism in postural orthostatic tachycardia syndrome remains unclear. However, evidence of autoimmunity, i.e. the presence of autoantibodies that activate adrenergic and muscarinic receptors [27], hyperadrenergic state [28], similar to loss of taste and smell, peripheral denervation [29] and deconditioning, causing blood pooling in the lower extremities and reflex tachycardia [9] can cause postural orthostatic tachycardia syndrome. It has not been established whether the same mechanisms are responsible for the postural orthostatic tachycardia syndrome and to what extent they contribute to the post-acute COVID-19 syndrome. Inappropriate sinus tachycardia is defined as on 24-hour ECG monitoring mean heart rate exceeding 90 bpm or resting heart rate > 100 bpm [9]. It includes a gain-of-function mutation in the hyperpolarization-activated and cyclic nucleotide-gated (HCN4) channel [30] of the cardiac pacemaker, heart intrinsic sinus node abnormality, autoimmunity, excessive sympathetic activation or vagal retraction [31] In addition to the direct and indirect damage caused by viral infection, there may be other mechanisms contributing to the post-COVID-19 tachycardia syndrome. For example: (i) Persistent lung injury or exacerbation of underlying lung disease that causes desaturation and reflex tachycardia [32], (ii) persistent or intermittent fever that may increase heart rate [33], (iii) pain, (iv) anxiety and depression [33], (v) neuroinflammation and (vi) hypovolemia [33]. We also observed that de-novo fQRS, dyspnea, high troponin and IgG values, high diastolic dysfunction, low EF value and left atrial diameter were determined as independent risk factors for post-COVID-19 tachycardia syndrome in follow-up. Given the novelty of the disease and the lack of basic and clinical data, several unknown mechanisms may also play a role in the post-COVID-19 tachycardia syndrome. Tachycardia can be considered as universal and readily available quantitative marker of severity for post-acute COVID-19 syndrome.

Limitations of our study

Since this is a retrospective and single-center study, the number of our patients is low and there is no long-term follow-up, the possibility of more serious morbidity in patients who develop de-novo fQRS and its relation with other mortalities is not known clearly. If the number of patients had been higher, we might have seen a higher tachycardia rates perhaps in non-fQRS group. Therefore, large studies are required.

Conclusion

De-novo fQRS in the sixth month was found to be an independent risk factor to determine post-COVID-19 tachycardia syndrome. The de-novo fQRS in SARS-COV-2 may be a predictor of future more important adverse cardiovascular outcomes and this should alert clinicians.

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