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SEROLOGICAL AND MOLECULAR INVESTIGATION OF ZOONOTIC POTENTIAL OF HEPATITIS E VIRUS AMONG FARM ANIMALS IN TURKIYE

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ABSTRACT

The Orthohepevirus A strain of hepatitis E virus (HEV) is one of the world's leading zoonotic viruses and poses significant public health concerns. HEV susceptibility has been demonstrated in a wide range of animal species and have the capacity to transmit the virus to humans. However, the contribution of Orthohepevirus A serotypes to HEV epidemiology remains poorly understood. Blood serum samples were collected from 188 domestic animals from different farms selected by random sampling in Burdur province of Türkiye. The animal group consisted of 22 horses, 22 donkeys, 30 sheep, 25 goats, 27 cattle, 35 cats and 27 dogs. An overall HEV seroprevalence of 4.79% was observed. The presence of HEV antibodies in goats, horses, and donkeys was detected for the first time in Türkiye. Statistical tests performed to determine the difference between seropositivity rates according to animal species were found significant at $p \leq 0.05$. Orthohepevirus A RNA was undetectable in all samples using gel-based nested RT-PCR. In this first report on HEV in farm animals in Türkiye, the presence of HEV antibodies suggests that farm animals may have an important role in spreading infection.

Keywords: Domestic animals, Hepatitis E virus, HEV antibodies, Türkiye, Zoonotic potential

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INTRODUCTION

The Orthohepevirus a species of the Hepatitis E virus (HEV) (family Hepeviridae) is currently considered the leading viral agent responsible for acute hepatitis in humans globally (WHO, 2020). Annually, approximately 20 million individuals are infected, resulting in around 50,000 fatalities (Forni *et al.*, 2018). Humans in developing countries contract HEV genotypes 1 and 2 (HEV-1 and HEV-2) through illnesses spread through contaminated water and faeces (Rein *et al.*, 2012). Although genotypes HEV-1 and HEV-2 are not associated with any known animal reservoirs, HEV-3, HEV-4, and HEV-7 have been shown to exhibit zoonotic potential, with infections primarily originating from animals or animal-derived products (Woo *et al.*, 2014; Pavio *et al.*, 2017). Among these, HEV-3 and HEV-4 are most commonly detected in domestic pigs, wild boars, deer, and rabbits (Pavio *et al.*, 2017). However, a broader host range has been reported, including various mammals such as cattle, horses, goats, dogs, cats, and sheep (Spahr *et al.*, 2018). In contrast, genotypes 5 and 6 have only been identified in wild boars, while genotypes 7 and 8 have recently been reported in dromedary camels and Bactrian camels, respectively (Bernardini *et al.*, 2022). HEV-3, the most prevalent genotype in Europe, consists of 11 recognized subtypes (3a–3j and 3ra). Despite the current classification, many subgroups are still unassigned. This is primarily attributed to the frequent identification of new HEV strains, as reported by Smith (2016), Miura (2017), and De Sabato (2018).

In developed nations, animals play a crucial role in the transmission dynamics of HEV (Di Profio *et al.*, 2022; Sayed *et al.*, 2022). Several animal species—including pigs, wild boars, rabbits, ruminants, and deer—serve as reservoirs and potential sources of infection. Transmission may occur via direct contact with infected animals (Doceul *et al.*, 2016), environmental exposure (Abravanel *et al.*, 2017; Garcia-Bocanegra *et al.*, 2019), or consumption of contaminated products (Bernardini *et al.*, 2022; Caballero-Gómez *et al.*, 2022b).While information on zoonotic HEV transmission in Türkiye is limited, some studies indicate that ruminant milk and

domestic cats might act as potential infection sources (Demirci *et al.*, 2019; Cagirgan *et al.*, 2022).

