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Epidemiology, Risk Factors, And Effectiveness Of Treatment Of Crimean Congo Hemorrhagic Fever In Turkey, 2007-2012

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Title: Epidemiology, risk factors, and effectiveness of treatment for Crimean Congo Hemorrhagic Fever in Turkey, 2007-2012

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INTRODUCTION

Crimean Congo Hemorrhagic Fever (CCHF) is a tick-borne viral hemorrhagic fever that is caused by a *Nairovirus* of the *Bunyaviridae* family.[1] Routes of transmission include an infectious tick bite, generally of the *Hyalomma* or *Rhipicephalus* genera, contact with blood or bodily fluids from an infected individual or contact with blood or tissue of infected animals, including livestock.[2] Nosocomial infections also occur.

CCHF was first recognized in the Crimean Peninsula in 1944.[3] Since then, it has been reported from other countries, including Bulgaria, Russia, Iran and Iraq.[3] Currently, CCHF has the largest geographic range of any other tick-borne virus.[4] The infection has been reported in more than 30 countries in Africa, Asia, the Middle East, and southeastern Europe where *Hyalomma* ticks are abundant. *Hyalomma marginatum marginatum* ticks are the main vector for CCHF virus transmission in the Balkans, Crimea and Southern Russia.[3, 5]

The CCHF virus in *Hyalomma* and *Rhipicephalus* ticks can undergo vertical, transovarial, as well as horizontal transmission (from mammalian hosts to ticks). Transmission between ticks may also occur during co-feeding and is transstadial.[6] Ticks involved in CCHF transmission prefer a warm, arid climate with fragmented vegetation in areas below the 46^{o}N latitude: all factors that are consistent with Turkey's geography.[6] Studying the spatial determinants of disease, especially in areas that may have been further fragmented as people settle in previously uninhabited land, is an important element when considering the spread of CCHF.

Hyalomma and *Rhipicephalus* ticks are "two-host" ticks. Larvae and nymphs feed on small animals including rodents, hares, and ground-feeding birds. Adults feed on larger animals including sheep, cattle and humans.[6] *Hyalomma marginatum* ticks can be aggressive and are known as "hunting" ticks since they can seek their host who may up to 400 meters away.[6]

Turkey's first case of CCHF was identified in 2002.[3] Since then, the number of cases and the geographic extent of affected area have increased. With more than 7,100 cases in a ten-year period, the outbreak of CCHF in Turkey represents the largest epidemic of this disease since its initial identification in the Crimean Peninsula.[2, 3] Through the years, the areas affected have expanded from its epicenter in the northern region of Turkey to other provinces across the country.[2] While infections have been identified year round, most cases occur in the warmer months from March to October, with the greatest incidence in June and July, corresponding to tick season.[7] Turkey's great abundance of *H. marginatum marginatum* ticks can explain Turkey's ongoing outbreak.[2]

Recognizing the severity of the outbreak, the Turkish Ministry of Health (MoH) declared CCHF a reportable disease in December 2003. The MoH's Communicable Diseases Department created a surveillance system to track the outbreak.[3] Through this system, all cases suspected of CCHF based on clinical features consistent with CCHF were referred to secondary healthcare centers. At these secondary healthcare centers, a confirmed diagnosis, based on PCR testing and testing of sera for antibodies to CCHF, was made and reported to the MoH.[3] Patient information reported to the MoH also included epidemiologic and clinical features.[3] Patients were required to submit a second serum sample to MoH laboratories two weeks post-diagnosis or upon hospital discharge.[3]

In effort to monitor and control the outbreak, the MoH also created a scientific advisory commission in 2003.[7] Through regular meetings, the commission addressed issues concerning patient treatment as well as disinfection and isolation measures.[7] In 2004, the MoH collaborated with the Ministry of Agriculture and Rural Affairs to educate the public, especially those living in high-risk areas, about the disease, including routes of transmission, methods to protect animals, especially livestock, and appropriate responses to tick bites.[7] In 2008, a larger education campaign was implemented. This involved the dissemination of information regarding the risks of CCHF through brochures, posters and television commercials. In high-incidence locations members of the MoH went door-to-door educating residents about the dangers of tick bites and the proper methods to check for and remove ticks.[7] Public health educators also taught residents of the importance of limiting exposure to tissues, blood, and bodily fluids of livestock that might be infected and recommended the use of permethrin repellent 0.5% on clothing for humans.[7]

