



Molecular detection and characterisation of Canine Adenovirus type 1 in dogs with haemorrhagic enteritis in northern Kerala, India[#]

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Abstract

Infectious canine hepatitis caused by Canine Adenovirus type 1 (CAV-1) is a systemic disease of domestic and wild canids. Despite the availability of effective vaccines, sporadic infections continue to occur, while information on the molecular epidemiology of CAV-1 in Kerala remains limited. The present study investigated the occurrence and molecular characteristics of canine adenoviruses in dogs from Wayanad and Kozhikode districts of northern Kerala. A total of 45 samples, comprising rectal swabs from 21 dogs with haemorrhagic enteritis, 18 apparently healthy dogs, and tissue samples from six fatal cases, were screened by PCR targeting the E3 genomic region. Thirteen samples (28.9%) were positive for CAV-1, including one from an apparently healthy dog, while two post-mortem samples were positive for CAV-2. Affected dogs exhibited haemorrhagic diarrhoea, vomiting, anorexia, lethargy and icterus, with multisystemic lesions observed in fatal cases. Two representative CAV-1 amplicons were subjected to Sanger sequencing and phylogenetic analysis. The sequences exhibited 99.12 per cent reciprocal nucleotide identity and high similarity with Indian and international CAV-1 strains. Amino acid analysis revealed Trp126Ser and Thr184Met substitutions in one isolate, whereas these substitutions were absent in the other. Phylogenetic analysis based on the partial E3 gene and flanking regions confirmed both isolates as CAV-1 and demonstrated their association with different groups of Indian strains, suggesting the circulation of genetically distinct CAV-1 variants in the region. The findings confirm the continued circulation of CAV-1 in northern Kerala and highlight its potential association with haemorrhagic enteritis and systemic disease in inadequately immunised dogs.

Keywords: Canine mastadenovirus A, CAV-1, haemorrhagic enteritis, E3 gene

Infectious canine hepatitis (ICH), or Rubarth's disease, is a systemic viral disease of domestic dogs and other susceptible canids caused by Canine Adenovirus type 1 (CAV-1). CAV-1 is a non-enveloped, icosahedral, double-stranded DNA virus belonging to the species *Canine mastadenovirus A* of the family *Adenoviridae*. It is antigenically related to canine adenovirus type 2 (CAV-2); however, the two viruses differ in their tissue tropism and clinical manifestations. CAV-1 primarily causes infectious canine hepatitis, whereas CAV-2 is mainly associated with infectious

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tracheobronchitis (Appel, 1987; MacLachlan & Dubovi, 2011). The E3 genomic region, which encodes proteins involved in modulation of host immune responses, exhibits characteristic differences between CAV-1 and CAV-2 and is therefore widely used for molecular differentiation and characterisation of canine adenoviruses (Burgert & Blusch, 2000; Hu et al., 2001; Lichtenstein et al., 2004).

CAV-1 infection can range from subclinical disease to severe systemic illness and death. Viral replication in hepatocytes and vascular endothelial cells may result in necrohaemorrhagic hepatitis, vasculitis, disseminated intravascular coagulation and glomerulonephritis, with clinical manifestations including fever, anorexia, vomiting, diarrhoea, jaundice and haemorrhagic signs (Wigton et al., 1976; Decaro et al., 2008). The virus is shed through saliva, faeces and urine, and prolonged urinary shedding may facilitate its persistence and transmission among susceptible dogs (Poppensiek & Baker, 1951). Despite the availability of effective vaccines, CAV-1 continues to circulate among domestic and wild canids worldwide.

In India, information on the epidemiology and genetic diversity of CAV-1 remains limited. Molecular detection of CAV-1 has been reported from different regions of the country (Chaturvedi et al., 2008; Parthiban et al., 2009), while subsequent studies have demonstrated its occurrence in dogs with gastroenteritis and in association with other enteric viruses (Chethan et al., 2021; Syamili et al., 2023). Therefore, the present study investigated the molecular detection of CAV-1 and CAV-2 in clinical and post-mortem samples from dogs and characterised selected CAV-1 strains based on partial sequencing and phylogenetic analysis of the E3 gene and its flanking regions.

