RESEARCH PAPER

Evolutionary and Historical Study of Crimean-Congo Hemorrhagic Fever Virus (CCHFV)

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Received: 20.09.2023 Accepted: 10.10.2023

Abstract

Background: Crimean-Congo Hemorrhagic Fever Virus (CCHFV) is a zoonotic virus that infect life stock then transfer to human via direct contact with animal or by ticks that live on animals as a parasite through their bites. The infected people appear some symptoms such as, malaise, vomiting, mucosal and gastrointestinal (GI) bleeding, hypotension, and edema. The minimum evolution phylogenetic tree was also analyzed for the main eight strains collected from different countries including South Africa, Uganda, Nigeria, China, Pakistan, Russia, Congo and Senegal.

Objectives: Determining the origin of infection geographically, drawing phylogenetic tree among viruses strains, and give the chance to detect and identify the viruses and attempt to making vaccines.

Methods: It has been depending on database available on NCBI website for searching on accession number of recorded viruses gene sequences, and used the minimum evolution phylogenetic tree algorithm for drawing phylogenetic trees.

Results: The first record of the virus was in the Crimean Peninsula in Russia in 1944, then recorded in the Congo basin in the middle of Africa in 1956. The virus was also recorded in some countries in Asia, Africa and Europe. In Iraq, the infection of CCHFV appeared and was recorded in 1979, then in 1992, 1996 and 2012.Genomic of the virus was detected at the molecular level and sequenced. The local molecular studies showed three strains of the virus. Strain 1 was the same clade as strain 1 of Oman, whereas strain 2 was located with the same clade as of strain 2 of Turkey. Strain 3 of the virus in Iraq, Oman and China were in one clade. The phylogenetic tree showed that South Africa and Uganda were located in one clade, and Nigeria shared the same ancestor. China and Pakistan were the same clade. Whereas Russia, Congo and Senegal were out groups.

Key words: Crimean-Congo hemorrhagic fever virus, phylogenetic trees, virus evolution, Viral Haemorrhagic Fever

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Introduction

Viral hemorrhagic fevers are infectious diseases that cause severe life-threatening illness. It threatens through making damage in the walls of small blood vessels, and the occurrence of thrombosis.[1] The internal bleeding that results from this condition is usually not life threatening, but the diseases themselves can endanger on life. Some types of viral hemorrhagic fevers include Dengue, Ebola, Lassa, Marburg and Yellow fever. Viral hemorrhagic fevers are spread by contact with infected animals or insects. The viruses that causes viral hemorrhagic fevers live in many

species of animals and insects, and most commonly include mosquitoes, ticks, rodents and bats. Rodents and arthropods are the main reservoirs for viruses causing VHFs.[2] The multimammate rat, cotton rat, deer mouse, house mouse, and other field rodents are examples of reservoir hosts. Arthropod ticks and mosquitoes serve as vectors for some of the illnesses. Viral hemorrhagic fevers (VHFs) are a set of acute systemic febrile sicknesses caused by four families of viruses: Arenaviridae, Bunyaviridae, Filoviridae, and Flaviviridae.[3] They are a group of febrile illnesses caused by RNA viruses from several viral families.[4,5] These highly infectious viruses lead to a potentially lethal disease syndrome characterized by fever, malaise, vomiting, mucosal and gastrointestinal (GI) bleeding, edema, and hypotension (Figure-1). Dangerous factors for VHFs include travel to geographic areas where these diseases may naturally occur, handling of animal carcasses, contact with animals or people with the disease, and arthropod bites.[6]

Crimean-Congo Hemorrhagic Fever Virus (CCHFV):

CCHFV is endemic in all of Africa, the Balkans, the Middle East and Asia.[7-14] The disease was first described in the Crimean Peninsula in 1944 and given the name Crimean hemorrhagic fever in 1969 it was recognized that the pathogen causing Crimean haemorrhagic fever was the same as that responsible for an illness identified in 1956 in the Congo Basin.

Pathogenesis of CCHFV:

The virus of haemorrhagic fever diminish the immune system of the host through infecting and manipulation cells that detect the exist of viruses. The virus replication synchronizes with disorganization of the lymphocyte and vascular.[15] Endothelium can be attacked directly by virus replication or by some factors that mediate the infection causing endothelial disrupt. Endothelial damage leads to hemostatic disorder by enhancing platelet accumulation and degranulation.[16] The clinical course starts within 3-7 days after exposure to tick bite or contact with animal products which begins with fever (39-41ºC), headache, vertigo, and myalgia.[17] Additional signs such as, nausea, diarrhoea and disgorge, in some cases it can note hyperemia of the face, neck, and chest, congested sclera, and conjunctivitis are generally observed and called pre haemorrhagic that continue as an average of 3 days , which can be followed within 3-5 days by hemorrhagic appearance start from petechial bleeding to vast hematomas on the mucous membranes and skin.[18] The commonly most bleeding take in the nose, digestive (hematemesis and intra - abdominal and melena), menometrorrhagia, hematuria and hemoptysis via respiratory tract. Other symptoms were observed like the bleeding in the vaginal, cerebral and gingiva. The convalescence period begins in survivors about the convalescence period begins in survivors about 10-20 days after the emergence of infection represented by unstable pulse, tachycardia, loss of hair, xerostomia, polyneuritis, hardness in breathing, poor vision, loss hearing and memory. All of these symptoms will cure later.[19]