Symptoms of CCHF are not immediately apparent following infection. There are four major stages of disease progression: the incubation phase, pre-hemorrhagic phase, hemorrhagic phase, and convalescence phase.[8] The typical incubation phase following a tick bite is 1-3 days and 5-6 days post-exposure to infected animal or human tissues, blood, or bodily fluids, although there is considerable range to these values.[7] After the incubation phase, the disease can progress to a pre-hemorrhagic phase, which typically lasts for 3 days, but ranges from 1 to 7 days.[8] This phase is characterized by fever, myalgia, dizziness, headache, and vomiting.[8] The short hemorrhagic phase follows, normally lasting between 2 and 3 days.[8] This phase is characterized by epistaxis, gastrointestinal, urinary and respiratory tract bleeding, development of petechia, and splenomegaly.[8] In severe cases, ecchymosis and systemic bleeding may occur, frequently resulting in death during the hemorrhagic phase.[1] Surviving patients convalesce, but suffer from a range of symptoms that last for varied periods of time; symptoms include weakness, dizziness, nausea, and loss of memory among other outcomes.[8]

Differences in outcome and duration of each stage may be due the dose of the inoculum, severity of disease, and variation in the pathogenicity of the virus or time to treatment.[7] Variation in treatment may also contribute to differences in patient outcome. Active treatment includes platelet transfusions, fresh frozen plasma, interferon injections and the administration of ribavirin.[9]

Treatment with antibodies derived from animals or humans who recovered from CCHF infection have not proven successful in treating disease among the few patients studied. Supportive

therapy, such as fluid and electrolyte balance, oxygenation and hemodynamic support are important for primary treatment.[10]

The effectiveness of active therapies such as the administration of ribavirin is debatable. Some studies suggest it is effective when administered immediately after disease is suspected, while others have reported no positive impact on disease course.[11] Ribavirin is an anti-RNA virus inhibitor that is commonly used with interferon-α to treat patients with Hepatitis C and hemorrhagic diseases, caused by Arenaviruses, Filoviruses and Hantaviruses.[9, 12, 13] Ribavirin was first used to treat CCHF in Iran during an outbreak of the disease in 1999 to 2001.[14] A study conducted by Mardani *et al.* showed that among those treated with oral ribavirin, the case fatality was 11.6%, whereas the case fatality among untreated patients was 58.3% ($p < 0.001$).[11] Given the success of oral ribavirin treatment for CCHF patients in Iran, the World Health Organization recommended it as the main treatment option for those infected with the CCHF virus.[14] The one caveat to this recommendation is wide genetic diversity and dissimilarity that exists between strains of the CCHF virus in different regions. While ribavirin may be effective for treatment of the strain of CCHF in Iran, it may not necessarily be as effective for the treatment of the particular strain of CCHF in Turkey, a distant phylogenetic relative.[6] Furthermore, other studies have produced conflicting results, indicating that oral ribavirin does not provide significant benefit to patients with CCHF infection.[15] Only one randomized control trial has been conducted to assess the efficacy of ribavirin for the treatment of CCHF.[16] This prospective randomized trial indicated that there was no positive effect among those patients treated with both ribavirin and supportive therapy and those receiving only supportive therapy.[16] A meta-analysis of 21 studies, including the randomized control trial and 20 observational studies, found no clear evidence of the benefit of ribavirin treatment.[17] However, confounding factors, such as only treating patients with severe disease or the delay in treatment onset, prevent firm conclusions to be drawn from many studies.[9] Currently, there is no vaccine for CCHF. New treatments are being developed, however, most of the efficacy of these drugs are based on testing in suckling mice, as no other laboratory animal models for CCHF exist.[9] The lack of effective treatment and vaccination makes vector control, public awareness, and other protective measures paramount in controlling the spread of this disease.

METHODS

A cross-sectional study of all CCHF cases was conducted in Turkey between January 1, 2007 and December 31, 2012. All 6,070 subjects were diagnosed with CCHF, by epidemiologic and clinical characteristics and confirmed by laboratory testing. The protocol for identifying a patient with CCHF involved the use of polymerase chain reaction (PCR) for the identification of the CCHF virus and/or IgM test. Patient outcomes included survival and death.

Case data was obtained from an unpublished surveillance database from the Turkish Ministry of Health's National Public Health Directory, Communicable Diseases Department, Section of Zoonosis. This database contained information regarding each case's clinical features and outcome as well as epidemiologic and laboratory findings.

