Seroepidemiological survey of the Crimean-Congo Hemorrhagic Fever Virus (CCHFV) infection amongst domestic ruminants in Adana province, East Mediterranean, Turkey

ABSTRACT

This study, thus, aimed to investigate the seroepidemiological status of Adana province for CCHFV in ruminants, according to species, breed, age, gender and geographical location. The study was carried out in 15 districts from sea level to plateaus (0-1472 m), within a 14,030 km² area. Total of 485 serum samples (165 cattle, 169 sheep and 160 goats) were collected from domestic ruminants. A modified human-based IgG ELISA kit was used for the detection of CCHFV specific antibodies in cattle, sheep and goats. Statistical analyses indicated a significant relationship between antibody presence and animal age, species, breed and location but there was no relation with animal gender. Out of 485 samples, 154 were seropositive (31.8%). It was determined that the statistical cluster varied between 5.8% and 74.3% according to location and seropositivity. The most important variable associated with antibody presence was geographic location. While high seropositivity is found at altitudes above 555 meters, it is found to be 7% and 3% at sea level. The results indicate that Adana province is at risk for CCHFV infection, especially in high altitude regions.

Keywords: Crimean-Congo Hemorrhagic Fever Virus, ruminants, ELISA, seroepidemiology, Adana Province, East Mediterranean.

INTRODUCTION

Crimean-Congo hemorrhagic fever virus (CCHF) is considered to be one of the most medically important and highly pathogenic tick-borne zoonoses affecting humans, first seen in Crimea in 1944 and later in Congo in 1956 (Appannanavar and Mishra, 2011; Leblebicioglu et al., 2016). CCHFV is a negative-sense single-stranded RNA (ssRNA) virus and depicted for *Nairoviridae* family of *Bunyavirales* order and is widely distributed around the world (Appannanavar and Mishra, 2011; Leventhal et al., 2021). More than 10000 patients have been reported since the first CCHFV cases in Turkey in 2002 (Aydın and Coşkun, 2019; Leblebicioglu et al., 2016; Yilmaz et al., 2009). It has been reported that estimated subclinical infections in humans range from 88% and case fatality rates range from 5% to 40%. (Yilmaz et al., 2009; Gunaydın et al., 2010; Appannanavar and Mishra, 2011; Leblebicioglu et al., 2016; Bodur et al., 2012; Aydın and Coşkun, 2019). Veterinarians, health, agriculture and livestock workers have a higher risk of occupational infection and the route of transmission may vary (Al-Abri et al., 2017; Athar et al., 2005; Leblebicioglu et al., 2015).

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Research Article

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Hard-shelled ticks, especially the Hyalomma genus, serve as both reservoirs and vectors for CCHF virus and transmission to humans mainly occurs through contact by infected ticks or blood or fluids from infected animals. Transmission also occurs in hospitals through contact with the blood or body fluids of an infected person, or through improper sterilization of medical equipment, reuse or accidental puncture of injection needles, and contamination of medical supplies (Leblebicioglu et al., 2014; World Health Organization, 2013).

In previous studies in Turkey, the genome segment of CCHFV was found in R. bursa and H.m.marginatum ticks collected from domestic ruminants in Kelkit valley (Tonbak et al., 2006). CCHFV specific antibodies were detected in cattle in the Central Anatolia region (Şevik, 2018) in sheep and goats in Northern Anatolia (Albayrak et al., 2012) and two isolates of CCHFV RNA in ticks on migratory birds were detected which is suggesting a role for ticks in CCHFV epidemics in Turkey and the spread of CCHFV by birds (Al-Abri et al., 2017).

There were no previous seroepidemiological data of CCHFV infection in ruminants in Adana province and was reported as CCHFV non-endemic region. In addition, sporadic human infections and deaths have been observed since 2015 (Kuşcu et al., 2017).