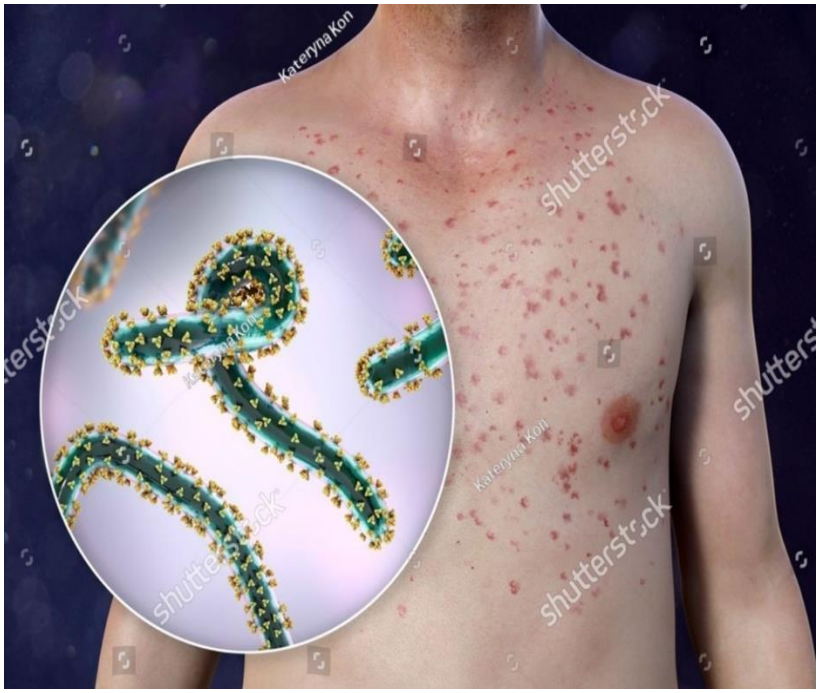


Fig 1. A person infected by viral hemorrhagic fever shows blood spots on his skin.

(https://www.shutterstock.com/image-illustration/skin-rash-on-chest-patient-marburg-2292931629)[20]

Aims of study:

1. Identify the evolutionary relationship between the virus strains that appeared in Iraq and other countries, as well as the origin of the strains.
2. Determine the treatment using artificial intelligence.
3. Searching for epitopes of local strains to investigate the vaccine and diagnose the virus.

Methodology

1. For data collection, we depended on data recorded by previous finding authors.
2. Analyze the samples to construct phylogenetic trees and explain the predicted time of virus evolution.
3. Blast our results on NCBI web site to find the similarities and variations.

Results

The historical records of *C. congo* showed the incidence of disease between 1944 to 2021 in Asia, Africa and Europe, these records included the occurrence and recurrence of infections in the countries located in the mentioned continents (Fig-2). The evolution of the phylogenetic tree of the main strains of CCHFV was constructed. It seems that SPU116/87 in South Africa SPU128/81 in Uganda belong to the same ancestor; similarly, the strains HY-13 in China and JD-206 in Pakistan within the same clade, and these group altogether related to IBAr10200, the Nigerian strain an old ancestor. Whilst, the Russian strain, Drosdov; the Congo strain, UG3010 and the Senegal DAK8194

are outgroups (Fig-3). This may suggest the geographical boundaries and distances between the countries that contribute in the spread of strains. In Asia, it was constructed three strains recorded of CCHFV using the minimum evolution phylogenetic tree. The first strain,[1] Baghdad and Oman were the same clades and they shared Pakistan, China and Greece common evolutionary ancestor (Monophyletic), but paraphyletic with the first strain of Turkey (Fig-4A). Whilst strain 3 group was monophyletic including Oman, China, Baghdad, Pakistan and Turkey; meanwhile Oman and China shared the earliest ancestor (Fig-4B). Regarding the strain 2, Baghdad and Turkey were monophyletic, likewise China and Pakistan had same clade, and with Oman they formed monophyletic group; except Greece, in strain 2 group Baghdad and Turkey are paraphyletic with Pakistan, China and Oman (Fig-4C). Here in strain 2, Greece was our the group. In Iraq during last two years, and according to local infection (Data from Iraqi Ministry of Health, 2022-2023), there were fluctuations in infection. The curvograph of infection showed high contagion through weeks 19 and 24 in 2022 and in weeks 19 and 27 of 2023 (Fig-5). As the rate of mortality increased during the weeks 18, 23 and 29 in 2022 and in weeks 12, 18, 23 and 27 of the year 2023. (Fig-6).