Case Definition
Epidemiologic risk factors, clinical features, and laboratory findings were obtained for laboratory confirmed cases of CCHF. Epidemiologic risk factors included tick exposure including tick-bite or contact; occupation in animal husbandry, farming, or presence in a laboratory setting; exposure to blood or bodily fluid from a CCHF-infected patient or animal; and close contact with a CCHF case.[7] Clinical features included headache or body aches of acute onset, myalgia or arthralgia, weakness, nausea or vomiting, abdominal pain or diarrhea, fever, and bleeding.[7] Laboratory findings include thrombocytopenia (platelet <150,000/mm^3) and/or leukopenia (WBC <4,000/mm^3), elevated levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and creatine kinase (CK).[7]

RT-PCR detection of the virus or IgM positivity using ELISA was used to confirm CCHF diagnosis. If a PCR result came back positive for a patient with suggestive clinical findings, then the patient was a proven case; 90% of the cases in the database were confirmed by PCR. If the individual's PCR result was negative, but the individual still showed symptoms consistent with CCHF, then the individual's CCHF specific IgM levels would be measured. If the results were positive, then the individual would again be identified as a proven case. This can occur when viral levels are very low. If an individual's IgM levels were low CCHF, yet the individual presented clinical features consistent with CCHF, then a second blood sample would be tested for IgM levels two weeks after the first test was tested. Only proven cases confirmed either by PCR or CCHF specific IgM were included in the study, which rarely occurred. Laboratory diagnostics were carried out in the National Virology Reference Lab of the Public Health Directory of Turkey.[7]

Statistical Analysis
Statistical methods used to analyze data included chi-square, t-test and univariate statistical comparisons. These methods were used to determine associations between risk factors and death by CCHF. Multivariate logistic regression was used to determine the risk factors associated with fatal outcome. The full model was constructed using stepwise forward model selection; variables were included when their log-likelihood ratio test generated a p-value <0.1 and were excluded when the p-value was >0.3. The full model contained the following variables: gender; age; if a patient had leukopenia and thrombocytopenia; was exposed to other infected individuals; was hypotensive; experienced bleeding of any sort including spontaneous bleeding, bloody diarrhea, petechia, ecchymosis, hematuria, or vomited blood, or experienced bleeding from the gums, anus, vagina, or gastrointestinal tract; had elevated levels of aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), or creatine kinase (CK); lived in a village; had a history of a tick bite; and if a patient received ribavirin treatment. All analyses were performed using SAS software (SAS Institute, Cary, NC), version 9.3.

Given the large amount of missing data for history of tick bite, in 2007 and 2012, both years were excluded from a second analysis of the odds of death caused by CCHF, presented in Table 7. It was important to consider this specific variable, history of tick bite, as the main route of transmission of the virus is through the bite of an infectious tick. The caveat with this analysis, however, is that history of tick bite is important for descriptive epidemiology but not for survival analyses. Since it is an intermediate variable, it is not a confounder, however, it was still interesting to see the effect of this variable on the odds of death caused by CCHF. Bivariate and

multivariate logistic regressions were rerun to determine the risk factors associated with a fatal outcome. As with the previous model, the full model was constructed with the same stepwise forward model selection. The full multivariate model contained the same variables as the first model.

Distribution of CCHF in Turkey
ArcGIS was used to map yearly incidence of CCHF per 100,000 people per province. ArcGIS was also used to map the six-year (2007-2012 inclusive) cumulative CCHF incidence per 100,000 people per province. Population data was obtained from the Turkish Statistical Institute. Census data from 2000 was used in incidence calculations for 2007, 2008, 2009, 2010, and 2011. Census data from 2012 was used for incidence calculations for 2012. To calculate the cumulative incidence per province, the average of population data for 2000 and 2012 was used.

Evaluation of ribavirin as effective treatment for CCHF
Propensity scores were used to determine the effectiveness of ribavirin in treatment of CCHF. This method has been used the first time for determining the effectiveness of ribavirin treatment among CCHF patients. Propensity scores serve as a method of correcting for confounders and balancing groups that received treatment and those that did not, using selected covariates. The estimated propensity score is the predicted probability that an individual would have been treated with ribavirin based on that individual's observed pretreatment characteristics.[18, 19] Propensity score analysis is becoming a popular method to efficiently control large numbers of confounders in database studies.[18, 19] In our study we used baseline characteristics of the patients to estimate the propensity scores using a logistic model. These covariates were gender, age, average days of symptoms before hospital admission, headache, body ache, weakness, nausea, vomiting, diarrhea, stomach ache, bleeding, unconsciousness, bleeding gums, hypotension, vomiting blood, ecchymosis, splenomegaly, gastrointestinal bleeding, anemia, leukopenia, thrombocytopenia, exposure to infected individuals, fever, AST/ALT, LDH, and CK levels, and the year of infection. To explore the performance of variables for the prediction of ribavirin use, we used the c-statistic.[20] In the propensity score analyses, different ways of using these scores to control for confounding can be helpful. We used a stratified analysis and logistic regression adjusted for the propensity scores as decile categories.[19]

