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**RESEARCH ARTICLE**

# New Insight for the Prognosis of CCHF: Clinical, Laboratory and Sonography Findings

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**Abstract:** ***Background*:** Crimean Congo Hemorrhagic Fever (CCHF) is an acute and fatal disease with various clinical and paraclinical characteristics.

***Introduction*:** In this article, we report data on confirmed CCHF cases from Iran and describe the association between studying factors and outcomes of the disease.

***Methods*:** In the study design, we evaluated demographic characteristics, clinical, laboratory and sonographic findings of 160 CCHF confirmed cases during 2003 and 2012 in Zabol (A city in Sistan and Baluchestan province of Iran). The association between these factors and the fatal outcome were evaluated by regression analysis.

***Results*:** The disease had a fatal outcome in 7 (4.4%) patients. Females had more severe symptoms and higher odds for death (odds ratio11.57, p=0.005). Leukocytosis (p<0.001), PT (p<0.001) and PTT (p=0.008) elongation, AST (p=0.010) and ALT (p>0.001) elevation were significantly associated with fatal outcome. CNS related symptoms (odds ratio 5.9, p=0.027) in clinical examination and ascites (odds ratio 38.4, p=0.012) and liquid in the pelvic cavity (odds ratio 24.2, p=0.004) were also identified as risk factors of death in this study.

***Conclusion*:** Our data suggest that in addition to clinical and laboratory findings practitioners consider sonography for CCHF prognosis.

**Keywords:** Crimean-Congo hemorrhagic fever, viral, fatal disease, clinical, laboratory, sonography.

## 1. INTRODUCTION

Crimean-Congo hemorrhagic fever (CCHF) is a lethal viral infectious disease caused by CCHF virus (genus Nairovirus, family Bunyaviridae). In the present age, CCHF was primarily illustrated as a clinical entity in 1944-1945, when about 200 Soviet military personnel were infected in Crimea during World War II [1-3].

CCHF is now widely seen all over the world [1] and is endemic in Africa, the Balkans, the Middle East, and Asia. The virus causes acute and rigorous disease, with an average case fatality rate of about 30% [1]. The geographic distribution of CCHF virus is very widespread, and it makes this virus an extremely significant human pathogen with public health importance (Fig. **1**). The virus is transmitted to humans by tick bites and through contact with tissues or blood from infected livestock. This virus can also be passed *via* human-to-human transmission [1, 3].

The disease starts suddenly with flu-like symptoms including fever, myalgia, headache, and then continues with bleeding. Bleeding may occur inside the body (internal bleeding) or on the skin and internal mucous membranes (such as in the nose and gums) with a wide range of intensities [1]. Thrombocytopenia, elongation of prothrombin time, and activated partial thrombin time are some of the laboratory features of the CCHF infection. In these patients, the levels of aspartate aminotransferase (AST), lactate dehydrogenase (LDH) and creatine phosphokinase (CPK) are usually higher than the normal threshold [4].

An increase in the number of patients worldwide has raised the awareness of physicians on the disease. Sonographic results have been recommended to be used for help-