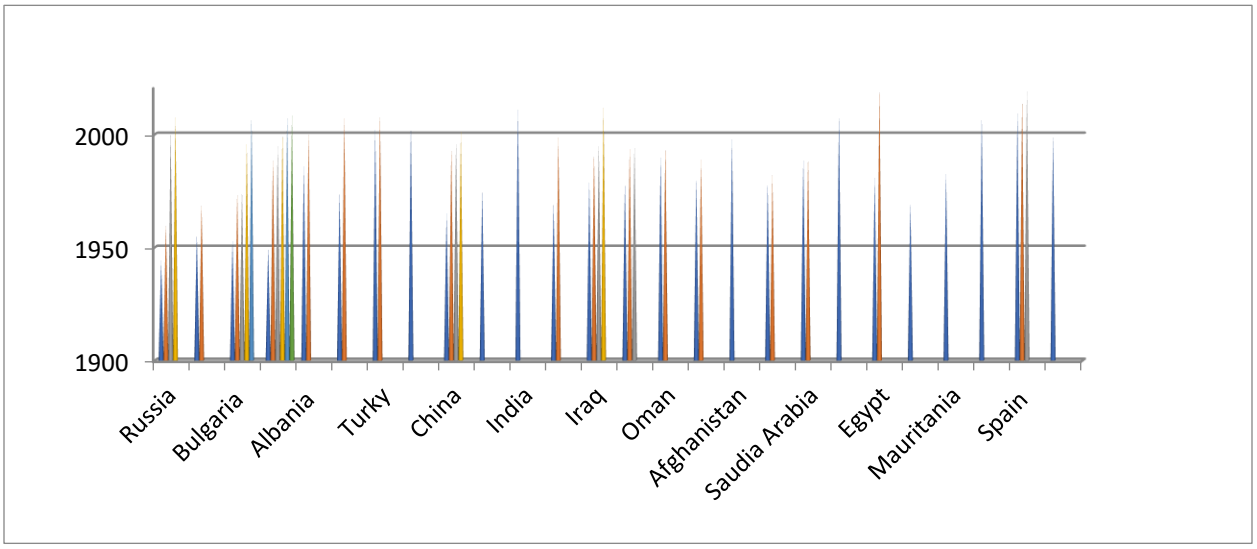


Fig 2. Historical records of *C. congo* in the Asian, Africa and Europe (from 1944 to 2021)

