# Evaluation of cases with a preliminary diagnosis of Crimean- Congo hemorrhagic fever and comparison of characteristics in patients admitted to a secondary care hospital in Kastamonu, Turkey.

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**Abstract:**

**Background:** Crimean-Congo hemorrhagic fever (CCHF) is an endemic disease in Turkey. The clinical presentation and laboratory findings are not specific especially in cases without hemorrhagic findings**.**

**Objective:** We aimed to evaluate CCHF cases and compare them with non-CCHF cases in terms of their characteristics during admission.

**Methods:** Cases with a preliminary diagnosis of CCHF at a secondary care hospital in Kastamonu in 2013 were evaluated, retrospectively. Cases testing RNA/IgM positive were considered as CCHF. Cases testing both RNA and IgM negative were considered as non-CCHF. The two groups were then compared in terms of their clinical, laboratory and epidemiological characteristics during admission.

**Results:** A total of 41 cases were tested and CCHF was found in 46.3% of cases. Fatality was 5.3% in CCHF cases. The frequency of tick bites and CK elevation in CCHF cases was significantly higher than non-CCHF cases ($p<0.05$). There were no significant differences between the two groups regarding other characteristics ($p>0.05$).

**Conclusions:** In cases with a preliminary diagnosis of CCHF, especially in cases without a history of tick bite and with normal CK levels during admission, performing tests for the differential diagnosis may be advisable without waiting for the results of tests for CCHF.

**Kewords:** Crimean-congo hemorrhagic fever, Kastamonu, Turkey

**DOI: http://dx.doi.org/10.4314/ahs.v14i4.15**

## Introduction

Crimean-Congo hemorrhagic fever (CCHF) is a tick-borne viral zoonotic infection acquired by a tick bite, transmitted from body fluids or blood of domestic animals and cases with CCHF virus (CCHFV); this virus belongs to the genus Nairovirus in the family Bunyaviridae. The clinical spectrum of the disease varies from a subclinical infection to severe disease and death, with a reported fatality rate of 15–30% in human cases [1-10]. It was reported in the Crimean Peninsula in 1944 for the first time[11]. Since then, CCHF has been reported from different parts of Africa, Eastern Europe, the Balkans, the Middle East, Central and Southern Asia[9], [10, 12, 13]. The first case of CCHF infection in Turkey was reported in the Kelkit Valley region in 2002.

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Turkey has become the country with the highest number of CCHF cases among the countries that report CCHF cases annually. This infection is an endemic zoonosis appearing every year during spring and summer in Turkey with approximately 1000 cases reported annually [1-10]. Majority of cases in Turkey were from 15 cities in Kelkit Valley and its environs including Kastamonu Province. CCHF cases from countries that border Turkey including Bulgaria, Greece, Iran and Iraq have also been reported [6, 13-18]. According to various studies, the fatality rate of CCHF ranged from 15-30%. However, the crude fatality rate was 5% in 2002-2007 according to the reports of the Turkish Ministry of Health surveillance [1-10].

There are a few studies evaluating cases with a preliminary diagnosis of CCHF and reporting the rate of confirmed CCHF cases among suspected CCHF cases. This rate ranges between 21% and 57%[19-22]. In this study, cases of CCHF admitted to a secondary care hospital in Kastamonu in 2013 were evaluated in terms of their clinical, laboratory and epidemiological characteristics. Cases with CCHF were also compared in terms of these characteristics with non-CCHF cases whose reverse transcriptase-polymerase chain

reaction (RT-PCR) and ELISA IgM tests were negative for CCHFV.

**Methods**

In 2013, cases admitted with a preliminary diagnosis of CCHF to the Dr Münif Islamoğlu Hospital (Kastamonu Province, Turkey) were included in this study. A preliminary diagnosis of CCHF was made if cases presented with at least two of: (a) sudden onset of high-grade fever; (b) headache; (c) weakness; (d) nausea and vomiting; (e) diarrhea; and one of: (a) thrombocytopenia (platelet count of $<150 \times 10^9$/L); and/or (b) leucopenia (white blood cell count of $<4 \times 10^9$/L); and also one of: (a) history of tick bite; (b) close contact with animals; (c) living in rural areas or travelling to rural areas; (d) being a laboratory worker; or (e) contact with people with similar symptoms in the past 15 days.