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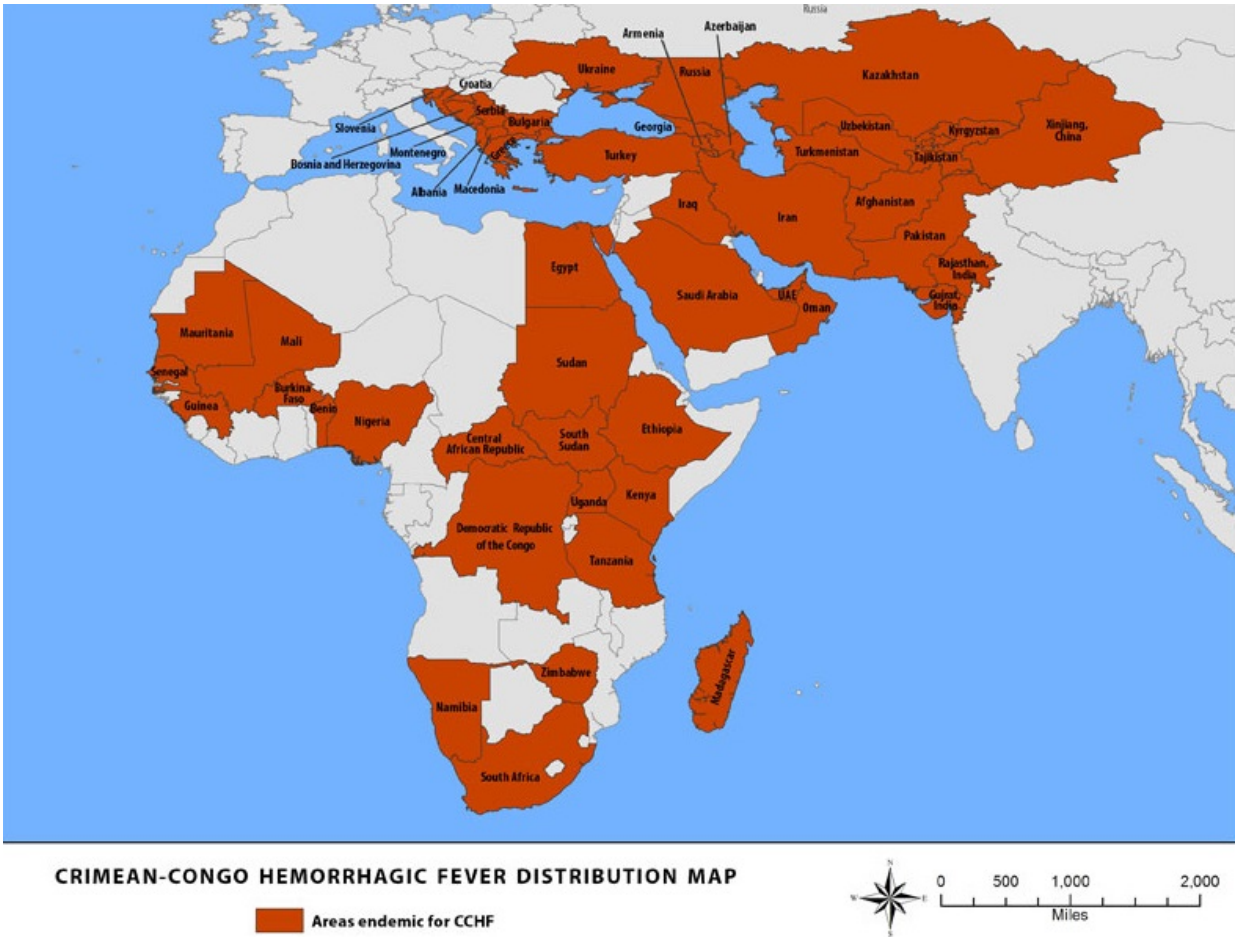


**Fig. (1).** The distribution map of CCHF in the world (Source: https://www.cdc.gov/vhf/crimean-congo/resources/distribution-map.html, last updated: March 5, 2014, Website view date: February 13, 2017). *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

ing in the diagnosis of the CCHF disease. Nevertheless, not enough studies on the sonographic findings of this disease are found in the literature [5]. Hepatomegaly, splenomegaly, and gallbladder wall thickening are some of the common sonographic findings in the CCHF cases [5, 6].

Iran has one of the most efficient and accurate surveillance systems for CCHF and every year several cases of CCHF are reported from different regions of Iran [7]. In Iran, the surveillance and control program of CCHF was established in 1999. According to this program, all the probable cases of CCHF are transferred to the National Reference Laboratory. Any probable cases of CCHF in which the serum has positive immunoglobulin M (IgM) antibodies and/or is positive by RT-PCR detection of viral RNA are considered as CCHF confirmed cases [3]. Sistan and Baluchestan province of Iran has been the most infected region since 2000. Zabol is a city in the northeast of Sistan and Baluchestan and is neighbored with Afghanistan in which CCHF is endemic [2, 8].

In this study, we gathered a wide range of demographic, clinical, laboratory and sonographic information of 160 confirmed cases of CCHF in Zabol. This information was used to investigate possible prognosis factors of CCHF fatal outcome.

## 2. MATERIALS AND METHODS

A total of 160 confirmed cases of CCHF patients admitted to Amir-Al-Momenin Hospital of the city of Zabol city between 2003 and 2012 year were included in this study.