Until now, the serological and molecular presence of HEV has been revealed in different animal species and in different countries. Understanding HEV's range of susceptible hosts is vital for clarifying its patterns of zoonotic spread and epidemiology. Nevertheless, global research on HEV circulation among farm animals remains limited, with most studies concentrating on particular animal species. Similarly, in Türkiye, investigations on HEV across various animal types are sparse. This study sought to assess both the serological and molecular distribution and presence of HEV across multiple animal species, including horses, donkeys, sheep, goats, cattle, cats, and dogs, within Türkiye.

MATERIALS AND METHODS

Ethical approval was obtained from the Ethics Committee of the Faculty of Veterinary Medicine at Burdur Mehmet Akif Ersoy University (approval number 1004/2023).

Sampling: Blood serum samples were collected from 188 domestic animals (22 horses, 22 donkeys, 30 sheep, 25 goats, 27 cattle, 35 cats, 27 dogs) from different farms selected by systematic random sampling in the province of Burdur between February and November 2022. Samples were taken from cats and dogs living around farms. Jugular vein punctures were used to collect blood samples. The collected blood samples were transported in cold chain to Burdur Mehmet Akif Ersoy University, Faculty of Veterinary Medicine, Department of Virology. After centrifuging the sera at 400 g for 10 minutes, they were stored at -80°C until they could be analyzed in the laboratory.

ELISA Assay: Polyclonal anti-HEV IgG and IgM antibodies were identified using a commercial total antibody ELISA kit (Dia.Pro, Diagnostic Bioprobes Srl, Milan, Italy). In summary, 100 µl of each sample, along with the positive and negative controls, was dispensed into microplate wells and incubated at 37°C for 45 minutes. After three washes, 100 µl of conjugate was added, followed by a 45-minute incubation at 37°C and another wash. Then, 100 µl of chromogen/substrate was introduced, and the reaction was halted after 15 minutes of incubation at 20°C. To calculate the detection of true positives and minimize false negatives, the cutoff value was determined by adding 0.301 to the mean optical density (OD) of the negative control, as measured with a microplate reader. Samples with a competition value over 1.1 were considered positive, values between 0.9 and 1.1 were deemed inconclusive, and values below 0.9 were regarded as negative.

RNA Extraction and RT-PCR: Following the protocol of a commercial kit (Roche, Germany), total nucleic acids were extracted from 200 µl of blood serum. The RNA obtained was tested for Orthohepevirus a by performing nested PCR to amplify the ORF1 region. Additionally, a pan-hepevirus heminested RT-PCR was employed to target a 337 bp segment of the RdRp region, which is conserved across all Hepeviridae family members (Table 1).

Amplification was carried out using the Xpert One-Step RT-PCR Kit (Grisp Research Solutions, Porto, Portugal) in a total reaction volume of 25 µl, with primers at a final concentration of 0.4 mM. The thermocycling conditions were as follows: reverse transcription at 45°C for 15 minutes, initial denaturation at 95°C for 3 minutes, followed by 35 cycles of denaturation at 95°C for 10 seconds, annealing at 55°C for 10 seconds, and extension at 72°C for 15 seconds. A final extension step was conducted at 72°C for 1 minute. PCR products were run on a 1.5% agarose gel containing ethidium bromide and visualized under UV illumination.

Table 1. Primers sequence in the study.

Assay	Primers	Sequence 5′ -3′	Target	Reference
RT-PCR	HEV-F4228	ACYTTYTGTGCYYTITTTGGTCCITGGTT	RdRp	Drexler *et al.*, (2012)
	HEV-R4598	GCCATGTTCCAGAYGGTGTTCCA		
	HEV-R4565			
RT-PCR	ORF1F	CCAYCAGTTYATHAAGGCTCC	ORF1	Fogeda *et al.*, (2009)
	ORF1R	TACCAVCGCTGRACRTC		
	ORF1FN	CTCCTGGCRTYACWACTGC		
	ORF1RN	GGRTGRTTCCAIARVACYTC		

Biochemical analysis: Levels of ALP (alkaline phosphatase), AST (aspartate aminotransferase), ALT (alanine transaminase), GGT (γ-glutamyl transferase) and lactate dehydrogenase (LDH)in serum sampleswere determined using commercial test kits on the Mindray BS-240 (China) autoanalyzer through spectrophotometric methods.