Serum samples of all cases were collected within 24 hours of admission and were sent to the Public Health Institution of Turkey, National Virology Reference Laboratory to determine CCHF IgM antibodies by ELISA and CCHFV RNA by RT-PCR. ELISA was not performed on serum samples already detected by RT-PCR as positive for viral RNA. Cases with viral RNA or IgM antibody positivite were considered as CCHF cases. Cases with both viral RNA and IgM antibody negative were considered as non-CCHF cases. Cases with a history of suspected CCHF in the past four months were excluded from the study because, serum CCHF IgM antibodies detected by ELISA remain positive for four months after the infection [2, 4, 9, 10]. The incubation period of cases with tick exposure was defined as the period between contact with tick and onset of symptoms. Pediatric cases (≤16 ages) were excluded from the study.

Moreover, there were no pediatric cases with a definite diagnosis of CCHF in our hospital in 2013. CCHF cases were evaluated retrospectively in terms of their clinical and laboratory features during admission to the hospital and epidemiological features within 15 days, and these characteristics of CCHF cases were compared with non-CCHF cases.

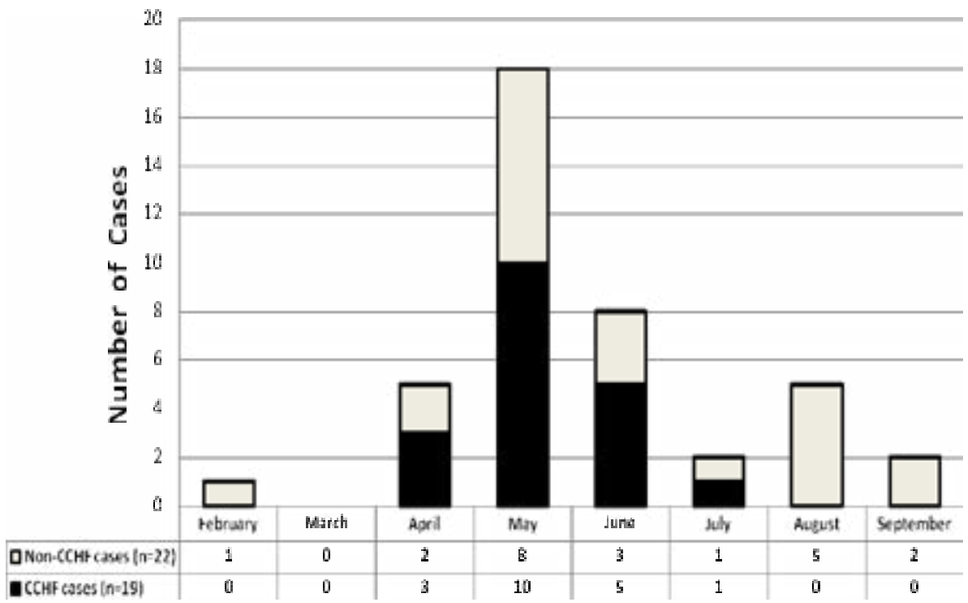
Statistical analysis was performed using SPSS version 15—0 (SPSS Inc., USA). Descriptive statistics (median, minimum and maximum value, mean and standard deviation, count and percentage) were used to summarize the results. Nominal variables were compared using $\chi 2$ test with Yates' correction and Fisher's exact test. Continuous variables were compared using Mann Whitney U test. When a p-value was found less than 0.05, the result was considered as statistically significant and the null hypothesis was rejected.

**Results**

In 2013, a total of 41 cases with a preliminary diagnosis of CCHF were followed up at our hospital. Three had a positive IgM by ELISA and 16 cases had a positive RT-PCR for CCHFV RNA. A total of 19 cases (46.3%) were diagnosed with definite CCHF. The remaining 22 cases (53.7%) were found negative by both tests and were considered as non-CCHF cases. 52.6% (10) of the CCHF cases were female, while 47.4% (9) were male. Besides, 54.5% (12) and 45.5% (10) of the non-CCHF cases were female and male, respectively. The median age of CCHF cases and non-CCHF cases was 54.0 (16-83) and 51.5 (20-78), respectively. There were no statistically significant differences between the two groups regarding gender and age ($p > 0.05$). Six cases from the CCHF group were transferred to a tertiary care hospital. One of the transferred CCHF cases died while the other 18 cases were cured. Case who died was a 42 years old female patient with no comorbid diseases and the cause of her death was multi organ failure. She did not receive ribavirin therapy. Thus, fatality rate was 5.3% (1/19) in the CCHF group. Three of the transferred cases in the CCHF group and none of non-CCHF cases recieved oral ribavirin.