Materials and methods

Study design

The study included 45 dogs from Wayanad and Kozhikode, comprising both animals with clinical signs or pathological lesions suggestive of infectious haemorrhagic enteritis and apparently healthy dogs. Between 2025 and 2026, a total of 45 samples were collected, comprising 21 rectal swabs from live dogs with haemorrhagic enteritis, 18 rectal swabs from apparently healthy dogs and 6 specimens obtained from dogs that had died of the disease. All samples were processed in the Department of Veterinary Microbiology, College of Veterinary and Animal Sciences (CVAS), Pookode, for diagnostic investigation.

Molecular assays were employed to screen for CAV-1. The identified CAV-1 strains were further subjected to sequence and phylogenetic analysis. Relevant clinical and pathological information, including signalment, anamnesis, vaccination status and anatomopathological findings, was retrieved from the Teaching Veterinary Clinical Complex, Pookode and the Department of Veterinary Pathology, CVAS, Pookode.

Virus screening

Tissue samples (lungs, spleen, liver, intestine, kidneys) and rectal swabs were collected and stored at -80°C until use. Tissue samples were homogenised, and the resulting supernatants were subjected to total DNA extraction using the DNeasy Blood & Tissue Kit (Qiagen, Germany), following the manufacturer's instructions. Rectal swabs were immersed in 500 μL of nuclease-free water, vortexed, and pressed against the tube wall before being discarded. Subsequently, 200 μL of the resulting suspension was subjected to DNA extraction using the phenol-chloroform method.

The presence of CAV-1 was evaluated by a diagnostic PCR assay using a primer pair for detecting both CAV-1 and CAV-2, as previously described (Hu et al., 2001), targeting the E3 gene (Table 1). The cycling conditions for amplification of the E3 gene were 94°C for 5 min (initial denaturation), 35 cycles of 94°C for 30 sec (denaturation), 58°C for 1 min (annealing) and 72°C for 1 min (extension), followed by a single cycle at 72°C for 5 min (final extension). An amplicon of 508 bp was amplified in the PCR. Each amplicon was analysed by electrophoresis on a 1.5% agarose gel supplemented with ethidium bromide.

Sequence and phylogenetic analysis

For sequencing of the partial CAV-1 E3 gene and its flanking regions, including the U-exon gene, two representative CAV-1-positive amplicons obtained during virus detection, one each from Wayanad and Kozhikode, were selected and submitted to GeneSpec Private Limited, Kochi, India, for Sanger sequencing. The quality of the obtained nucleotide sequences was assessed by visual inspection of the chromatograms using FinchTV v1.4.0.

The obtained sequences were analysed using the NCBI BLASTn algorithm (Zhang et al., 2000) to identify closely related sequences available in the GenBank database. Phylogenetic analysis of the partial E3 gene and its flanking regions was performed using MEGA11

Table 1. Details of PCR primers used for the detection of CAV-1

Sl. No.	Primer Name	Sequence 5'-3'	Target region/ Gene	Product size (bp)	Reference
1	HA1	CGCGCTGAACATTACTACCTTGTC	E3	508	Hu et al. (2001)
	HA2	CCTAGAGCACTTCGTGTCCGCTT			