Statistical Analysis: Statistical analyses were conducted using SPSS software (version 26.0, Windows). The Chi-square (χ^2) test was applied to determine whether there was a significant association between hepatitis E prevalence and different domestic animal species. A p-value below 0.05 was accepted as statistically significant.

RESULTS

HEV antibodies were identified in 9 out of 188 serum samples from farm animals, resulting in an overall prevalence of 4.79%. Table 2 presents the seropositivity rates according to different farm animal species.

Internal quality control for the ELISA was ensured by meeting the following criteria: the OD450 value of the blank well was required to be below 0.100, the mean OD of the triplicate negative control not exceeding 0.150, and the positive control OD greater than 1.000. In this study, the OD values recorded were 2.096 for the positive control and 0.051 for the negative control. According to the kit instructions, the OD cut-off was set at 0.301, and the test serum samples were evaluated using the formula: ODSample/ODcut-off (with ODcut-off set at 0.301).

In the present study, serum samples from hepatitis E-positive cattle, donkeys, goats, and cats were analyzed for liver enzyme profiles. The levels of ALT and AST enzymes in all hepatitis E-positive specimens are presented in Table 3. In addition to ALT and AST, an increase in GGT levels was observed across all animal species, while LDH levels were elevated only in cattle.

Table 2. Clinical data and diagnostic findings were recorded for animals that tested seropositive.

Species	Number of samples	Positivity / SeroprevalenceRate (%)	Negativity	p-value
Cattle	27	3 (11.11%)	24	
Sheep	30	-	30	
Goat	25	1 (4%)	24	
Horse	22	1 (4.54%)	21	**0.042**
Donkey	22	3 (13.64%)	19	
Cat	35	1 (2.86%)	34	
Dog	27	-	27	
Total	**188**	**9 (%4.79)**	**179 (%95.21)**	

Table 3. Liver enzyme levels in blood serum collected from animal species that tested positive for antibodies.

Animal Species	Biochemistry Parameters				
	ALP (U/L)	AST (U/L)	ALT (U/L)	GGT (U/L)	LDH (U/L)
Cow-140	52.9	323.7	145.4	57.3	2454.45
Cow-174	15	141.7	61.3	25.3	727.08
Cow-175	62.8	136.8	175.9	19.5	1068.51
Reference Range	*0-488*	*60-125*	*11-40*	*6-17.4*	*24-388*
Donkey-2	38.1	531.4	71.5	64.4	72.78
Donkey-5	141.9	621,8	88.9	87.8	357.71
Donkey-21	100.4	470.2	26.3	33.7	237.02
Horse-5	227.1	485.7	36.4	213.5	310.61
Reference Range	*143-395*	*160-412*	*3-23*	*6-32*	*12-456*
Goat-4	101.1	875.3	32.6	59.7	361.52
Reference Range	*93-387*	*167-513*	*6-19*	*20-56*	*123-392*
Cat-69	44.3	54.7	143.1	34,3	96.23
Reference Range	*0-45*	*7-38*	*25-97*	*6-28*	*58-120*

Gel-based nested RT-PCR analysis did not detect Orthohepevirus A RNA across the examined sample set. Additionally, all serum samples tested negative upon re-screening with pan-hepevirus RT-PCR.

DISCUSSION

Hepatitis E virus (HEV) is a significant zoonotic pathogen capable of crossing the species barrier from animals to humans (da Silva *et al.*, 2018; Kenney *et al.*, 2019). Although HEV has been identified in a wide range of animal hosts (Di Profio *et al.*, 2022), data on its prevalence in Turkish animal populations remain limited. Previous studies conducted in Türkiye have largely focused on species such as domestic cats, sheep, and cattle (Cagirgan *et al.*, 2022; Tonbak *et al.*, 2022).