Between 2007 and 2012, a total of 1,069 individuals infected with CCHF received ribavirin treatment. Due to a large amount of missing data across covariates used to model ribavirin treatment, all data from 2007 was excluded from this propensity score analysis. Between 2008 and 2012, it was reported that a total of 984 individuals received ribavirin treatment while 4,369 individuals did not receive ribavirin treatment. Due to a large amount of missing data across other variables, only 4,152 individuals were used for this propensity score analysis. This analysis included 814 individuals who received ribavirin treatment and 3,338 individuals who did not receive ribavirin treatment.

RESULTS

Distribution of CCHF in Turkey
Areas of northern Turkey had the highest incidence of CCHF (Figures 3-9). The maps also indicate a heavy concentration of new cases in the north central region of Turkey in 2007 (Figure

3), followed by a spread of greater incidence to the northeastern region of Turkey in 2008 and 2009 (Figures 4 and 5). In 2010 and 2011, however, the outbreak was once again more concentrated in north central provinces of Turkey (Figures 6 and 7). By 2012, the outbreak had spread through the north central and northeaster provinces of Turkey (Figure 8). The greatest single year incidence of CCHF per province occurred in 2009 in Karabük; there were 54.20 new cases of CCHF per 100,000 people (Table 6). Over the six-year study period, the five provinces with the greatest cumulative incidence were Gümüşhane, Tokat, Karabük, Çorum, and Kastamonu (Figure 9, Table 6).

During the six-year study period between 2007 and 2012, 6,070 human cases of CCHF were identified in Turkey. From this total, 301 patients succumbed to the disease. The greatest number of CCHF cases occurred in 2008, with 1,315 cases. The greatest number of deaths caused by CCHF occurred in 2008 and 2009, with 63 deaths each year.

Table 1 depicts the characteristics of all patients infected with CCHF. More males than females were infected with CCHF and the average age of those infected was 44.2 years (SD ± 19.7). Many cases were farmers (34.5%) or housewives (21.9%), had been exposed to animals (75.6%), and resided in villages (82.5%). Housewives include those who work in the house and in the field. Furthermore, most cases had a history of a tick bite (75.9%) and the majority of cases had been admitted to a hospital 0 to 3 days after the onset of symptoms consistent with CCHF (66.4%). Table 2 depicts clinical and laboratory features of laboratory confirmed CCHF cases. Most cases experienced headache (71.0%), body aches (73.9%), weakness (86.9%), nausea (57.8%), fever (82.2%), leukopenia (74.5%), thrombocytopenia (78.7%), elevated AST/ALT levels (67.7%), elevated LDH (54.9%), and elevated CK levels (53.4%).

Tables 3 and 4 depict the epidemiologic and clinical risk factors associated with death caused by CCHF infection. Significant risk factors include older age ($p < 0.001$), exposure to infected individuals ($p = 0.02$), history of tick bite ($p < 0.001$), and average days of symptoms before hospital admission ($p < 0.01$; protective). Significant clinical risk factors include hypotension ($p < 0.001$) tachycardia ($p < 0.001$), bleeding ($p < 0.001$), anemia ($p < 0.001$), leukopenia ($p < 0.001$), thrombocytopenia ($p < 0.001$), and elevated levels of AST/ALT ($p < 0.001$), LDH ($p < 0.001$), CK ($p < 0.001$) and creatinine ($p < 0.001$). Fever was not a significant clinical risk factor of death due to infection ($p = 0.20$).

Among the 5,769 cases that survived, 1,019 (17.7%) received ribavirin treatment. Among the 301 deaths caused by CCHF, 50 (16.6%) received treatment; ribavirin treatment did not significantly influence survivorship ($p = 0.64$). Conversely, receiving supportive therapy such as thrombocyte suspension ($p < 0.001$), fresh frozen plasma ($p < 0.001$), or erythrocyte suspension ($p < 0.001$) significantly improved survivorship.