Table 2. Deduced amino acid variations in E3 region

ID NUMBER	YEAR	ORIGIN	HOST	AMINO ACID POSITION OF E3					
				105	107	126	179	184	193
U55001	1987	Canada	Dog	N	H	W	L	T	G
M60937	1991	Canada	NA	N	H	W	L	T	G
EF057101	2006	India	Dog	N	H	W	P	T	G
MF344653	2008	Norway	Red Fox	N	H	W	L	T	G
GQ340423	2009	UP, India	Dog	D	H	W	L	T	G
KJ451612	2011	China	Dog	N	H	W	L	T	G
KT853096	2013	Australia	Dog	N	H	W	L	T	G
KT853097	2013	Australia	Dog	N	H	W	L	T	G
MH469715	2014	Spain	Brown bear	N	H	W	L	T	G
KU755710	2015	UK	Red Fox	N	H	W	L	T	G
KU755712	2015	UK	Red Fox	N	H	W	L	M	G
KU755719	2015	UK	Red Fox	N	R	W	L	T	G
KX181846	2015	India	Dog	N	H	W	L	T	G
KX545420	2015	Italy	Dog	N	H	W	L	T	G
MH048659	2015	France	Wolf	N	H	W	L	T	G
PV743807	2015	AP, India	Dog	N	H	W	L	T	E
KY272053	2016	India	Dog	N	H	W	L	T	G
MN652563	2018	Telangana, India	Dog	N	H	W	L	T	G
MW650920	2019	Italy	Dog	N	H	W	L	T	G
LC557010	2020	Japan	Dog	N	H	W	L	T	G
PV743826	2020	Tripura, India	Dog	N	H	W	L	T	G
PV743828	2020	Tripura, India	Dog	N	H	S	L	M	G
PV743829	2020	Tripura, India	Dog	N	H	W	L	T	G
MZ574094	2021	Wayanad, India	Dog	N	H	S	L	M	G
OP851367	2021	Italy	Fox	N	H	W	L	T	E
PV743811	2021	Manipur, India	Dog	N	H	W	P	T	G
PV743817	2021	Nagaland, India	Dog	N	H	W	L	T	G
PV743823	2021	Sikkim, India	Dog	N	H	W	L	T	G
OP326595	2022	India	Bear	N	H	W	L	T	G
OP501873	2022	Thrissur, India	Dog	N	H	W	L	T	G
OQ871567	2022	India	Dog	D	H	W	L	T	G
PV743819	2022	Nagaland, India	Dog	N	H	S	L	M	G
PV743821	2022	Nagaland, India	Dog	N	H	W	L	T	G
OR855466	2023	UP, India	Dog	N	H	W	L	T	G
PQ765503	2024	India	Dog	N	H	W	L	T	G
PZ044133	2026	Odisha, India	Dog	N	H	W	L	T	G
64/MIB/25*	2025	Kozhikode, India	Dog	-	H	S	L	M	G
114/MIB/25*	2025	Wayanad, India	Dog	-	H	W	L	T	G

*samples from our study

software. The phylogenetic tree was constructed using the neighbour-joining method based on the Kimura two-parameter nucleotide substitution model. The robustness of the tree topology was assessed using 1,000 bootstrap replicates, with bootstrap support values indicated at the corresponding nodes.

Results and discussion

Molecular detection and epidemiological characteristics of CAV-1

Of the 45 samples screened by PCR targeting
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the E3 genomic region, 13 (28.9 per cent) were positive for CAV-1, including one sample from an apparently healthy dog (Fig.1). In addition, two post-mortem samples were positive for CAV-2. The detection of CAV-1 in dogs with haemorrhagic enteritis indicates its possible involvement in canine enteric disease. Although CAV-1 is primarily recognised as the causative agent of infectious canine hepatitis (ICH), gastrointestinal manifestations, including vomiting, diarrhoea and haemorrhagic enteritis, have also been reported in infected dogs (Pratelli et al., 2001; Decaro et al., 2008). Recent investigations have similarly demonstrated the occurrence of CAV-1 among dogs