This pilot study represents the first effort to assess HEV seroprevalence across a broader spectrum of

animal species in Türkiye, including horses, goats, and donkeys. The overall seroprevalence among farm animals—including horses, donkeys, sheep, goats, cattle, cats, and dogs—was determined to be 4.79%, with statistically significant differences observed among species ($p \leq 0.05$).

Among goats, HEV antibodies were detected in 1 out of 25 animals, corresponding to a seroprevalence of 4%. This figure aligns closely with rates reported in Laos (5.0%) (Tritz *et al.*, 2018), yet it exceeds those found in Spain (1.4%–2.1%) (Peralta *et al.*, 2009; Caballero-Gómez *et al.*, 2022a). In contrast, significantly higher seroprevalence rates have been documented in several countries: 28.4% in Burkina Faso as reported by Ouoba *et al.* (2019), 41.6% in China by Li *et al.* (2017), and 8.3% in Jordan according to Obaidat *et al.* (2020). Similarly, El-Tras *et al.* (2013) identified a 9.4% prevalence in Egypt, while Favorov *et al.* (1998) reported an even higher rate of 67.0% in Turkmenistan.

HEV antibodies were not detected in any of the 30 sheep samples, which is in line with the findings reported by Arankalle *et al.* (2001) and Vitral *et al.* (2005). However, higher seroprevalence rates have been documented in several countries, including China (9.8%) as noted by Chang *et al.* (2009), Portugal (16.6%) by Mesquita *et al.* (2020), Italy (21.3%) by Palombieri *et al.* (2020), and India, where Shukla *et al.* (2007) reported extremely high values ranging from 77.6% to 100%.

Importantly, this is the first study to investigate HEV seroprevalence in equids in Türkiye, and the first to report antibody detection in donkeys and horses. Seropositivity was observed in 4.54% of horses and 13.64% of donkeys. These findings are in line with previous reports from Egypt (13%) (Saad *et al.*, 2007) and China (16.6%) (Zhang *et al.*, 2008).Equines are recognized as potential hosts for HEV; however, data on HEV infection among equids is limited. In Spain, HEV RNA was identified in 0.4% (3 out of 692) of horses and 1.2% (1 out of 86) of donkeys (Garcia-Bocanegra *et al.*, 2019).Aside from these existing studies, there are not many serological or molecular studies on HEV in horses and donkeys.

The seroprevalence found in cats was 2.8%. In the first study in Türkiye on domestic cats, the seroprevalence was found to be 5.4% (Cagirgan *et al.*, 2022). The observed rate of 2.8% is comparable to those reported in Italy (3.1%) (Capozza *et al.*, 2021) and Japan (2.0%) (Mochizuki *et al.*, 2006). In various European countries, cats exhibited higher HEV antibody prevalence rates. These rates were recorded as 11.0% (6/54) (Li *et al.*, 2020), 14.9% (7/47) (Dahnert *et al.*, 2018), and 32.3% (21/65) (Li *et al.*, 2020), respectively. Despite the fact that dogs are more susceptible to HEV than cats and that they share the same habitat, no antibody positivity was found in dogs in this study, contrary to prior studies that suggested cats and dogs would not necessarily have the same sensitivity to HEV (Mochizuki *et al.*, 2006; Li *et al.*, 2020).

This study identified an 11.1% seroprevalence in cattle. Our findings showed higher seroprevalence than previous studies reported in cattle in Brazil and Laos, seroprevalence levels were recorded at 1.4% (Vitral *et al.*, 2005) and 7% (Tritz *et al.*, 2018), respectively, while greater values were observed in the US (30%), Egypt (21.6%), and Burkina Faso (26.4%) (Yugo *et al.*, 2019; El-Tras *et al.*, 2013; Ouoba *et al.*, 2019). Tonbak and Atasever (2022) indicated that HEV was common (16.5%) in cattle farms in Türkiye. The seroprevalence rate in this study showed similarity to our findings.