Table 5 shows the bivariate and multivariate associations between study variables and death caused by CCHF between 2007 and 2012. The unadjusted model indicated that among those who were infected with CCHF, persons with leukopenia were 58% less likely to die than those who had did not have leukopenia (95%CI 0.33-0.54). This model also indicated that those patients experiencing thrombocytopenia were 2.36 times more likely to die (95%CI 2.07-5.44). The unadjusted model also indicated that patients with bleeding in any location of the body, were

3.04 times more likely to die compared to those that did not experience bleeding (95%CI 3.19-5.11). Having a history of a tick bite was protective; those who had a history of a tick bite were 44% less likely to die due to CCHF infection that those who did not have a history of a tick bite (95%CI 0.43-0.73).

Once corrected for gender, age, leukopenia, thrombocytopenia, exposure to infected people, days of symptoms before hospital admission, hypotension, bleeding, anemia, elevated levels of AST/ALT, LDH, or CK, village residence, animal exposure, tick bite history, and ribavirin treatment, the adjusted model indicated that those individuals who were greater than 51 years of age had a significantly higher risk of dying. Patients with leukopenia were 80% less likely to die than those who were not leukopenic (95%CI 0.14-0.30). Those who had thrombocytopenia were 7.75 times more likely to die due to CCHF than those who did not have thrombocytopenia (95%CI 3.46-22.17). Bleeding was a significant risk factor for death due to CCHF. Patients who experienced bleeding were 2.88 (95%CI 2.75-5.48) times more likely to die than those who did not experience bleeding. While history of a tick bite was significant in the unadjusted model, the adjusted model indicates that prior tick bite was not significantly associated with death (OR: 0.23, 95%CI 0.57-1.14).

Table 7 shows the bivariate and multivariate associations between study variables and death caused by CCHF between 2008 and 2011. Despite the removal of 1,513 observations from the analysis, this new analysis did not result major changes to study findings. With the exception of one variable in the bivariate analysis, age 31-40 years, none of the other variables lost statistical significance, nor did any variable become statistically significant in either the bivariate or multivariate regression analysis.

Evaluation of ribavirin as effective treatment for CCHF – Propensity Score Analysis
Table 8 presents deciles of propensity scores, which represent the likelihood that individuals within that specific group will receive treatment based on all of the covariates in the predictive model. Table 8 also includes the number of individuals in each decile group that succumbed to CCHF and the odds of death based on receiving ribavirin treatment per decile group.

The table reveals no general trend in survival in response to treatment. One would expect to see better survival among patients treated with ribavirin, in the higher decile groups if the ribavirin treatment had any effect. Since patients with higher propensity scores are the patients who were mostly likely to receive ribavirin in the database (i.e. doctors mostly put the indication of ribavirin treatment for these patients) and they actually received it. While some of the calculated empirical odds ratios indicate a seeming protective effect of ribavirin treatment, none of these odds ratios were statistically significant.

Tables 9 and 10 contain the adjusted odds ratios for death caused by CCHF among infected individuals between 2008 and 2012. In these models we wanted to see the effect of ribavirin independent from other confounders. In the first model (Table 9), ribavirin treatment was adjusted for using only the propensity scores and although the propensity scores were highly significant there ribavirin effect was non-significant. The second model (Table 10) was adjusted for age and gender in addition of propensity scores, and still there was no effect of ribavirin on

survival. This method allowed for all confounders to be adjusted for and once again revealed that ribavirin treatment did not provide a statistically significant benefit in either adjusted model.

DISCUSSION

This cross-sectional study identified risk factors associated with death caused by CCHF infection among 6,070 individuals who contracted the disease in Turkey between 2007 and 2012. Significant risk factors associated with death included older age, thrombocytopenia, exposure to an infected individual, hypotension, bleeding, anemia, and elevated levels of AST/ALT, LDH, or CK. Most cases of CCHF occurred in the northern region of Turkey; however, through the years, the infection has spread to surrounding provinces of Turkey, perhaps as a result of the movement of humans and animals through increased commerce and development of once uninhabited, forested regions of the northeastern interior of Turkey.