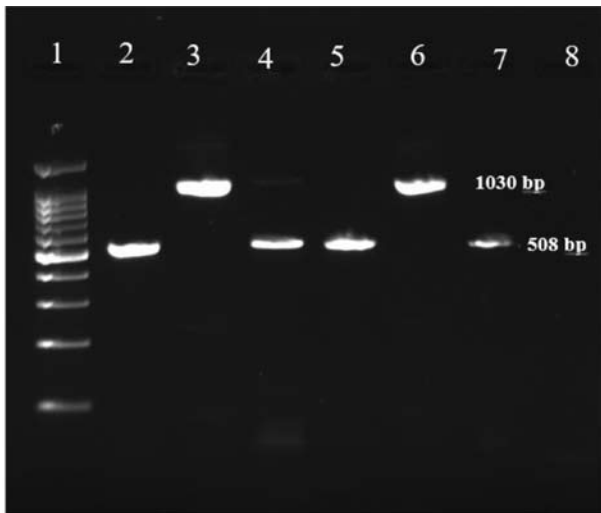


Fig. 1. Agarose gel electrophoresis of PCR products targeting the partial E3 region using gene-specific primers

Lane 1: 100 bp DNA Ladder, Lane 2: Positive control – 508 bp partial E3 gene PCR amplicon of CAV-1 (MZ574094), Lane 3: Positive control – 1030 bp partial E3 gene PCR amplicon of CAV-2 (Megavac), Lane 4: Positive for CAV-1 and CAV-2, Lane 5 & 7: Three representative CAV-1 positive samples, Lane 6: CAV-2 positive samples

presenting with gastrointestinal disease, suggesting that the virus should be considered in the differential diagnosis of canine enteric disease (Chethan et al., 2021; Mira et al., 2022).

The CAV-1 positivity recorded in the present study (28.9 per cent; 13/45) was higher than that reported in several previous investigations. Chethan et al. (2021) detected CAV-1 as a single infection in 5.55 per cent (12/216) of dogs with gastroenteritis and as a concurrent infection with CPV-2 in 12.03 per cent (26/216) of cases, resulting in an overall CAV-1 positivity of 17.59 per cent (38/216). Similarly, Alves et al. (2018) detected CAV-1 in 2.77 per cent (9/325) of faecal samples. Ramidi et al. (2020) reported an overall canine adenovirus positivity of 5.0 per cent (15/302) among clinically affected dogs; however, all typed viruses in that investigation were identified as CAV-2. Earlier studies by Chaturvedi et al. (2008) and Parthiban et al. (2009) also confirmed the occurrence of CAV-1 in clinical samples from dogs in India. The comparatively higher positivity observed in the present investigation may be attributable to differences in the study population, case selection criteria, geographical distribution, vaccination status, sample types, and diagnostic approaches employed across studies.

All CAV-1-positive dogs in the present study were mixed-breed animals ranging from one month to 11 years of age and had either absent, incomplete or inadequate vaccination histories. Although CAV-1 infection can occur in dogs of any age, young animals, particularly puppies below six months of age, are considered more susceptible to clinical disease (Greene & Decaro, 2012; Decaro et

al., 2008). Chethan et al. (2021) similarly reported CAV-1 infection predominantly among young puppies and dogs with absent or incomplete vaccination histories. None of the fully vaccinated dogs examined in the present study was positive for CAV-1, highlighting the importance of complete primary vaccination and appropriate booster immunisation for protection against ICH. In contrast, Ramidi et al. (2020) detected canine adenovirus in 15 of 302 clinically affected dogs, of which eight reportedly had a history of vaccination; however, all typed viruses in that study were CAV-2 rather than CAV-1.

The CAV-1-positive dogs originated from different locations across Wayanad and Kozhikode districts and were presented to the Teaching Veterinary Clinical Complex, Pookode. The geographical distribution of the positive cases indicates the circulation of CAV-1 over a wider area rather than its restriction to a single locality. Transmission of CAV-1 occurs through direct contact with infected animals or through exposure to contaminated saliva, faeces and urine. Prolonged urinary shedding following infection may contribute to environmental persistence and transmission among susceptible dogs (Poppensiek & Baker, 1951; Decaro et al., 2008). Accordingly, both faecal and urine samples have been employed for the molecular detection of canine adenoviruses (Chaturvedi et al., 2008; Mohammadi et al., 2011).