Serological research has revealed that antibodies against HEV are found in numerous animal species, with notable variations in low or high prevalence across distinct geographic locations and species. This may result from variations in the serological techniques utilized, the study designs, the epidemiological context, and/or the age of the animals sampled. Although this study was conducted on a small population, it has revealed that zoonotic HEV is circulating in all farm animals in Türkiye.

In this study, no HEV RNA was detected in the samples, despite the use of both HEV- and pan specific degenerate primers. Despite the use of serum samples—commonly free from PCR inhibitors—for RT-PCR, the short duration of viremia in HEV infections may have hindered successful detection may have led to a missed detection window for HEV RNA. Furthermore, HEV strains responsible for seropositivity might be genetically diverse enough that even broad-spectrum RT-PCR assays fail to detect them. Recent studies have highlighted the challenges associated with HEV genetic diversity and detection. For instance, a 2023 study in New Caledonia reported an outbreak caused by HEV Genotype 3, where viral sequencing revealed 98-100% nucleotide similarity among most of the detected strains, yet the high genetic variability within HEV genotypes still poses a challenge for molecular detection (Abravanel *et al.*, 2023). Additionally, a study identified HEV-3 and HEV-C1 in rodents, demonstrating the virus's ability to circulate in different hosts, further complicating detection efforts (Porea ve ark., 2023; Yadav ve ark., 2023). These findings emphasize that even RT-PCR assays with a pan-spesific may not detect highly diverse HEV strains. For example, the similarity of nucleotide sequence between chicken-derived avian HEV and mammalian HEVs is roughly 50%, while moose HEV shows only 37–63% identity and cutthroat trout HEV shares just 27% identity with mammalian HEVs (Yugo *et al.*, 2019). The increasing evidence of HEV's genetic diversity across hosts and regions underscores the need for continuous adaptation of molecular diagnostic tools to improve detection accuracy.

The increase in ALT and AST enzyme levels observed in all hepatitis E-positive specimens (Table 3) is consistent with previous studies evaluating liver damage caused by hepatitis E infection in a number of animal species (Saad *et al.*, 2007; Li *et al.*, 2008; Gardinali *et al.*, 2017; Long *et al.*, 2017; Cagirgan *et al.*, 2022). Elevated ALT and AST levels indicate hepatocellular injury, which aligns with the most common clinical manifestation of hepatitis E: acute hepatitis, similar to other forms of viral hepatitis (Aggarwal *et al.*, 2011). Furthermore, an increase in GGT levels was detected across all examined species, suggesting potential bile duct involvement or hepatic stress. Interestingly, LDH enzyme levels were elevated exclusively in cattle, possibly reflecting species-specific variations in liver response to HEV infection. These findings highlight the impact of hepatitis E infection on liver function and emphasize the need for further studies to understand the pathophysiological mechanisms underlying these enzymatic alterations.

Conclusions: The seropositivity observed in this study suggests that animals in Türkiye, even within a limited population, are exposed to HEV infection. Additional research is necessary to clarify HEV seroprevalence variations and assess the transmission risk associated with this virus.

Conflicts of Interest: The authors state that there are no conflicts of interest.

Data Availability: Data and materials supporting the conclusions of this research are accessible from the corresponding author, Caglar Okulmus, at okulmuscaglar@gmail.com, upon reasonable request.

Authors' Contributions: Performed the experiments: AAC, CO, YY, ÖSKA, AK Data analysis: AAC, YY, CO Writing of the manuscript: AAC Revised manuscript: YY and Conceived and designed the experiments: AAC, CO, YY, ÖSKA, AK.

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