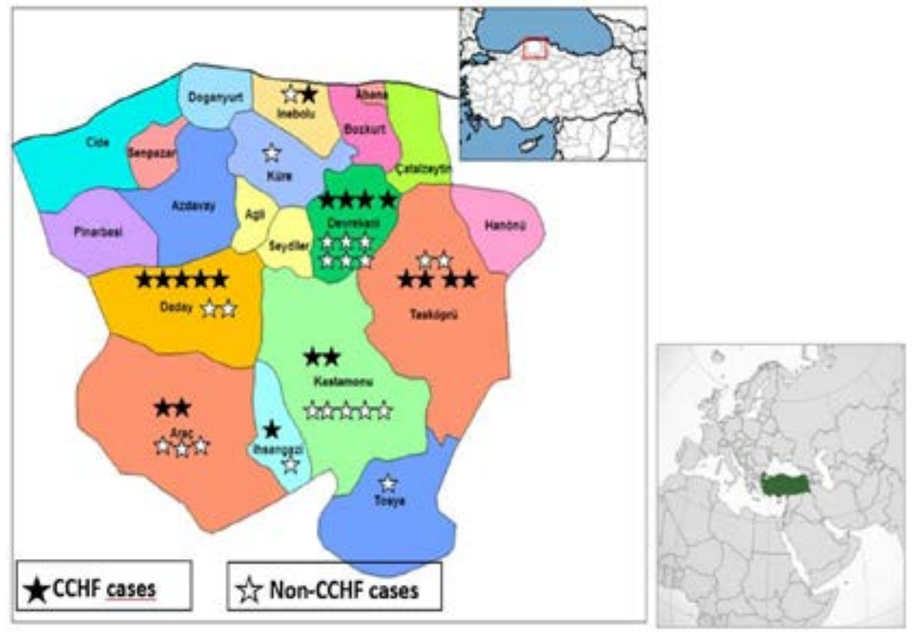
When looking at the monthly distribution of the CCHF cases, it was shown that the first case was detected in April and the highest number of cases was admitted in May (Figure 1).

**Figure 1: Monthly disturbution of cases with a preliminary diagnosis of Crimean-Congo hemorrhagic fever.**




Five cases were from Daday and four cases were from Devrekani and Taskopru which are districts of Kastamonu. The distribution of cases with a preliminary diagnosis of CCHF by districts is shown in Figure 2.

**Figure 2: The distribution of cases with a preliminary diagnosis of Crimean- Congo hemorrhagic fever by districts.**



In both groups, the most common clinical symptoms during admission were weakness, widespread muscle pain, fever, headache, nausea and vomiting, respectively. The frequency of abdominal pain, diarrhea and maculopapular rash was higher in CCHF cases. Bleeding was observed in four (18.2%) cases in the non- CCHF group during admission. There was no bleeding during admission in the CCHF group. There were no statistically significant differences between the two groups in terms of clinical symptoms during admission (p> 0.05) (Table 1).

**Table 1: Clinical symptoms of cases with a preliminary diagnosis of Crimean-Congo hemorrhagic fever during admission.**

| | CCHF cases (19) | Non-CCHF cases (22) | p value |
|---|---|---|---|
| **Clinical symptoms** | **% (n)** | **% (n)** | |
| **Weakness** | 100 (19) | 95.5 (21) | p>0.05 |
| **Widespread muscle pain** | 94.7 (18) | 86.4 (19) | p>0.05 |
| **Fever** | 84.2 (16) | 72.7 (16) | p>0.05 |
| **Headache** | 84.2 (16) | 72.7 (16) | p>0.05 |
| **Nausea and vomiting** | 84.2 (16) | 68.2 (15) | p>0.05 |
| **Abdominal pain** | 36.8 (7) | 31.8 (7) | p>0.05 |
| **Diarrhea** | 36.8 (7) | 18.2 (4) | p>0.05 |
| **Maculopapular rash** | 26.3 (5) | 18.2 (4) | p>0.05 |
| **Altered level of consciousness** | 10.5 (2) | 4.5 (1) | p>0.05 |
| **Bleeding*** | 0.0 (0) | 18.2 (4) | p>0.05 |

***** Includes hematoma,hemoptysis,hematuria and nose, gingival, vaginal, gastrointestinal, intra-abdominal and intracranial bleeding.