Numerous domestic and wild animals such as cattle, goats, sheep, rodents and birds serve as amplifying hosts for the CCHF virus. Ruminants harbor the virus, amplify it and develop specific antibodies; therefore, routine seroepidemiological surveillance studies with ELISA tests among ruminants in a particular endemic or non-endemic area and determining the prevalence of antibodies are accepted as the preferred basic research methods as an indicator of the presence of the virus in a particular region. (Commission decision, 1999, Mertens et al., 2016; Schuster et al., 2016; Tuncer et al., 2014). Domestic ruminants in the pasture feeding in the districts of Adana province have been the focus of the sampling as an indicator of the presence of the circulating CCHF virus in this particular region. The novel ELISA methods modified from the CCHFV IgG ELISA technique in humans was reported to work in the serum of ruminants with high specificity and sensitivity (Mertens et al., 2015; Schuster et al., 2016). The aim was to determine the seroprevalance of CCHFV infection in pasture-fed domesticated ruminants according to species, breed, age, gender and geographical location in Adana province, Eastern Mediterranean zone, Turkey.

MATERIAL and METHOD

Study Area and Sampling

Adana province is located in the East Mediterranean region of Turkey and has a 14.030 km² surface area. The northern neighbor is The Central Anatolia, which is CCHFV endemic. *Kelkit Valley* is a transitional zone between Central Anatolia and the Black Sea regions geographically and Euro-Siberian and Irano-Turanian phytogeographically (Karaer& Kılınç, 2001). In the Northern Hemisphere, the transmission of CCHFV is common between May and September, with a peak incidence in June and July (Leblebicioglu et al., 2016). From the reported cases in Turkey, 68.9% had a history of tick-bite or contact and 84.1% were seen in May, June, and July (Yilmaz et al., 2009). Samplings were carried out during the tick season at this research and were collected from healthy animals.

Sampling was done at randomly chosen locations in 15 districts at varying altitudes from sea level to highlands (0-1472 m) within the province of Adana from pasture-fed ruminants with a high risk of tick contact from June 2016 to May 2017. After examining the health status, blood samples (n=485) were

collected from the jugular vein of 165 cattle, 169 sheep and 160 goats. In the Tufanbeyli district, additional blood samples were collected from ruminants in a village where the death cases were recorded in humans in July 2015 due to sporadic CCHFV infection.

Samples were kept in a cold chain, centrifuged at 2500 rpm for 15 minute to obtain the serum, and stored at -20 ºC. Epidemiological data; age, breed, gender, geographical location and species were recorded for statistical analyses. The regions where sampling was done from sea level to highlands are Yumurtalık, Karataş, Ceyhan, Yüregir, Seyhan, Çukurova, Sarıçam, İmamoğlu, Karaisalı, Kozan, Pozantı, Aladağ, Feke, Saimbeyli and Tufanbeyli, respectively.

Investigation of anti-CCHFV IgG

The modification and optimization of the ELISA assay were done by a commercial human CCHFV antibody kit and validated antibodies for animals. The conjugation of the test (anti-human IgG peroxidase) was replaced by cattle, sheep and goat conjugates (anti-Cow IgG peroxidase, anti-sheep IgG peroxidase and anti-goat IgG peroxidase). The commercial multi-species conjugate (ID.Vet Grabel, France) was used. Positive and negative serum samples were obtained from previous studies of Samsun Veterinary Control Institute and Ondokuz Mayis University Faculty Veterinary Faculty. Two positive and two negative serum samples were used for each animal species independently. Vector Best, D-5052, Vecto Crimean-CHF-IgG ELISA kit (Vector Best, Novosibirsk, Russia) was used.

Validity

The negative controls average did not exceed the 0.250 OD value and the average of the positive controls was higher than the 1,000 OD value. The control samples used in the tests were determined according to the conditions mentioned below. Serum samples were considered negative as equal to or less than 0.500 OD, suspicious as 0.500-0.800 OD, and positive as more than 0.800 OD. Both the validation processes and the evaluation of OD values were based on Mertens et al. (2015) and Schuster et al. (2016).

Data Statistical Analyses

Data were analyzed by R Statistics program. Data were evaluated with CHAID (Chi-squared Automatic Interaction Detection) analysis, estimates of combined categories and sub-groups of the variables predicted to be effective on antibody presence (location, species, breed, age and gender) were performed. Multiple correspondence analyses were performed to examine the pattern of the relationship between antibody presence and variables of geographical location, species, breed, age and gender. The relationship between the presence of antibodies against CCHFV and the variables of species, breed, age and gender was examined with CHAID analysis. The categorical result variable was considered as the dependent variable for CHAID analysis. Geographical location, species, breed, gender and age variables were considered as independent variables. To determine the relationship between variables, the CHAID analysis breaks down the population into separate sub-groups that are defined by a set of independent variables (Rokach&Maimon, 2008). The graphical procedures of multiple correspondence analyses are designed to describe the relationship between observations or variables and to reduce the dimension (Rencher, 2002).