These patients had presented to Amir-Al-Momenin Hospital with general CCHF symptoms, including high fever, myalgia, headache, vomiting, and bleeding, and were considered as probable cases of CCHF according to standard national clinical and epidemiological criteria [3]. The CCHF diagnosis of all these patients was confirmed by serological (specific ELISA with recombinant antigen) and molecular (gel-based and real-time RT-polymerase chain reaction) assays at the Pasteur reference laboratory of CCHF in Iran.

The baseline information and clinical, laboratory and sonographic findings of each patient were noted in specially designed forms.

Information about sex, age, occupation, inhabitant (urban or rural), nationality (Iranian or Afghan), suspected mode of transmission, blood group and season of infection obtained from 160 CCHF confirmed cases was obtained at the first day of admission. Then clinical examination was performed and clinical signs and symptoms were documented.

White blood cell count (WBC), Platelet count (Plt), Hemoglobin (HB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), prothrombin time (PT), activated partial thromboplastin time (aPTT or APTT), total bilirubin, erythrocyte sedimentation rate (ESR), creatinine (Cr), creatine phosphokinase (CPK), lactate dehydrogenase (LDH) were evaluated at the first day of hospitalization for every patient. WBC, PLT, and HB were also measured during hospitalization.

Sonography was available for 144 cases. Any abnormal sonographic findings were recorded for each patient, including thickening of the wall of the gall bladder, hyper echoic liver, ascites, liquid in the pelvic cavity, pleural effusion, hepatomegaly, splenomegaly, liquid in Morison space, hyperechoic cortex of kidney.

## 3. STATISTICS

The association between each of the clinical, laboratory and sonographic findings and the fatal outcome was evaluated using logistic regression analysis for clinical and sonographic findings (binary variables) and for laboratory ones the linear regression analysis (continuous variables). P values<0.05 in models were considered significant. Statistical analysis was performed using STATA version 12.

## 4. RESULTS

In this study, 160 confirmed cases of CCHF from 2003 to 2012 were examined and factors associated with fatal outcomes were evaluated in these patients.

One-hundred twenty-eight patients out of 160 were male (80%) and 32 (20%) were female. The mean age of patients was 32.9 (SD=13.67). Most of the cases were observed in summer (38.7%) and spring (38.1%). One hundred forty patients were Iranian (87.5%) and 20 (12.5%) were originally from Afghanistan. 60 (37.5%) resided in urban areas and 100 (62.5%) in rural areas. The disease had a fatal outcome in 7 (4.4%) of the patients and 153 (95.6%) discharged with recovery. Fever (99.4%), headache (92.5%) and myalgia (90%) were the three most common clinical symptoms. Bleeding was observed in 101 (63.1%) patients. Fever was observed in all the non fatal and in 6 out of 7 fatal cases, which was statistically significant (P=0.07). The frequency of CNS related symptoms in fatal and non fatal cases was 3 (42.9%) and 17 (11.8%) respectively (P=0.027).

Thickening of the wall of the gall bladder (34%), Ascites (31.2%) and hyper echoic liver (23.6%) were the most prevalent sonography findings. The frequency of ascites (P=0.012) and the presence of liquid in pelvic cavity (P=0.004) were significantly higher in fatal cases.

Total leukocyt count (0.011), PT (P<0.001), a PTT (0.008), AST (0.01) and ALT (<0.001) were also statistically different in fatal and none fatal cases. The difference in other clinical and para-clinical symptom was not statistically significant in fatal and non fatal cases.

The treatment process of probable cases of CCHF began promptly and before receiving the Pasteur institute confirmation of cases. The treatment protocol of CCHF has two main parts; supportive and pharmacological treatment with Ribavirin. Supportive treatment includes blood and platelet transfusion, febrifuge drugs administered according to the patient's situation. Oral ribavirin was administered after the onset of symptoms at the dosage recommended by the World Health Organization (WHO) (30 mg/kg as an initial loading dose, then 15 mg/kg every 6 h for 4 days, and then 7.5 mg/kg every 8 h for 6 days). The total duration of treatment was 10 days.