The most common physical finding during admission was fever, which was present in 68.4% (13) of CCHF and 50% (11) of non-CCHF cases. In the CCHF group, five (26.3%) cases had maculopapular rash, two (10.5%) had altered level of consciousness and hypotension, and one (5.3%) had ecchymosis, petechiae and tachycardia during admission. In the non-CCHF group, four (18.2%) cases had hemorrhagic findings, three (13.6%) had tachycardia, two (9.1%) had ecchymosis and hypotension, and one (4.5%) had maculopapular rash and altered level of consciousness. There was no statistically significant difference between the two groups in terms of physical findings during admission (p> 0.05). The most common laboratory findings in the cases with a preliminary diagnosis of CCHF were thrombocytopenia, leukopenia, and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevation, respectively. 94.7% (18) of CCHF group and 95.5% (21) of non-CCHF group had thrombocytopenia. The proportion of cases with platelet counts between 150-101 x $10^9$/L, 100-51 x $10^9$/L and <51 x $10^9$/L was 26.3%(5), 52.6% (10) 15.8% (3) in the CCHF group and 54.5%(12), 27.3% (6) 13.6% (3) in the non-CCHF group, respectively.



While elevated creatine phosphokinase (CK) and lactate dehydrogenase (LDH) levels were detected more frequently in the CCHF group, anemia was detected more frequently in the non-CCHF group. The frequency of CK elevation in CCHF cases (57.9%) during admission was significantly higher than non- CCHF cases (22.7%) (p<0.05). Other laboratory findings were similar between the two groups (p> 0.05) (Table 2).

**Table 2: The distribution of the laboratory findings of cases with a preliminary diagnosis of Crimean-Congo hemorrhagic fever during admission.**

| | CCHF cases (19) | Non-CCHF cases (22) | p value |
|---|---|---|---|
| **Laboratory findings** | **% (n)** | **% (n)** | |
| **Thrombocytopenia** | 94.7 (18) | 95.5 (21) | p>0.05 |
| **Platelet count ranges from:** | | | |
| **150-101 x $10^9$/L** | 26.3 (5) | 54.5 (12) | p>0.05 |
| **100-51 x $10^9$/L** | 52.6 (10) | 27.3 (6) | p>0.05 |
| **50.000-0 x $10^9$/L** | 15.8 (3) | 13.6 (3) | p>0.05 |
| **Leukopenia** | 89.5 (17) | 63.6 (14) | p>0.05 |
| **AST-ALT elevation** | 84.2 (16) | 59.1 (13) | p>0.05 |
| **LDH elevation** | 68.4 (13) | 59.1 (13) | p>0.05 |
| **CK elevation** | 57.9 (11) | 22.7 (5) | **P<0.05** |
| **Anemia** | 47.4 (9) | 63.6 (14) | p>0.05 |
| **INR elevation** | 38.8 (7) | 22.7 (5) | p>0.05 |

When the cases were evaluated according to their occupations, majority were farming-animal husbandry with 68.2% (15) and 73.7% (14) in the CCHF and the non- CCHF groups, respectively. The remaining cases had no occupational risk. Among CCHF cases, 94.7% (18) were living in rural areas, 89.5% (17) had contact with animals and 84.2% (16) had a history of tick bite within15 days before the onset of symptoms. In non-CCHF cases, these proportions were 86.4% (19), 77.3% (17) and 27.3% (6), respectively. In CCHF cases, a history of tick bite in the last 15 days was significantly higher than non-CCHF cases (p<0.05). Statistically significant differences were not found between the two groups in terms of other epidemiological characteristics (p> 0.05) (Table 3).