RESULTS

Descriptive statistics according to the relation between antibody presence and variables of Adana city province districts sorted by altitudes in meters are presented in Table 1.

Table 1: Descriptive statistics of location; The districts are sorted to their altitude in meters.

Variable	Category	Altitude (m)	Frequency	Percentage	Positive Cases	Percentage
Location	Tufanbeyli	1415	35	7.2	26	74.3
	Saimbeyli	971	30	6.2	11	36.7
	Aladağ	858	30	6.2	14	46.7
	Pozantı	786	30	6.2	20	66.7
	Feke	558	30	6.2	15	50
	Karaisali	257	29	6.0	4	13.8
	Kozan	137	29	6.0	18	62.1
	Çukurova	120	31	6.4	5	16.1
	Sarıçam	120	60	12.4	14	23.3
	Imamoğlu	78	31	6.4	2	6
	Ceyhan	31	30	6.2	14	46.7
	Seyhan	28	30	6.2	6	20
	Yureğir	26	30	6.2	2	7
	Karataş	11	30	6.2	1	3
	Yumurtalık	10	30	6.2	2	7

Descriptive statistics according to the relation between antibody presence and variables of species, breed, gender and age are presented in Table 2.

Table 2: Descriptive statistics of species, breeds, gender and age; sorted by the sampling frequency.

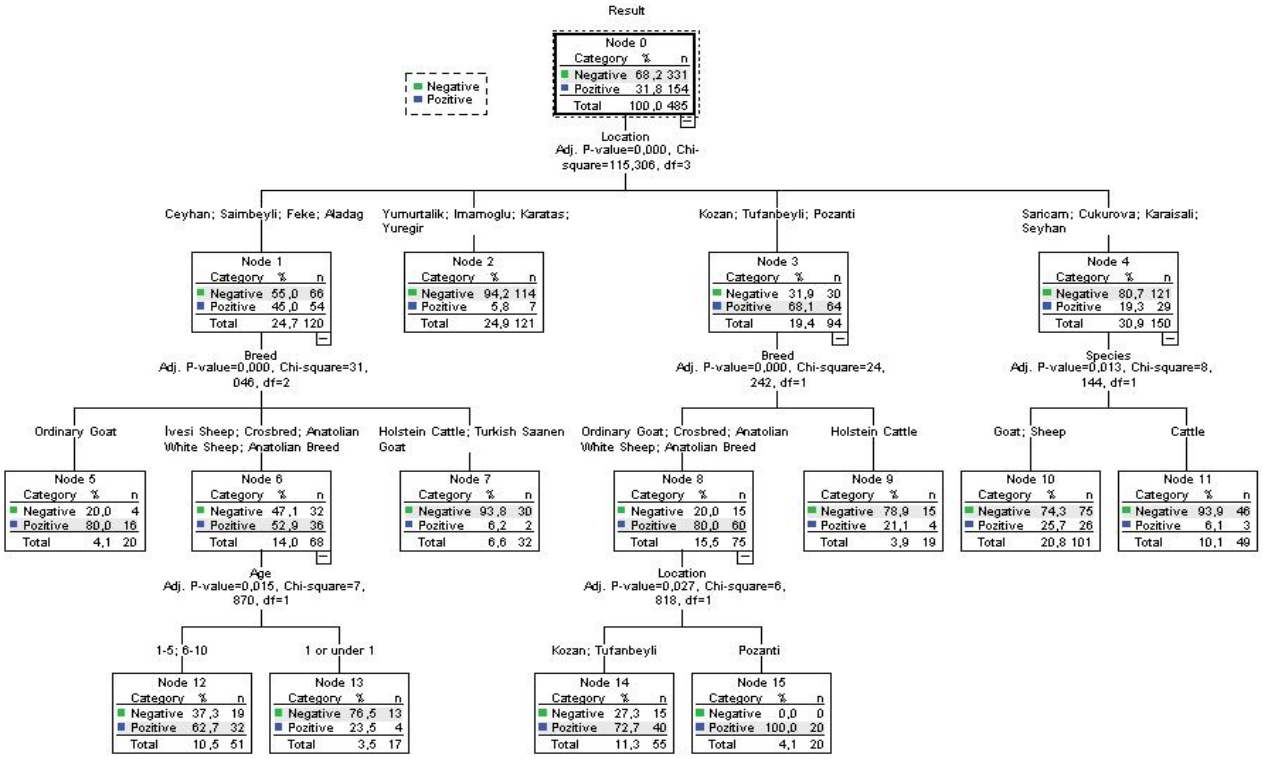
Variable	Category	Frequency	Percentage	Positive Cases	Percentage
Species	Cattle	165	34.0	36	23.3
	Sheep	160	33.0	61	39.6
	Goat	160	33.0	57	37.1
Breed	Holstein Cattle	117	24.1	10	8.5
	Anatolian Cattle	48	9.9	26	54.1
	Anatolian Sheep	79	16.3	36	45.6
	Ivesi Sheep	37	7.6	10	27.0
	Crossbred Sheep	44	9.1	15	34.1
	Turkish Saanen	26	5.4	6	23.1
	Ordinary Goat	87	17.9	44	50.6
	Aleppo Goat	28	5.8	1	3.6
	Crossbred Goat	19	3,9	6	31.6
Gender	Female	422	87.0	142	33.6
	Male	63	13.0	12	19.1
Age*	≤ 1	71	14.6	12	16.9
	1-5	324	66.8	109	33.6
	6-10	80	16.5	28	35.0
	≥ 10	10	2.1	5	50.0