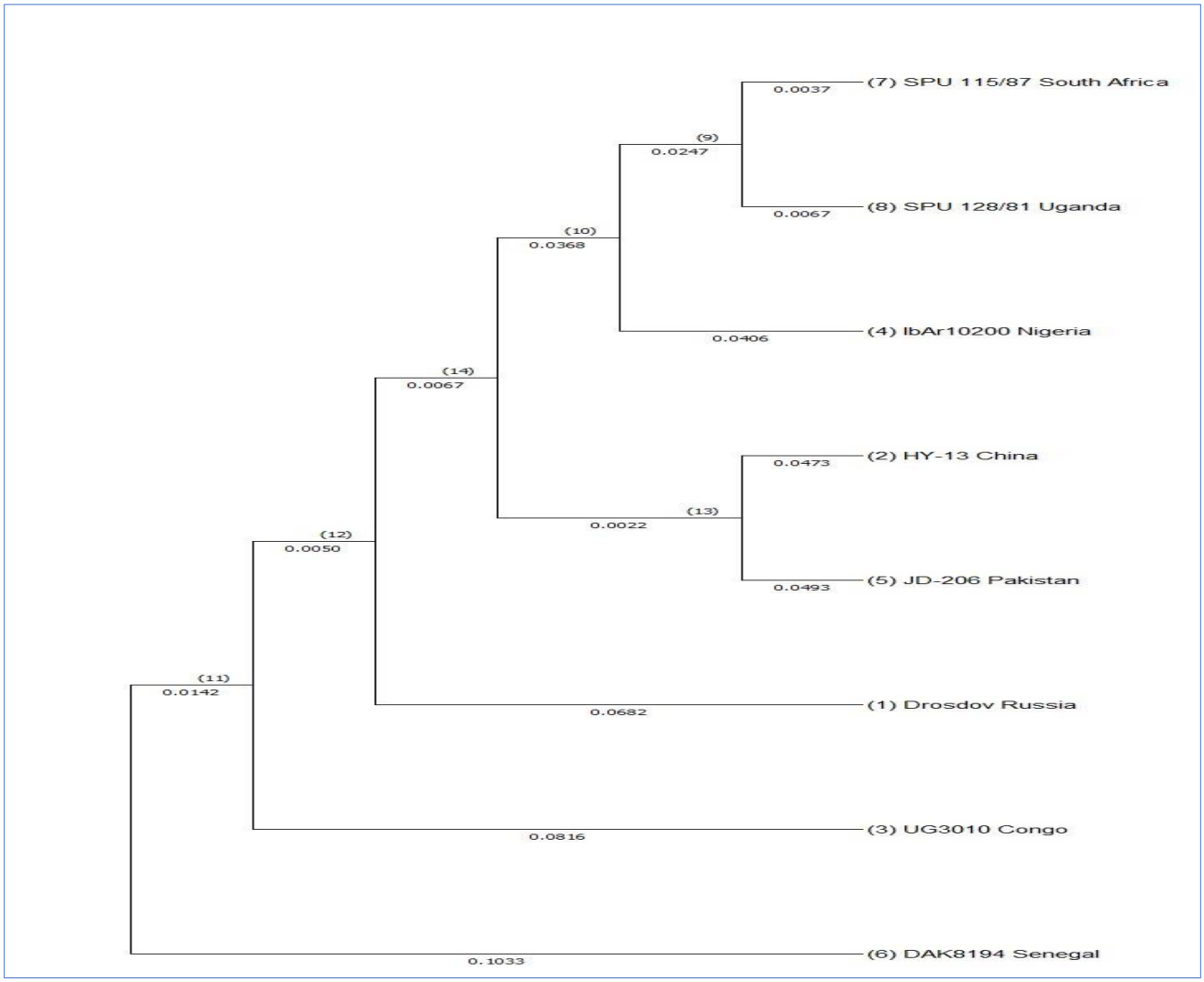
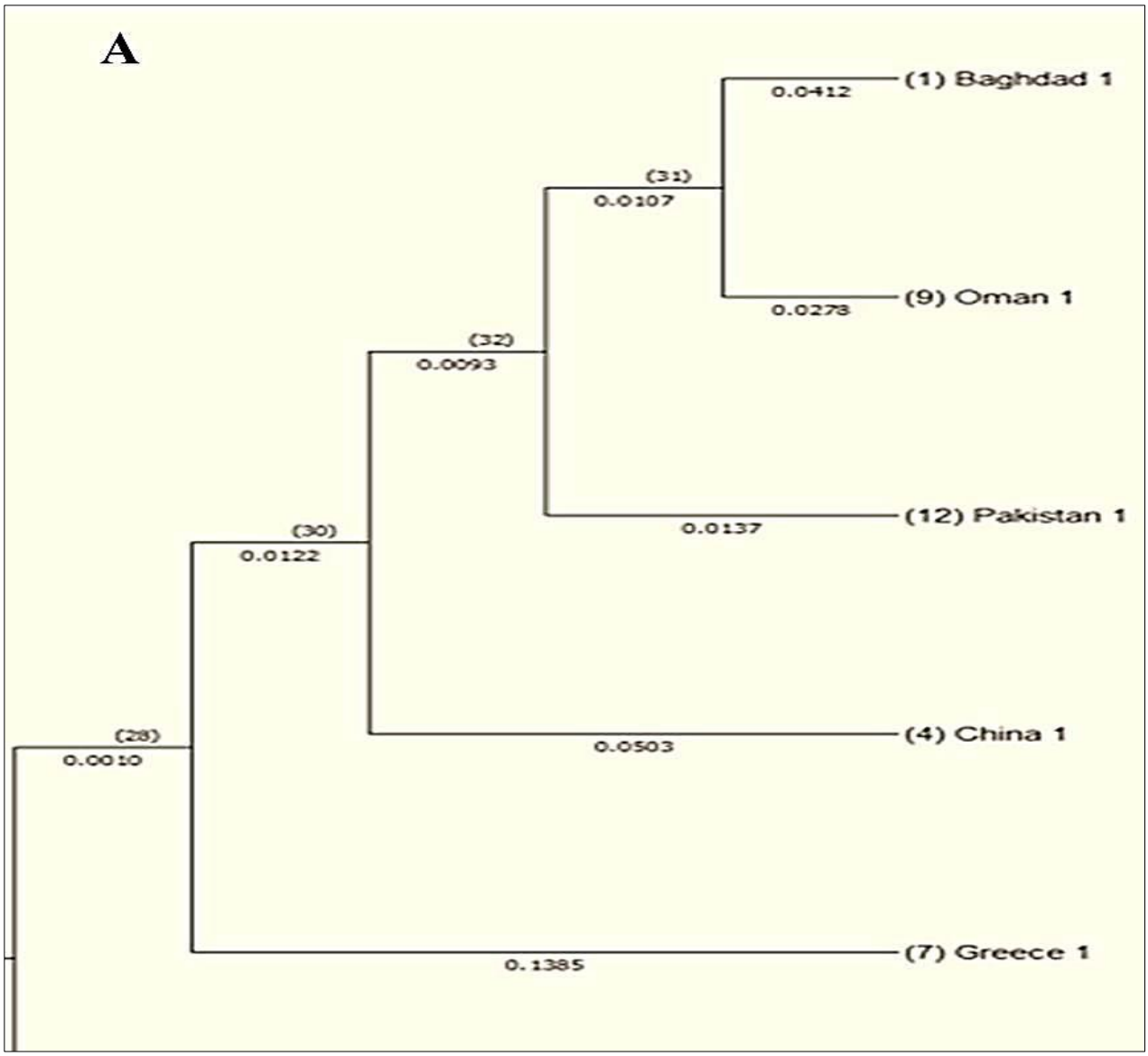