**Table 3. The distribution of epidemiological characteristics of cases with a preliminary diagnosis of Crimean-Congo hemorrhagic fever within the last 15 days.**

| | CCHF cases (19) | Non-CCHF cases (22) | p value |
|---|---|---|---|
| **Epidemiological characteristics** | **% (n)** | **% (n)** | |
| **Living in rural areas** | 94.7 (18) | 86.4 (19) | p>0.05 |
| **Contact with animals** | 89.5 (17) | 77.3 (17) | p>0.05 |
| **Tick bite** | 84.2 (16) | 27.3 (6) | **P<0.05** |
| **Contact with body fluids, tissue or blood of animals** | 42.1 (8) | 36.4 (8) | p>0.05 |
| **Traveling to rural areas** | 10.5 (2) | 18.2 (4) | p>0.05 |
| **Contact with CCHF cases** | 0.0 (0) | 0.0 (0) | p>0.05 |

The mean incubation period of cases with tick exposure was 3.8 ± 3.3 days in the CCHF group. The median day of illness on which patients were admitted was 2.0 (0-6) and 1.5 (0-9) days in CCHF and non-CCHF patients, respectively and the difference was not statistically significant (p> 0.05). The median elapsed time from admission of cases to the conclusion of RT-PCR and/or ELISA was 3.0 (1-6) days for CCHF cases, while it was 5.0 ± (2-10) days for non-CCHF cases. In the non-CCHF group, the elapsed time was significantly higher than the CCHF group (p <0.05).

## Discussion

The number of male and female CCHF cases in Turkey is similar. Two thirds of cases are farmers or housewives. Housewives in rural areas work actively particularly in farming and animal husbandry in Turkey [23-27]. No housewives were included in our study, because, housewives live mostly in rural areas and work in animal husbandry and farming sector. Between 2004-2007, the proportion of health care workers among CCHF cases was 0.4% in Turkey and seroprevalence among healthcare workers in endemic areas was 2% [6, 28]. In our study, there was no health care worker. In Iran, 34.3% of the 2536 cases with suspicion of CCHF was confirmed as CCHF and the probability of positive results for male samples was higher than that for female samples during 1999-2012 [20]. In our study, the proportion of CCHF cases was 46.3% among cases with a preliminary diagnosis of CCHF and there was no significant difference between the two groups in terms of gender (p>0.05).

The fatality rate of CCHF was approximately 15–30% 1-10. The mean fatality rate for Turkey was about 5% in 2002-2007. The fatality rate was calculated as 8.8% in Bolu Province located in the Western Black Sea region of Turkey in 2006-2012 [21]. In our hospital, 342 CCHF cases were diagnosed in 2005-2010 and the fatality rate was found to be 2.9%[29]. In 2013, we diagnosed 19 CCHF cases and the fatality rate was 5.3%. Although this rate was similar to that of other parts of Turkey, the differences among studies in different regions may be associated with the use of ribavirin. Compared to previous years, the number of cases was lower and the fatality rate was higher in our hospital in 2013. This may be explained by the use of ribavirin, because, three of 19 CCHF cases received oral ribavirin in 2013 while the rate of the use of ribavirin was approximately 85% in 2005-2010 in our hospital [29].

CCHF cases usually occurred between April and September, with a peak incidence in June and July [2, 4, 9, 10]. In Turkey, the frequency of tick-bite / tick contact in CCHF cases in 2007-2009 was 68.9%, and 84.1% of such cases occured during May, June and July 6. In 2013, the first CCHF case at our hospital was detected in April as expected. However, it was interesting that the peak incidence was in May and there were no cases detected in August. However, besides our hospital, there is one more private hospital that could follow up cases with CCHF in Kastamonu. Therefore, CCHF cases might have been admitted to this hospital, or a hospital outside of Kastamonu, during the same period.

The most common symptoms in cases with CCHF are fever, headache, myalgia, nausea, vomiting, abdominal pain, diarrhea and hemorragic findings, respectively[6,9,10]. In some studies, fever, bleeding, vomiting, headache and diarrhea were reported more frequently in cases with CCHF than non-CCHF cases[20, 21]. In our study, there were no significant differences between the two groups in terms of clinical findings during admission (p>0.05). Unexpectedly, there were no hemorrhagic findings among CCHF cases during admission. This may be due to the fact that patients were in early phase of CCHF. Because, in our study, the median day of illness on which CCHF cases were admitted was 2.0 days. On the other hand, this may be due to the fact that cases with hemorrhagic findings were admitted to other clinics/hospitals and/or they were misdiagnosed in other departments.