*Age category of sampled animals: ≤ 1 = Up to 1 year old, 1-5 = between 1 to 5 years old, 6-10 = between 6 to 10 years old, ≥ 10 = elder than 10 years old.

The CHAID analysis diagram where classifications are shown with nodes to identify relationships between variables is provided in Figure 1. The tree contains 15 child nodes for the independent variables of location, species, breed and age. The attribute with the highest Chi-square value (Chi-square=115.306; $p<0.05$) among the independent variables, whose effect on antibody presence was found statistically significant, is placed in the first row in the CHAID diagram. Geographical location was found the most significant variable related to antibody presence. The fourth node contains 150 (30.9%) samples collected from Sarıcam, Çukurova, Karaisali and Seyhan. The second node contains 121 (24.9%) samples collected from Yumurtalık, Imamoglu, Karataş and Yüregir. The first node contains 120 (24.7%) samples collected from Ceyhan, Saimbeyli, Feke and Aladağ. The third node contains 94 (19.4%) samples collected from Kozan, Tufanbeyli and Pozantı. The frequencies of

antibody observations in these nodes were 29, 7, 54 and 64, respectively.

Figure 1: Tree diagram of the relation between antibody presence and geographical location, species, breed and age



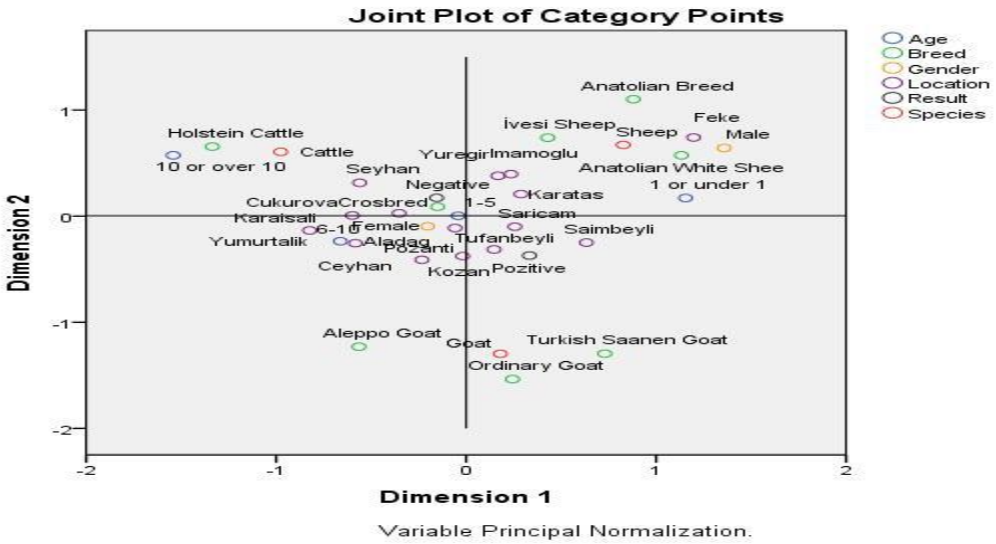
In the CHAID diagram, when the nodes in the second row were constructed, the relationship of the independent variables to the dependent variable was analyzed separately in four groups. Another statistically significant independent variable with the second-highest statistical relationship with the dependent variable was included for each node in the model. The variable that best explains the samples collected from Ceyhan, Saimbeyli, Feke and Aladağ is the breed (Chi-square=31.046; $p<0.05$), which consists of three sub-groups. The sub-groups that best describe the antibody presence were the group of Ivesi 10 (2%), crossbred 15 (3.1%), and Anatolian breeds sheep 43 (8.9%); the group of Holstein cattle 32 (6.6%), Turkish Saanen and ordinary goat 20 (4.1%). The sub-group that best describes Ivesi, crossbred and Anatolian breeds sheep at these districts were the age data (Chi-square=7.870; $p<0.05$), which is composed of two sub-groups. Of these breeds, 51 (10.5%) of the samples were in the 1-5, 6-10 age range and included in the first sub-group; and 17 (3.5%) of them were 1 year old and younger and included in the second sub-group. The frequencies of antibody observations in these nodes were 32 and 4, respectively.