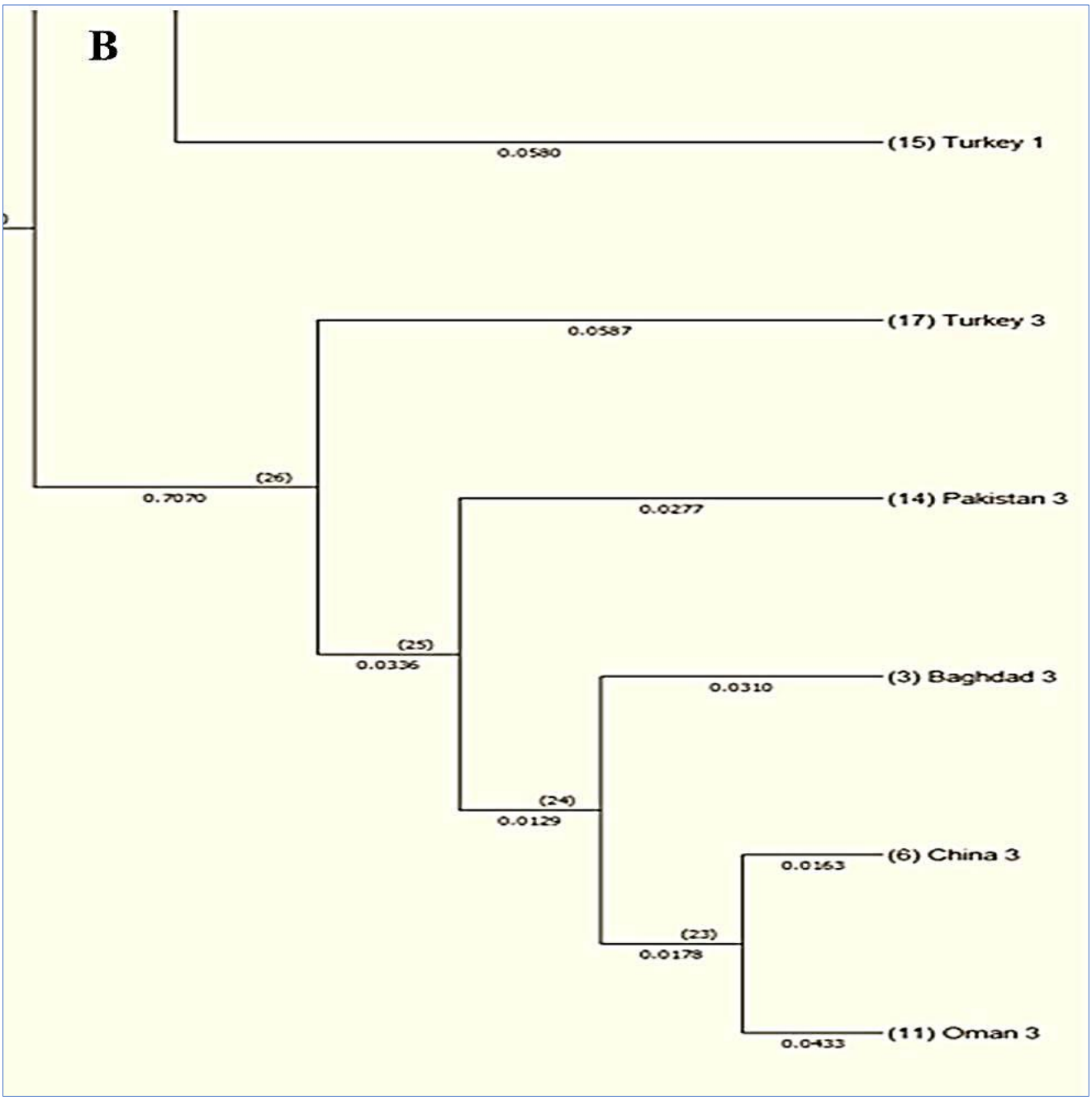