In Table **1** the distribution of each clinical, laboratory and sonographic findings has been shown in fatal and non-fatal CCHF separately and you can observe the main risk indicators of the fatal outcome in Fig. (**2**).

**Table 1. Distribution of clinical, laboratory and sonography changes included in the univariable regression models of fatal CCHF cases (160 cases, Iran, 2003–2012).**

| - | Non-fatal | Fatal CCHF | a | P-value |
|---|---|---|---|---|
| **Clinical findings** | | | | |
| Fever[a], n (%) | 153 (100) | 6 (85.7) | 0.0 | **0.011** |
| Bleeding, n (%) | 94 (61.8) | 6 (85.7) | 3.7 | 0.231 |
| Headache, n (%) | 142 (93.4) | 5 (71.4) | 0.2 | 0.053 |
| CNS related signs, n (%) | 17 (11.18) | 3 (42.9) | 5.9 | **0.027** |
| Abdominal pain, n (%) | 96 (63.2) | 3 (42.9) | 0.4 | 0.290 |
| Diarrhea, n (%) | 42 (27.6) | 1 (14.3) | 0.4 | 0.449 |
| Vomiting, n (%) | 106 (69.7) | 4 (57.14) | 0.6 | 0.485 |
| Myalgia, n (%) | 138 (90.8) | 5 (71.4) | 0.2 | 0.120 |
| Skin rash, n (%) | 23 (15.1) | 2 (28.6) | 2.2 | 0.351 |
| Labial herpes, n (%) | 13 (8.5) | 0 (0.0) | 0.70 | 0.806 |

**(Table 1) Contd…**

| - | Non-fatal | Fatal CCHF | a | P-value |
|---|---|---|---|---|
| Hepatomegaly, n (%) | 6 (3.9) | 1 (14.3) | 4.1 | 0.227 |
| Splenomegaly, n (%) | 17 (11.2) | 1 (14.3) | 1.3 | 0.801 |
| Icterus, n (%) | 15 (9.9) | 2 (28.6) | 3.6 | 0.141 |
| Sudden onset of the disease, n (%) | 135 (88.8) | 6 (85.7) | 0.7 | 0.801 |
| **Laboratory Changes** | | | | |
| Platelet count ($\times 10^9$/L), mean±SD | 56.1±43.3 | 33.8±154 | -22.3 | 0.178 |
| Total leukocyte count ($\times 10^9$/L), mean±SD | 4.5±3.2 | 11.4±7.2 | 6.9 | **<0.001** |
| Hemoglobin (HB), mean±SD | 13.5±1.8 | 13.3±3.8 | -0.2 | 0.789 |
| Prothrombin time (PT) (Sec), mean±SD | 17.4±8.2 | 30.4±19.2 | 13.0 | **<0.001** |
| Activated partial thromboplastic time (aPTT) (Sec), mean±SD | 54.7±21.5 | 77.9±35.6 | 23.1 | **0.008** |
| Erythrocyte sedimentation rate (ESR)(mm/hr), mean±SD | 17.5±14.0 | 16.0±9.1 | -1.5 | 0.772 |
| Total bilirubin (mg/dl), mean±SD | 1.3±1.4 | 2.0±1.2 | 0.6 | 0.227 |
| Creatinine (Cr) (mg/dl), mean±SD | 1.1±0.9 | 1.4±1.1 | 0.4 | 0.238 |
| Creatine phosphokinase (CPK) (U/L), mean±SD | 1186.8±1785.7 | 1311.4±1427.5 | 224.6 | 0.744 |
| Aspartate aminotransferase (AST) (U/L), mean±SD | 446.4±1203.7 | 1729.4±2548.7 | 1283.0 | **0.010** |
| Alanine aminotransferase (ALT) (U/L), mean±SD | 149.9±320.0 | 891.8±1135.2 | 696.9 | **<0.001** |
| Alkaline phosphatase (ALP) (U/L), mean±SD | 324.2±327.6 | 534.6±250.5 | 210.4 | 0.096 |
| Lactate dehydrogenase (LDH) (U/L), mean±SD | 1172.2±1198.2 | 1415.4±1530.4 | 243.2 | 0.605 |
| **Sonography findings** | | | | |
| Thickening of the wall of the Gall bladder, n (%) | 46 (33.8) | 3 (42.9) | 1.5 | 0.625 |
| Hyper echoic liver, n (%) | 34 (25.0) | 0 (0.0) | 0.2 | 0.272 |
| Ascites, n (%) | 38 (27.9) | 7 (100.0) | 38.4 | **0.012** |
| Liquid in pelvic cavity | 27 (19.8) | 6 (85.7) | 24.2 | **0.004** |
| Pleural effusion, n (%) | 11 (8.1) | 0 (0.0) | 0.7 | 0.246 |
| Hepatomegaly, n (%) | 20 (14.7) | 1 (14.3) | 1.0 | 0.976 |
| Splenomegaly, n (%) | 25 (18.4) | 1 (14.3) | 0.7 | 0.785 |
| Liquid in Morison space, n (%) | 19 (14.0) | 0 (0.0) | 0.4 | 0.578 |
| Hyper echoic cortex of kidney, n (%) | 9 (6.6) | 1 (14.3) | 2.3 | 0.451 |