Thrombocytopenia, leucopenia, increased AST-ALT, CK and LDH levels are the most common laboratory findings in CCHF cases[6, 9, 10]. In some studies, thrombocytopenia, increased AST-ALT and LDH levels were reported more commonly among cases with CCHF than non-CCHF cases [20, 21]. In our study, CK elevation was more common in CCHF cases (p<0.05), but, other laboratory findings during admission were found to be similar between the two groups (p>0.05). Increased CK levels during admission in cases with CCHF may help to distinguish similar cases but our CCHF cases had milder clinical signs. This may account for the results of other laboratory investigations that were not significantly different.

A specific diagnosis may be made by testing a serum specimen for viral RNA by RT- PCR and for virus-specific IgM and/or IgG by ELISA or other methods. In general, virus can be detected for up to two weeks after the first clinical symptoms occur. An IgM antibody response is detectable from the fourth day after the onset of disease for up to four months. IgG antibodies can be found from sixth day after the incubation period up to five years [2, 4, 9, 10]. In our study, the mean elapsed time from the admission of cases to the conclusion of the tests was higher for non-CCHF cases than CCHF cases. As our hospital is a secondary care hospital having limited diagnostic facilities, excluding the diagnosis of CCHF can take more time. Therefore, performing tests for the differential diagnosis may be advisable during this time.

CCHFV transmission may occur by the bite of an infected tick or by exposure to the body fluids of a viremic animal or a CCHF case[2, 4, 9, 10]. Tick bites and animal husbandry have been reported as risk factors for seropositivity and a history of tick bite and animal husbandry was identified in majority of CCHF cases in Turkey. Seroprevalence was 10% in individuals with a history of tick bite. Seroprevalence was reported as 10–19.6% in endemic regions of Turkey. Seropositivity in individuals with a history of farming, animal husbandry, contact with animals and contact with ticks was 80%, 70%, 76% and 70% respectively[6, 8, 30, 31-34]. In Iran, contact with infected humans and animals was higher in the CCHF group than the non-CCHF group, but, a history of tick bite was not a risk factor[20]. Similarly, contact with animals was more commonly reported in CCHF cases than non-CCHF cases, but, a history of tick bite was similar between the two groups in Bolu, Turkey [21]. We found that the frequency of tick bites was significantly higher in CCHF cases than non-CCHF cases (p<0.05).

The efficacy of ribavirin in antiviral treatment remains controversial. Although most reports claimed a therapeutic benefit about ribavirin use, the quality of the evidence was low. In general, treatment of CCHF is mainly supportive therapy[9, 10, 35, 36]. In our study, the case who died did not receive ribarivin therapy and three of CCHF cases received oral ribavirin.

This study has several limitations. First, the study reports a retrospective, one-year, single center data and includes only participants who were admitted to our hospital. Second limitation is small sample size and low study power. Significant differences between the two groups may have not been detected. Third, the study evaluates characteristics of cases during admission, the patients were not evaluated during the course of the disease. Despite these limitations, all patients admitted to our hospital were included the study. There are a few studies evaluating cases with a preliminary diagnosis of CCHF [19-22]. In this regard, there is a need for more comprehensive research.

The disease still remains important in endemic regions of Turkey, although the fatality rate is low (5%) in Turkey than other endemic countries[1-10, 19, 21, 29]. The clinical presentation is not diagnostic and physical examination and laboratory findings are not specific especially in cases without hemorrhagic findings[2-4, 8-10]. In areas endemic for CCHF, clinicians should be aware of the possibility of other diseases in cases with a preliminary diagnosis of CCHF and should determine and consider clinical, laboratory and epidemiological characteristics during admission of such cases.

**Conclusion**

In cases with a preliminary diagnosis of CCHF, especially in cases without a history of tick bite and with normal CK levels during admission, performing tests for the differential diagnosis may be advisable without waiting for the results of RT-PCR and ELISA tests for CCHF. This may help reduce the number of cases misdiagnosed as CCHF and increase the overall probability of detecting CCHF cases.

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