Fig 3. The minimum evolution phylogenetic tree in the main strains of CCHFV. It Indicated that SPU 115/97 and SPU 128/81 are sister strains and represent polyphyletic to IbAr10200; the strains HY-13 and JD-206 are the same clade, and they all fall under common ancestor, whereas the others derived from separated strains


A
(1) Baghdad 1
0.0412
(31)
0.0107
(9) Oman 1
0.0278
(32)
0.0093
(12) Pakistan 1
0.0137
(30)
0.0122
(4) China 1
0.0503
(28)
0.0010
(7) Greece 1
0.1385


B
(15) Turkey 1
0.0580
(17) Turkey 3
0.0587
(26)
0.7070
(14) Pakistan 3
0.0277
(25)
0.0336
(3) Baghdad 3
0.0310
(24)
0.0129
(6) China 3
0.0163
(23)
0.0178
(11) Oman 3
0.0433

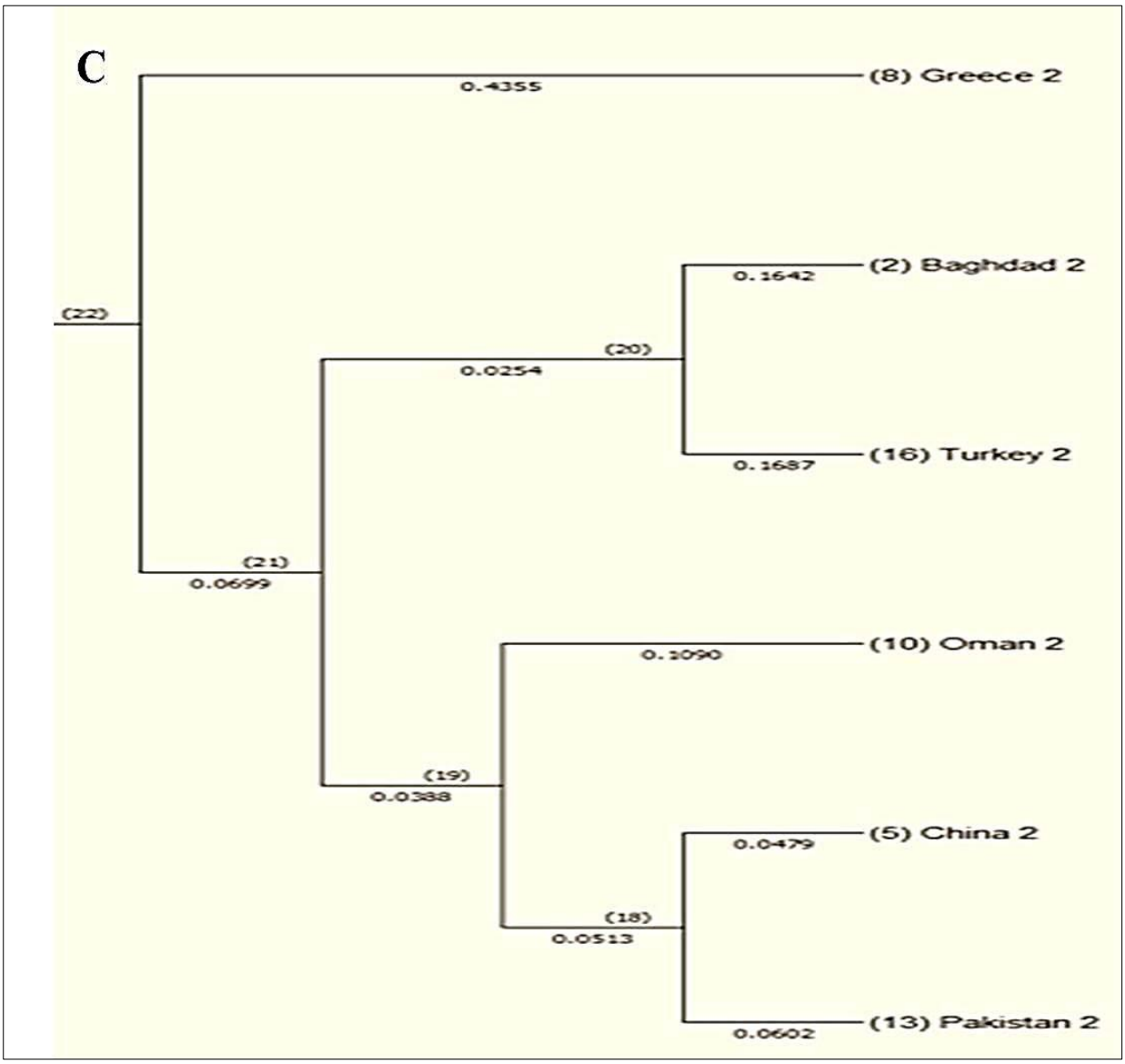


Fig.4. (A, B and C): The minimum evolution phylogenetic tree of local strains (Iraq) of CCHFV and other countries

Table-1, exhibited the rates of suspected and confirmed deaths caused by CCHF infection in Iraqi governorates indicating that the confirmed cases and death occurred in Thiqar (12) then Basrah (10), then Medical city (9), Erbil (5), Muthanna and Baghdad (3). The low rate was in Dahuk (2), Wasit (2), Babylon (2), Kirkuk (2), Salah aldin (1), Maysan (1), Kerbala (1) and Nineveh (1). In Anbar and Sulaymaniya no death was recorded.

Table 1. The rates of suspected and confirmed deaths caused by CCHF infection in Iraqi provinces. The data was provided by Iraqi Ministry of Health