Our findings concur with those of an earlier study that examined the epidemiology of CCHF in Turkey between 2002 and 2007.[3] In agreement with the findings of the earlier study, a larger proportion of cases resided in rural villages and the majority of cases were farmers or housewives.[3] Similarly, the crude case fatality during the earlier years of the outbreak was equal to that of the later six years of the outbreak; over the nine-year period that both studies span, the average crude case fatality was near 5% per year, ranging between 4.6% and 5.8%.[3]

The earlier study indicated that the majority of the outbreak occurred in the north central and northeastern regions of Turkey, which has also been found in this study.[3] The earlier study reported that most cases occurred between March and October, with peaks in June and July.[3] The study showed that in the last two years of the study, 2006 and 2007, the outbreak peaked in June, one month earlier than in previous years. This finding provided implications of the effect of global warming in early activation of ticks that cause disease.[3] This trend was also seen in our study. With the exception of 2008 and 2010, June represented the month of greatest CCHF incidence; in 2008, it was July and for 2010, it was May. Overall, the greatest incidence occurred in June, adding greater strength to the earlier study's implication of global warming that may occur when temperatures rise and rainfall decrease.[21]

While study findings did not indicate exposure to animals as a significant risk factor for death caused by CCHF, it is important to note that most cases were those who had contact with animals. Table 1 showed that most of the individuals infected with CCHF were farmers and housewives, both occupations that involve exposure to animals. While animals may be infected with the virus, they show no signs or symptoms of illness, instead animals serve as reservoirs for *H. marginantum marginantum* and *R. bursa* ticks; both tick species that serve as CCHF vectors. This is important as many farmers and housewives infected with CCHF reside in rural locations that may be far from medical facilities. While the Turkish MoH has worked to disseminate information regarding tick identification and removal procedures, the development of a vaccine is crucial in preventing disease in more remote locations.

Changes in areas of high incidence through the years may be explained by environmental factors, including temperature, rainfall, humidity, and vegetation, that may create ideal growing and survival conditions for infectious ticks. Climate change is often speculated as a driving factor in

changes to environmental factors, but has yet to be definitely proven as a sure cause of continued outbreak. Additionally, increased human interaction with the environment may also contribute to continued CCHF incidence as rural areas become urbanized. Greater human-environment interactions may result in greater contact with infecting ticks. Other theories for the CCHF outbreak in Turkey include an increase in the tick population as a result of the mass cull of poultry, including chickens that consume ticks, during the avian influenza outbreak of 2009. Others have attributed greater incidence as people begin to resettle in areas that had been abandoned during the Kurdish-Turkish conflict. Many fled rural regions of Turkey during the conflict, during which time it is hypothesized that the tick population flourished due to favorable environmental factors, such as increased vegetation. As settlers return to these now highly vegetated regions, they may have a greater chance of being exposed to infectious ticks.

Clinical features reported in the earlier report were consistent with those found in this study. Fatigue, fever, myalgia, and headache were previously reported as the most common symptoms and were among the most common symptoms in this report. Similarly, hemorrhagic findings were reported for nearly a quarter of cases; this was consistent with our report.[3] However, while the earlier study reported that 93.2% of cases had thrombocytopenia, 88.9% had leukopenia, and 85.9% had elevated transaminase levels, our study reported lower levels of these clinical outcomes with 78.7% cases with thrombocytopenia, 74.5% with leukopenia and 67.7% with elevated transaminase levels.[3] This is a possible indication of enhanced recognition and treatment of CCHF cases.

The propensity score analysis, which allowed for the evaluation of the effectiveness of ribavirin treatment for CCHF, indicated that ribavirin was not an effective drug. The analysis revealed no statistically significant benefit among those who received ribavirin treatment compared to those who did not. If ribavirin were an effective drug, we would expect to see a lower percentage of death among those with higher propensity scores who were treated with ribavirin. Individuals in this group had a greater likelihood of receiving ribavirin treatment, as these individuals were the sickest. However, this was not supported by our analysis. Furthermore, we would have expected to see a greater percentage of death among those infected individuals who did not receive ribavirin treatment compared to those who did receive ribavirin treatment; however, no such defined trend was determined. Ultimately, our propensity score analysis allowed us to remove the effects of confounding when analyzing treatment efficacy and determine that treatment was not effective.

There are a few limitations in this study. In 2010, the method of data collection was revised to allow for more patient information to be collected and recorded into the database. This should not diminish study findings.

In conclusion, CCHF continues to be a problem in Turkey. Despite the efforts of the Turkish MoH to control and prevent CCHF incidence and fatality, the case fatality remains constant at about 5% per year. This highlights the importance of better understanding the mechanisms that cause infection as well as the urgency for developing an effective treatment and vaccine for CCHF. The potential of this virus to be used as a biological warfare agent reiterates the importance of understanding risk factors associated with infection.

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