The affected dogs exhibited anorexia, lethargy, icterus, yellow-coloured vomiting and haemorrhagic diarrhoea. At necropsy, multisystemic lesions involving the gastrointestinal, hepatic, cardiovascular, respiratory, splenic and urinary systems were observed. The principal lesions included enteritis, hepatitis, multifocal haemorrhages, vascular congestion, endocarditis, splenomegaly, pulmonary congestion and serosanguineous effusions, indicating severe systemic involvement.

These clinical and pathological findings are consistent with the systemic pathogenesis of CAV-1 infection. Following initial replication in the tonsils and regional lymphoid tissues, viraemia results in systemic dissemination, with viral replication occurring predominantly in vascular endothelial cells and hepatic and renal parenchymal cells. The resulting endothelial damage, vascular injury and coagulation abnormalities may contribute to haemorrhagic manifestations involving multiple organs, including the gastrointestinal tract (Wigton et al., 1976; Greene & Decaro, 2012). The detection of CAV-1 from post-mortem tissues in the present investigation further supports its systemic distribution. Following viraemia, CAV-1 disseminates to several organs, particularly the liver, kidneys and vascular endothelium. Consequently, tissues collected during necropsy represent valuable diagnostic material, particularly in fatal cases with nonspecific clinical manifestations. Molecular detection of CAV-1 from the liver, kidneys, intestine and other tissues has also been reported in previous investigations (Duarte

et al., 2014; Wong et al., 2017).

PCR-based detection is particularly useful for the diagnosis of canine adenovirus infection because the clinical manifestations of CAV infection may overlap with those caused by other viral and bacterial pathogens. The E3 genomic region has been widely used for the detection and differentiation of CAV-1 and CAV-2 because of the characteristic difference in the length of this region between the two viral types (Hu et al., 2001; Chaturvedi et al., 2008). Primers targeting the E3 region generate products of approximately 508 bp and 1030 bp for CAV-1 and CAV-2, respectively, thereby facilitating their molecular differentiation.

Sequence and amino acid analysis

For molecular characterisation, single PCR products of the expected size corresponding to a 508 bp fragment comprising the partial E3 gene and its flanking regions were obtained from the tissues of one CAV-1-positive dog (114/MIB/25) and the rectal swab of another CAV-1-positive dog (64/MIB/25). The two sequences exhibited a high reciprocal nucleotide identity of 99.12 per cent, demonstrating considerable genetic conservation between the CAV-1 isolates detected in the two districts.

BLAST analysis of isolate 114/MIB/25 showed 100 per cent nucleotide identity with CAV-1 strains detected in a red fox from the United Kingdom in 2015 (KU755710), a dog from China in 2011 (KJ451612), a dog from Tripura, India, in 2020 (PV743826), and a dog from Uttar Pradesh, India, in 2023 (OR855466). Isolate 64/MIB/25 exhibited 99.5 per cent nucleotide identity with a CAV-1 strain detected in a red fox from the United Kingdom in 2015 (KU755712) and 99.77 per cent identity with canine CAV-1 strains reported from Tripura in 2020 (PV743828), Wayanad in 2021 (MZ574094), and Nagaland in 2022 (PV743819). The high nucleotide identities with CAV-1 strains from geographically distant domestic and wild canids indicate the considerable genetic conservation of the analysed genomic region.

The E3 genomic region selected for molecular characterisation is relevant to the investigation of genetic diversity and virus–host interactions. Although the E3 region is not essential for adenovirus replication in cell culture, its encoded proteins are involved in the modulation of host antiviral immune responses (Burgert & Blusch, 2000; Lichtenstein et al., 2004). The region also differs substantially between CAV-1 and CAV-2, with CAV-2 containing an additional sequence of approximately 500 nucleotides compared with CAV-1 (Linné, 1992), making it useful for molecular differentiation of the two viral types.