Province	Suspected	Confirmed	deaths suspected	deaths confirmed	CFR (S+C)	CFR confirmed	Reporting rate/100000	Cumulative Incidence	Positivity
Total	1827	511	42	65	5.9	12.7	95.1	20.8	28.0
Dahuk	12	8	0	2	16.7	25.0	0.6	0.2	66.7
Baghdad-Karkh	83	20	1	3	4.8	15.0	2.6	0.5	24.1
Wasit	104	31	2	2	3.8	6.5	0.3	0.07	29.8
Baghdad-Resafa	120	21	2	3	4.2	14.3	2.7	0.4	17.5
Muthanna	79	35	1	4	6.3	11.4	12.3	3.8	44.3
Maysan	86	27	1	1	2.3	3.7	8.9	2.1	31.4
Najaf	69	22	4	3	10.1	13.6	5.4	1.3	31.9
Babylon	86	25	0	2	2.3	8.0	4.7	1.1	29.1
Anbar	17	2	1	0	5.9	0.0	0.9	0.1	11.8
Diyala	68	12	1	2	4.4	16.7	4.3	0.6	17.6
Kirkuk	37	9	0	2	5.4	22.2	2.5	0.5	24.3
Salah aldin	26	6	0	1	3.8	16.7	1.8	0.3	23.1
Kerbala	33	7	1	1	6.1	14.3	2.9	0.5	21.2
Medical city	159	48	3	9	7.5	18.8	NA	NA	30.2
Erbil	34	13	1	5	17.6	38.5	2.2	0.6	38.2
Sulaymaniya	11	3	0	0	0.0	0.0	0.6	0.1	27.3
Basrah	273	83	18	10	10.3	12.0	10.8	2.5	30.4
Diwaniya	43	12	0	2	4.7	16.7	3.7	0.8	27.9
Thiqar	465	120	3	12	3.2	10.0	23.8	4.9	25.8
Nineveh	22	7	3	1	18.2	14.3	0.7	0.2	31.8
Total	1827	511	42	65	5.9	12.7	95.1	20.8	28.0

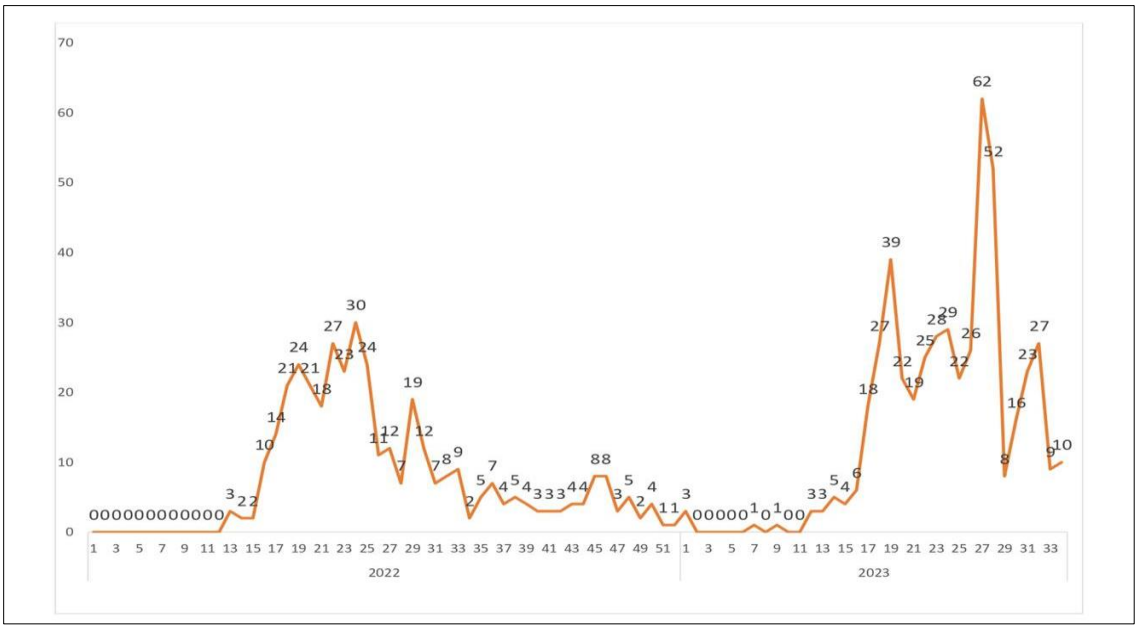


Fig 5. Trend of CCHF cases in Iraq for the last two years according to weeks

(Data from Iraqi Ministry of Health)

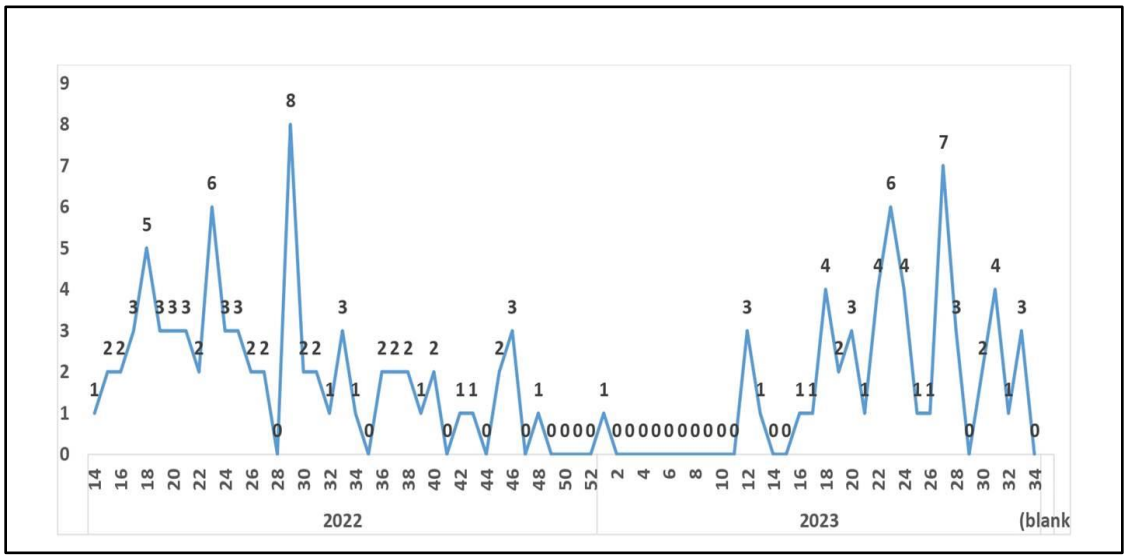


Fig 6. Trend of CCHF deaths in Iraq for the last two years according to weeks[21]