Note: The Odds Ratio (OR) of univariable logistic regression are reported for clinical and sonography findings and coefficient of univariable linear regression models are reported for laboratory changes.
Sonography was not available for 16 none fatal CCHF cases.
The normal ranges of laboratory findings are as followed: Platelet count: 150-450, Total leukocyte count: 4-11, HB: M: 14-18, F12-16, PT: 11-14, PTT: 25-35, ESR: 0-20, Total bilirubin: 0.2-1.2, Cr: 0.5-1.2, CPK: 22-198, AST: 12-37, ALT: 3-25 ALP: 40- 147, LDH: 88-230.

## 5. DISCUSSION

CCHF is an acute and suddenly progressing disease [1]. The case-fatality of CCHF has been reported from 2.8% to 70% in different studies [9]. One of the CCHF treatment reports in Iran from 2003 had reported the survival rate of 80% [10]. It is obvious that the appropriate diagnosis of the disease and consequently timely and optimal treatment approaches can lead better survival of the CCHF patients. In our study, CFR (Case fatality rate) was 4.4% and this may be due to the awareness of health care providers of clinical and paraclinical characteristics of the disease [11-13]. As we previously mentioned, CCHF is prevalent in Sistan and Baluchestan province of Iran and most of the health care providers are aware of promptly identifying probable cases and refer them to hospitals for further diagnostic and treatment procedures. Practitioners also know how to effectively treat the patients to get the best result. Despite all the efforts

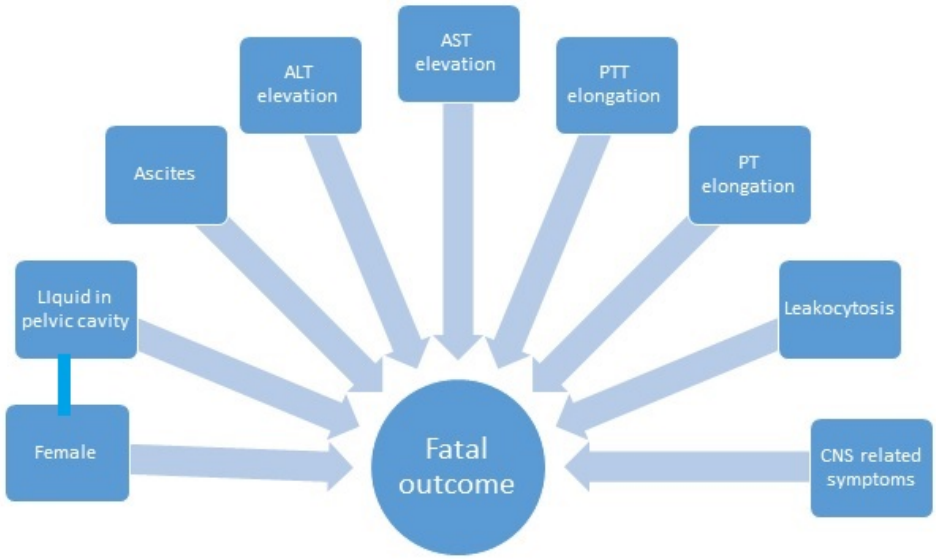


**Fig. (2).** The schematic chart of prognostic factors of CCHF. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

to cure the patients, seven of them had a fatal outcome. We considered all the accessible information to study the factors which were associated with the survival of the patients.