The variable that best explains the samples taken from Kozan, Tufanbeyli and Pozanti was the breed (Chi-square=24.242; $p<0.05$), which heaped together in two sub-groups according to their breeds. 75 (15.5%) were the ordinary goat, crossbred and Anatolian breeds; and 19 (3.9%) Holstein cattle. The frequencies of antibody observations were 60 and 4, respectively. The variable that best explains samples taken from Kozan, Tufanbeyli and Pozantı was the location variable.

The variable that best explains the samples taken from Sarıçam, Çukurova, Karaisali and Seyhan districts was the species (Chi-

square=8.144; p<0.05) which consists of two sub-groups. While 101 (20.8%) of the samples belong to goats and sheep, which spend more time in the pasture than cattle and spread over more areas between the plateau and the plain, 49 (10.1%) belong to cattle. The output for the multiple correspondence analyses is given in Figure 2.

Figure 2: Multiple correspondence analyses output.



Adana province map demonstrated in Figure 3. The results indicated the CCHFV exposure was varying at a mean value of 54.7%, 21.7%, 15% and 5.8% respectively at highlands indicated in red, at midlands indicated in orange and yellow, and at coastal districts indicated in green color.

Figure 3: Adana province map. The mean CCHFV seroprevalence of 15 districts was 31.7%. In the red, orange, yellow and green regions in Figure 3, the maximum rates are 74.3%, 23.8%, 16.1% and 7%, and the minimum rates are 36.7%, 20%, 13.8% and 3%, respectively.

DISCUSSION

High CCHFV seropositivity (n=154) was detected with an average seroprevalance of 31.8% (154/485) in total. Seropositivity reached 100% in the village where human deaths were observed in 2015 due to CCHFV infection and reached 74.3% in the Tufanbeyli district where this village is located. The results indicated the high exposure of these animals to the disease. The results of high seropositivity of CCHFV-specific antibodies in ruminants indicate a high risk of human infection. CHAID analysis

indicated a significant relation between antibody presence and each of age, species, breed and location, but no relationship was found between antibody presence and gender. Despite the lack of previous regional seroepidemiological studies on ruminants, Adana province was declared as a non-endemic region previously (Kuşcu et al., 2017). This inference was probably based on either lack of serologic surveillance study conducted on animals in the province or there was no reported human infection since 2015. In contrast, our results indicated that Adana province is at risk for CCHFV infection, especially in high altitude regions. In 2015, sporadic cases and human deaths were reported in Adana and human infections increases in Turkey (Leblebicioglu et al., 2016).

Adana province was identified as geographically high risk area in a study conducted with the spatial screening statistics (SaTScan) for CCHF infection cluster (Deka, 2017). Most of the CCHFV cases seen in Turkey have been associated with geographies dominated by mountainous lands bisected by riparian systems and scrub forests surrounding cultivated fields and pastures (Vatansever et al., 2007). Mediterranean basin, declared as suitable for ticks to survive as the vectors of CCHFV due to their climatic characteristics (Hoek et al.,2012). Similar to previous reports, our findings indicated that the high-altitude districts of Adana province with high seropositivity are located at the transition line with the Central Anatolia region and have similarities with CCHF infection endemic regions due to the geographical structure and ecological characteristics. The geospatial approach data reported by the spatial survey statistics and the maximum entropy modeling with environmental and geographical essential characteristics of CCHFV overlap with the high altitude regions of Adana province, which was sampled in this study.