Discussion

CCHFV is the most dangerous virus that can infect many organs in the human body causing failure in the function of the body organs, such as failure in the function of respiratory system, liver, kidneys and CNS. Moreover, it causes subcutaneous bleeding and sometimes coma. CCHFV is often considered an epidemic when it appears under vague circumstances. The lethality rate can reach 10 to 40%.[22] Many researchers studied the extent of its spread and the kinds of strains. The symptoms caused by CCHFV are common and similar, however it is still the molecular detection for determining the strains facing difficulties. This is due to the mutation that occurs in its genome every once in a while. So, many strains have emerged that may be associated with the time and place of infection. DNA viruses in general have a rate of mutation around 10^{-8} to 10^{-6} substitutions per nucleotide site for a cell infection.[23] The current study targeted where the main strains appear hence where they spread, as well as knowing the common ancestors for these strains. According to the biological status of the virus in which the rate of mutations are very fast in its genome, this is leading to a diversity of virus strains specially when it transmitted to different places or a period of time passes after it spreads. By deducing the results of an evolutionary phylogenetic tree, it seems the strains that shared a common ancestor and within the same clade exist in countries with close borders. The unique ability of some viruses to naturalize with new hosts and environments is extremely depending on their power to create de novo diversity in a standard and short time.[24-26] Locally in Iraq, the cases of infection showed oscillations and the severity of infection was concentrated during moderate temperature seasons and in certain areas. This suggest that the time of infection intensity was occurring during Spring, so this perhaps because the virus activity that immerge during certain seasons. Thiqar was the more city that recorded high number of infection and death, then Basrah. On the other hand, The Northern cities were the lowest number in the infection (Anbar, Sulaymaniya) (Table-1). This can be explained to the commercial exchange of livestock that may occur in Southern cities more than Northern. Or the reason is because un availably of infection dataset in some provinces. Despite many studies that included many aspects of the virus, it is ambiguity still and the question is: why do infections with such viruses appear and disappear betweenwhiles? And the other important question is: what is dividing line in classification of the virus into species level despite the great variation in the sequences of nitrogenous bases among strains? Many future studies are required to detect more details about CCHFV.

Recommendations

1. Making whole genome sequences for local infection, especially in recent years.
2. Further studies for new strains and determine the mutations from time to time.
3. Looking for parasites and organisms that transfer the virus (determine the species).

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دراسة تطورية وتاريخية لحمى القرم والكونغو النزفية فيروس (CCHFV)

فيروس حمى القرم-الكونغو النزفية (CCHFV) حيواني المنشأ يصيب الماشية ثم ينتقل إلى الإنسان عن طريق الاتصال المباشر بالحيوان أو عن طريق القراد الذي يعيش على الحيوانات كطفيلي من خلال لدغاتها. تظهر على المصابين بعض الأعراض مثل التوعك والقيء ونزيف الغشاء المخاطي والجهاز الهضمي وانخفاض ضغط الدم والوذمة. أول تسجيل للفيروس كان في شبه جزيرة القرم في روسيا سنة١٩٤٤، ثم سجل في حوض الكونغو وسط أفريقيا سنة ١٩٥٦. كما سجل الفيروس في بعض دول آسيا وأفريقيا وأوروبا. وفي العراق ظهرت الإصابة بفيروس CCHFV وتم تسجيلها في سنة ١٩٧٩، ثم في الأعوام (١٩٩٢،١٩٩٦، ٢٠١٢). وتم الكشف عن جينوم الفيروس على المستوى الجزيئي وتسلسله. وأظهرت الدراسات الجزيئية المحلية ثلاث سلالات من الفيروس. وكانت السلالة ١ هي نفس الفرع الحيوي للسلالة ١ في عمان، في حين أن السلالة ٢ تقع في نفس الفرع الحيوي للسلالة ٢ في تركيا. كانت السلالة ٣ من الفيروس في العراق وعمان والصين في فرع فرعي واحد. كما تم تحليل شجرة التطور الأدنى للسلالات الثمانية الرئيسية التي تم جمعها من بلدان مختلفة بما في ذلك جنوب أفريقيا وأوغندا ونيجيريا والصين وباكستان وروسيا والكونغو والسنغال. وأظهرت شجرة النشوء والتطور أن جنوب أفريقيا وأوغندا تقعان في فرع حيوي واحد، وأنهما يتقاسمان نفس الجد مع نيجيريا. وكانت الصين وباكستان نفس الفرع الحيوي. بينما خرجت روسيا والكونغو والسنغال من المجموعات.