Comparison of the deduced amino acid sequences with related CAV-1 sequences retrieved from the GenBank database revealed two non-synonymous

substitutions in isolate 64/MIB/25: Trp126Ser and Thr184Met. These substitutions were absent in isolate 114/MIB/25. The Trp126Ser substitution represents the replacement of a large hydrophobic aromatic amino acid with a smaller polar amino acid, whereas Thr184Met represents the replacement of a polar amino acid with a hydrophobic amino acid (Table 2). Similar amino acid variations have previously been reported among CAV-1 strains from Indian and European domestic and wild canids, suggesting either shared evolutionary patterns or circulation of genetically related viruses among different host populations (Syamili et al., 2023; Chakraborty et al., 2024).

The high sequence similarity observed among the analysed CAV-1 strains suggests a relatively conserved nature of the genomic region examined, consistent with the limited genetic variation reported among CAV-1 strains from different geographical origins. However, the biological significance of the observed amino acid substitutions remains unclear. As the E3 region encodes proteins involved in modulation of host immune responses, variations in this region may potentially influence virus–host interactions and warrant further functional investigation (Decaro et al., 2008).

Phylogenetic analysis

Phylogenetic analysis of the partial E3 gene and its flanking regions confirmed the classification of both study isolates as CAV-1, with clear separation from the CAV-2 vaccine strain used as the outgroup and supported by a high bootstrap value. Within the CAV-1 cluster, however, the sequences were intermingled, and the internal branching pattern was not clearly resolved, probably because of the limited number of comparable sequences, minimal sequence variation among the strains, and low bootstrap support for the internal nodes. These findings suggest that the analysed genomic region is highly conserved among CAV-1 strains. (Fig. 2).

Isolate 114/MIB/25 grouped closely with recent Indian CAV-1 strains, particularly those reported from Odisha (PZ044133.1; 2026), Manipur (PV743811.1; 2021) and Sikkim (PV743823.1; 2021). In contrast, isolate 64/MIB/25 clustered with a separate group comprising canine isolates from Tripura (PV743828.1; 2020), Nagaland (PV743819.1; 2022) and Wayanad (MZ574094.1; 2021). The two Kerala isolates therefore did not group in the same sub-cluster, indicating the circulation of genetically distinguishable CAV-1 strains in the region. Nevertheless, considering the high overall sequence identity and limited phylogenetic resolution of the partial genomic region analysed, interpretations regarding independent introductions or regional divergence should be made cautiously and would require confirmation through complete genome sequencing and broader sampling.