Location**;** the most significant predictor of antibody presence was the geographical location. The node 1 consisted of Yumurtalık, İmamoğlu, Karataş and Yüreğir, node 2 consisted of Sariçam, Çukurova, Karaisalı and Seyhan, node 3 consisted of Ceyhan, Saimbeyli, Feke and Aladağ and node 4 consisted of Koazan, Tufanbeyli and Pozantı. The frequencies of antibody observations in these nodes were 7, 29, 54 and 64, respectively. The seropositivity was highest (i.e., 64%) at CCHFV endemic regions boundary districts as Tufanbeyli, Pozantı and Kozan followed by Saimbeyli, Feke, Aladağ and Ceyhan with 54% seropositivity.

Altitude; the highest seroprevalence was found at Tufanbeyli (74.3%) followed by Pozantı (66.6%), Kozan (62%), Feke (50%), Ceyhan (46.7%) and Aladağ (46.7%) which are located at the highlands except for Ceyhan and Kozan. Results indicated that districts located at highlands borders at endemic regions of Midland Anatolia have higher seropositivity and are similar to previous reports (Deka, 2017; Yilmaz et al., 2009). The seroprevalence was highest with an average of 68,1% at node 3 as Tufanbeyli, Kozan and Pozantı then followed by Node 2 which was the second-highest value in Aladağ and Feke with an average of 45%. Previous reports indicated that CCHFV infection in Turkey presenting a peak transmission in the early summer months and a strong association with living at an altitude greater than 836.5 meters. Seasonal transmission specifically between April and August (most frequent in July 2005 and June 2006) at moderate altitudes, typically around 1000 meters or higher, has been reported in other studies, presumably reflecting optimum conditions for tick populations (Deka, 2017; Kadanalı et al., 2009; Leblebicioglu et al., 2016). Günaydın et al. (2010) reported that none of the CCHFV human cases was from the geographical regions where mountainous lands faced the sea and all cases were from areas

situated at 1100-2265 m above sea levels. Our results are similar to previous studies; as districts located at altitudes above 555 m have higher seropositivity and districts with altitudes at sea level have lower seropositivity. Interestingly higher seropositivity was shown in two neighboring districts located at lower altitudes, 46.6% in Ceyhan (29 m) and 62% in Kozan (137 m). The reason might be the animal movement rather than the exposure to the infection. Domestic ruminants can play a role in both ways at spreading the disease without developing a symptomatic infection; by amplifying the virus as a host and transport the ticks as infection vectors at the pasture feeding between the plateaus and plains. Ceyhan and Kozan districts offer plenty of grassland after seasonal harvest for the traditional feeding of sheep and goats. The results verified our theory that there were no seropositive cattle at Ceyhan and 0.08% at Kozan. Yumurtalık and Karataş, have the lowest altitudes of 2 and 10 meters and are located in the coastal regions, represented 7% and 3% seropositivity, respectively. This finding indicates that there is a relationship between the geographic location and the spread of the disease, and might explain that the disease was never reported in Northern Cyprus Turkish Republic, which has similar sea level located geographical features with Yumurtalık and Karataş districts (Kasi et al., 2019). Animal movements from the highlands to the plains may pose a risk of spreading the infection and its vector.

Breed; The cattle, sheep and goats breeds of the CCHF-specific IgG antibodies seropositive animals at this study were 8.5% Holstein cattle and 54.1% Anatolian Cattle, 45.6% Anatolian sheep, 27.0% Ivesi sheep, 34.1% crossbred sheep, 23.1% Turkish Saanen goat, 50.6% ordinary goat, 3.6% Aleppo goat and 31.6% crossbred goat. Blanco-Penedo et al., (2021) reported findings of high seropositivity in native Boran (50.7%), Zebu (45.9%) breeds fed in the pastoral area in Kenya. The seropositivity findings related to the breed were examined in our study; it was observed that Anatolian breeds had higher seropositivity than purebred cattle, sheep and goats. It was concluded that this finding may be related to the time spent in the pasture, exposure to the virus and its vector, age, sampling size, differences in care and nutrition, environmental conditions, and susceptibility to diseases.