In this study, some clinical, laboratory and sonographic findings were associated with fatal outcome. These factors can be considered as possible predictors of the CCHF disease.

The preliminary results of this manuscript suggest a strong association between CNS related symptoms and fatality in CCHF patients. It has been shown that CNS related signs such as seizure and unconsciousness are related to higher viral load and a consequently higher risk of death in CCHF patients [14].

Fever was another clinical symptom that was statistically associated with death in CCHF patients. Only one case did not present fever and this association has been probably produced by chance. If the number of patients without fever was higher and we still saw this relationship we could consider it an important factor in a fatal outcome in CCHF.

Bleeding has been known as a critical symptom causing death [15]. In our study, the rate of bleeding was higher in fatal cases, but the difference was not statistically significant.

In fatal CCHF group, leukocytosis was more severe than survived group. PT and aPTT were higher in fatal CCHF. AST and ALT were more elevated in patients with fatal outcome.

The results of the laboratory changes were in accordance with other studies. Leukocytosis, PT and aPTT elongation and AST, and ALT elevation have been previously introduced as important predictors of fatal outcome in several studies [15]. These laboratory findings are mostly associated with pathological aspects of the virus (direct infection of the endothelium, indirect damage by viral factors or virus-mediated host-derived soluble factors) leading to the occurrence of disseminated intravascular coagulopathy [16, 17].

Thickening of the wall of the gall bladder (GBWT), ascites, hyperechoic liver and liquid in the pelvic cavity were major sonographic findings of this case series.

Ascites and liquid in the pelvic cavity were two key sonographic changes that were significantly more frequent in fatal CCHF.

Our study is among the first studies which assesses sonographic results in CCHF patients. In one study GBWT and ascites were diagnosed as indicators of the disease's severity [6]. In this study, just the abdominal cavity was examined, but in our study, we also considered the pelvic cavity. The presence of liquid in the pelvic cavity turned out to be a very important fatal predictor. We do not know if this liquid was blood or not. It would have been better to aspirate and examine the liquid. Studying the components of this liquid might lead to a better understanding of the pathogenesis of the disease.

The liquid was more frequently seen in the pelvis of female patients. Female patients generally experienced more severe symptoms including; bleeding, hepatomegaly, lower level of platelet count, presence of liquid in the pelvic cavity, and hyperechoic cortex of the kidney. The odds of fatal outcome was about 11 times higher in female patients.

We used regression models to detect probable relationships between factors and fatal outcome. However, this analysis was appropriate to understand the relationships between factors, its result should be interpreted with caution. Because of the low number of fatal cases the power of the analysis is low. There may be some relationships between assessed factors and fatality which the statistical analysis was not able to detect as statistically significant.

## CONCLUSION

To our knowledge, this study is the first study in which an overall and comprehensive perspective of CCHF patients has been demonstrated. The results of this study can help

practitioners to reach a better diagnosis and prediction of CCHF cases.

## LIST OF ABBREVIATIONS

| | | |
|---|---|---|
| ALP | = | Alkaline Phosphatase |
| ALT | = | Alanine Aminotransferase |
| aPTT or APTT | = | Activated Partial Thromboplastin Time |
| AST | = | Aspartate Aminotransferase |
| CCHF | = | Crimean Congo Hemorrhagic Fever |
| CFR | = | Case Fatality Rate |
| CPK | = | Creatine Phosphokinase |
| Cr | = | Creatinine |
| ESR | = | Erythrocyte Sedimentation Rate |
| GBWT | = | Thickening of the Wall of the Gall Bladder |
| HB | = | Hemoglobin |
| IgM | = | Immunoglobulin M |
| LDH | = | Lactate Dehydrogenase |
| Plt | = | Platelet Count |
| PT | = | Prothrombin Time |
| WBC | = | White Blood Cell Count |
| WHO | = | World Health Organization |

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

## HUMAN AND ANIMAL RIGHTS

Not applicable.

## CONSENT FOR PUBLICATION

Not applicable.

## AVAILABILITY OF DATA AND MATERIALS

Not applicable.

## FUNDING

None.

## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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