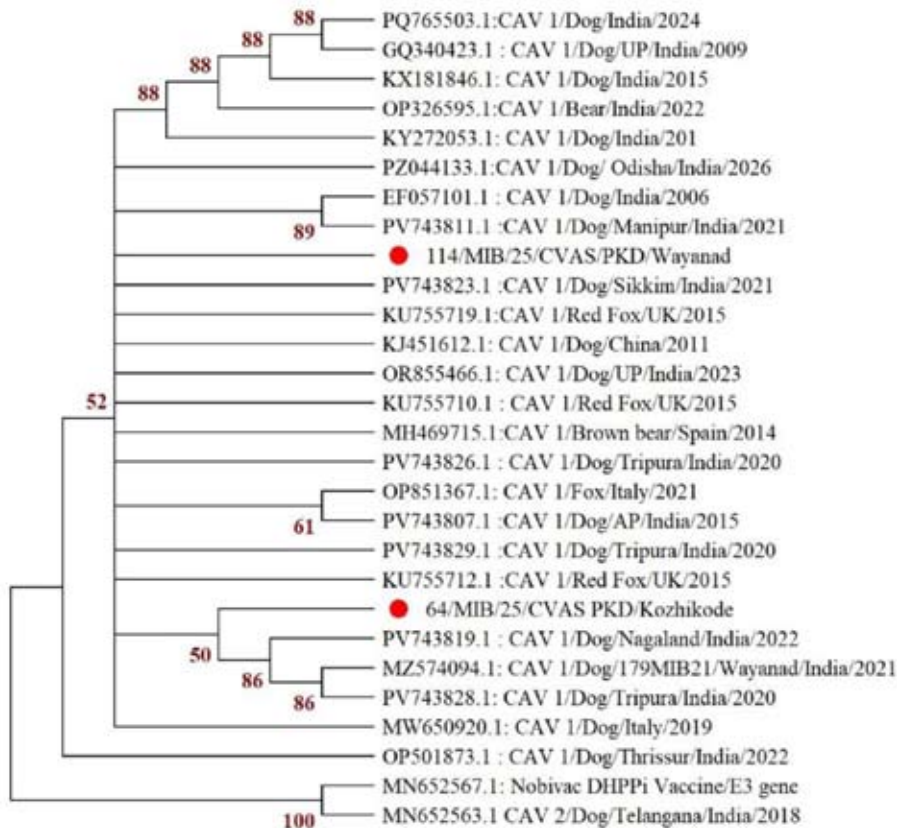


Fig 2. Neighbour joining tree constructed using 508bp E3 gene sequences of CAV-1. Naming was given in the model: Accession No. of reference isolates from NCBI GenBank/ CAV-1/ Animal/ country / collection year

Red-filled circle: sequence from this study ●

The clustering of isolate 64/MIB/25 with strains previously detected in Wayanad, Tripura and Nagaland, and of isolate 114/MIB/25 with other Indian and Asian strains, demonstrates close genetic relationships among CAV-1 strains circulating across geographically distant regions. Furthermore, the broader association of the study isolates with strains reported from countries including the United Kingdom, China, Italy, Norway, Japan and Canada suggests that the E3 region and its flanking sequences are highly conserved and that CAV-1 exhibits relatively limited genetic diversity across geographical regions. Similar phylogenetic patterns have been reported in previous investigations, in which Indian CAV-1 isolates showed close relationships with international strains, reflecting the high genomic stability and relatively slow evolutionary rate of the virus (Hu et al., 2001; Syamili et al., 2023; Chakraborty et al., 2024).

The clear phylogenetic separation of the study isolates from the CAV-2 vaccine strain confirmed their identity as naturally circulating CAV-1 field strains. Overall, the present investigation confirms the continued circulation of CAV-1 among dogs with haemorrhagic enteritis and systemic disease in northern Kerala. The relatively high CAV-1 positivity, its occurrence among inadequately immunised dogs, the detection of the virus in both clinical and

post-mortem samples, and the identification of genetically distinguishable CAV-1 isolates emphasise the importance of including CAV-1 in the differential diagnosis of canine haemorrhagic enteritis, particularly in cases showing multisystemic involvement. The combined application of PCR-based detection, nucleotide sequencing, amino acid analysis and phylogenetic analysis provides a useful approach for confirming CAV-1 infection and investigating the molecular epidemiology of circulating field strains.

Conclusion

Despite the relatively small sample size, CAV-1 was detected at a notable frequency among samples collected from dogs in Wayanad and Kozhikode districts. Molecular and phylogenetic analyses demonstrated a high degree of genetic conservation among the CAV-1 strains analysed, while also suggesting the circulation of genetically distinguishable variants in the region. These findings highlight the need to consider CAV-1 in the differential diagnosis of canine haemorrhagic enteritis, particularly in inadequately immunised dogs, and emphasise the importance of effective vaccination and continued molecular surveillance to better understand the epidemiology and genetic diversity of circulating CAV-1 strains.

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Conflict of interest

The authors declare that there is no conflict of interest in publishing this paper.

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