Age; The age of the CCHF-specific IgG antibodies seropositive animals at this study were 50% at 10 years and older, 35% between 6-10 years old, 33.6% between 1-5 years old and 16.9% up to 1 year old. The findings we obtained in the study are consistent with previous studies of other researchers who reported that as the age increases, animals spend more time in the pasture and as a result, the probability of their exposure to infected ticks, the vector of the disease (Bartel et al., 2014, Gergova et al., 2012, Kasi et al., 2019, Şevik 2018).

Species; Previously reported CCHF-specific IgG antibodies in cattle were 17% in Elazığ, Samsun, Sivas, Tokat and Yozgat cities in Turkey (Kırbaş 2010), 38.5% in Tokat city in Turkey (Özüpak 2017), 1.2% in the Central Anatolia and central-west part of the Aegean region of Turkey (Şevik 2018), 13% in the Marmara region of Turkey (Tuncer et al. 2014), 71% in Bulgaria (Barthel et al., 2014), 31% in Kosovo (Fajs et al., 2014) and 17.3% in the Vardar region of Republic of Macedonia (Mertens et al. 2015). Reported CCHF-specific IgG antibodies in sheep were 85.71% in Samsun, Tokat, Sinop and Sivas cities in Turkey (Albayrak et.al. 2012), 37% Elazığ, Samsun, Sivas, Tokat and Yozgat cities in Turkey (Kırbaş 2010), 83.3% in Tokat city in Turkey (Özüpak 2017), 31.8% in the Marmara region of Turkey (Tuncer et al. 2014), 74% in Bulgaria (Barthel et al., 2014), 10% in Kosovo (Fajs et al., 2014), and %19 in Pakistan (Kasi et al. 2017). Reported CCHF-specific IgG antibodies in goats were 66.66% in Samsun,

Tokat, Sinop and Sivas cities in Turkey (Albayrak et.al. 2012), 82.8% in Tokat city in Turkey (Özüpak 2017), 66% in the Marmara region of Turkey (Tuncer et al. 2014), 60% in Bulgaria (Barthel et al., 2014), 20% in Kosovo (Fajs et al., 2014) and 5% in Pakistan (Kasi et al. 2017). In this study, CCHF-specific IgG antibodies seroprevalance was found to be 23.3% in cattle, 39.6% in sheep and 37.1% in goats. Serological results that differ in the studies of researchers can be explained by the presence of factors such as species, sampling sites, environmental and climatic changes, test methods, number of samples examined, and age of animals, presence and exposure of vectors. In our study, we found that the seropositivity was higher in sheep and goats than in cattle, which was similar to the findings of other researchers (Albayrak et.al. 2012, Barthel et al., 2014, Kırbaş 2010, Özüpak 2017, Schuster et al., 2016, Tuncer et al., 2014). Species based results are probably depends on various factors such exposure to the vector and as host preferences, sampling size, animal movements, feeding style and animal characteristics as the CCHF virus and its vectors may adapt to different geographical regions.

Gender; obtained results of CHAID analysis represented no statistically significant relationship between antibody presence and gender.

The overall strategy for establishing CCHFV surveillance programs should involve multidisciplinary research among veterinarians, parasitologists, epidemiologists, medical practitioners, ecologists, geographers and livestock workers in collaboration with public administrators. This study was designed to determine the exposure status of cattle, sheep and goats in Adana Province, Eastern Mediterranean zone of Turkey. The results indicate that Adana province is at risk for CCHF infection, especially in high altitude regions.

CONCLUSION

CCHFV is an important tick-borne zoonotic infection. It is known that CCHF virus and its vectors may differ and adapt to different geographical regions depending on various factors such as host selection, exposure to the vector, animal movements, migration and host preferences. The results highlight the suitability of ruminants for seroepidemiological CCHFV monitoring studies in a particular region where the presence or absence of CCHFV is unknown. In this study it has been determined that seropositivity increases at altitudes of 555 m and above, and decreases as it approaches sea level and it has been concluded that the high altitude regions of Adana province are at risk for the disease.

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Ethical approval: Ethical clearance received from Adana Veterinary Research and Control Institute (2016/2890).

Conflict of interest: There is no conflict of interest.

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