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Genetic diversity and expanded epidemic area of novel tick-borne pathogen wetland virus in ticks, wild and domestic animals, and patient in China

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ABSTRACT

Wetland virus (WELV) is a recently identified segmented orthonairovirus associated with human febrile illness in northeastern China. To elucidate its ecological drivers and transmission patterns, we conducted multi-host surveillance in seven eco-climate regions across China through an integrated approach combining molecular and serological profiling. Over 33,000 questing and feeding ticks representing 11 species were systematically screened WELV-RNA alongside 1,493 wild small mammals, while 2,578 domestic animals and 3,921 patients presenting with outdoor field or tick exposure history underwent both WELV specific molecular and serological evaluation. WELV-RNA detection via real-time RT–PCR revealed low but widespread infection, including 0.54% (8/1,493) in wild rodents (*Apodemus chevrieri*, *Rattus norvegicus*), 1.12% (29/2,578) in domestic animals, and 0.86% (275/33,091) in ticks, including five newly confirmed vector species. Serological analysis via enzyme-linked immunosorbent assay (ELISA) demonstrated 2.44% (63/2,578) IgG seroprevalence in livestock. Clinical surveillance identified acute WELV infections in 1.81% (71/3,921) of febrile patients, predominantly as monoinfections (77.46%, 55/71). Coinfected patients exhibited elevated disease severity markers, with hospitalization rates doubling compared to single-infection cases (87.50% vs. 36.36%). Spatiotemporal analysis showed spring-summer predominance of WELV for both ticks and human patients. Phylogenetic analyses revealed remarkable genetic conservation patterns of WELV strains across diverse hosts and tick vectors; and clustering across geographical regions. These findings establish WELV as an emerging tick-borne virus with trans-regional spread across heterogeneous landscapes in China. The intersecting transmission cycles among wildlife reservoirs, domestic amplifier hosts, and expanding tick vectors underscore the imperative for integrated surveillance strategies to mitigate this growing public health threat.

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Introduction

Tick-borne viruses have emerged as a growing global health challenge, with their geographic range expanding with climate change and anthropogenic disturbances [1,2]. Among these, tick-borne segmented nairoviruses have gained increasing attention due to their growing public health significance [3,4]. Over the past decade, more than 40 novel viruses have been identified within the *Nairoviridae* family, resulting in the classification of seven highly divergent genera and a substantial number of unclassified nairoviruses (https://talk.ictvonline.org/). Of particular note is the genus *Orthonairovirus* in the family *Nairoviridae*, containing established threats like Crimean-Congo haemorrhagic fever virus (CCHFV) – responsible for case fatality rates up to 40% in endemic regions [5], alongside emerging viruses

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such as Nairobi sheep disease virus (NSDV), Tamdy virus (TAMV), Yezo virus (YEZV) [6], Dugbe virus (DUGV) [7], Tacheng tick borne 1 virus (TcTV-1) [8], Songling virus (SGLV) [9], causing human diseases that range from mild to severe clinical outcomes. This taxonomic diversity mirrors complex host-vector relationships, with mammalian reservoirs spanning wildlife (e.g. Bactrian camels for TAMV) to domestic animals (e.g. sheep for NSDV) [10,11].

Our recent discovery of Wetland virus (WELV) in Northeastern China expands the pathogenic landscape of the *Orthonairovirus* genus [12]. Phylogenetic analysis on the whole genome sequences confirmed WELV as a distinct member of the *Orthonairovirus* genus, forming a unique clade within Hazara orthonairovirus genetic group. Clinical surveillance revealed multi-organ pathogenicity of WELV, causing respiratory, haemorrhagic, and neurologic manifestations. Vector competence studies identified *Haemaphysalis concinna* as the principal tick vector. Seroprevalence in livestock suggests stable enzootic cycles in northeastern China [12]. Although the initial findings offer significant insights into the epidemiological and clinical features of this novel virus, critical knowledge gaps persist in its eco-epidemiological profile. The current distribution of human cases remains confined to northeastern China, raising questions about WELV's spillover potential across the wide range of *Ha. concinna* – a tick species with expanding geographic range across Eurasian warm temperate zones [13]. This biogeographic mismatch suggests either diagnostic under-recognition in endemic regions or ecological constraints on viral dispersal, paralleling the early emergence patterns of YEZV in Japan, where initial case clustering in Hokkaido belied the broader distribution potential of its *Ixodes* vectors [6]. Furthermore, the role of mammalian reservoirs in perpetuating enzootic cycles remains undefined, despite serological evidence in livestock from our preliminary study.

In this study, we implemented a nationwide surveillance framework across China's seven eco-climatic regions. By integrating longitudinal sampling of ticks, wildlife, and domestic animals with enhanced clinical screening at six sentinel hospitals, we are designed to explore the transmission dynamics, genetic evolution and clinical features that are related to the infection of WELV.

Methods

Sample collection for ticks, wildlife and domestic animals

An extensive collection of questing and engorged ticks, wild small animals and domestic animals had been conducted between June 2011 and November 2024 among seven eco-climate regions in China: northeastern China, northern China, central China, southwestern China, southern China, Qinghai-Tibet, and Inner Mongolia-Xinjiang [14] (Figure 1, Table S1). Free ticks were collected by dragging a flannel flag over vegetation, while engorged ticks were collected from domestic animals. Wild small animals were captured using standardized snap trapping protocols, with tissues sample collected following aseptic dissection. Taxonomic identification of tick species and captured wildlife was performed through morphological characteristics followed by molecular confirmation. Specifically, mitochondrial 16S ribosomal DNA (16S rDNA) sequencing was employed for tick species verification, while mitochondrial cytochrome b (*mt-cyt b*) gene sequencing was utilized for wild animal identification (Table S2). Serum samples collected from domestic animals (canines, ovines, and bovine) underwent comprehensive testing including both molecular detection and serological analysis for WELV. All collected samples were stored at −80°C until processing. This study strictly adhered to national ethical standards for animal research, according to the Guidelines for Laboratory Animal Use and Care and the Rules for the Implementation of Laboratory Animal Medicine (1998) issued by the Ministry of Health. All field collection procedures and experimental protocols received prior approval from the institutional animal ethics committee.

Surveillance of WELV-infected patients

A multicentre surveillance study for WELV infection was implemented across six provincial-level administrative divisions (Heilongjiang, Liaoning, Inner Mongolia Autonomous Region, Henan, Shandong, and Yunnan), representing four major eco-climate zones in China with confirmed WELV-positive tick distributions (Table S1). Patient recruitment occurred at six sentinel hospitals: Inner Mongolia General Forestry Hospital, Heilongjiang Red Cross Sengong General Hospital, First Affiliated Hospital of Jinzhou Medical University, 154th Hospital in Henan province, Yantai Qishan Hospital in Shandong province, and Yunnan Institute of Endemic Disease Control and Prevention. Eligibility criteria required participants to have either (1) documented outdoor field exposure or (2) reported tick bite incidents within 30 days preceding symptom onset. Whole blood and serum samples were collected for dual assessment: WELV-RNA detection via quantitative reverse transcription PCR (qRT-PCR) and WELV-specific IgM/IgG antibody quantification through enzyme-linked immunosorbent assay (ELISA). Clinical records were systematically reviewed to extract epidemiological data, clinical data, laboratory findings, and therapeutic interventions. The study protocol received ethical approval from the Academy of Military Medical Science Institutional Review Board,

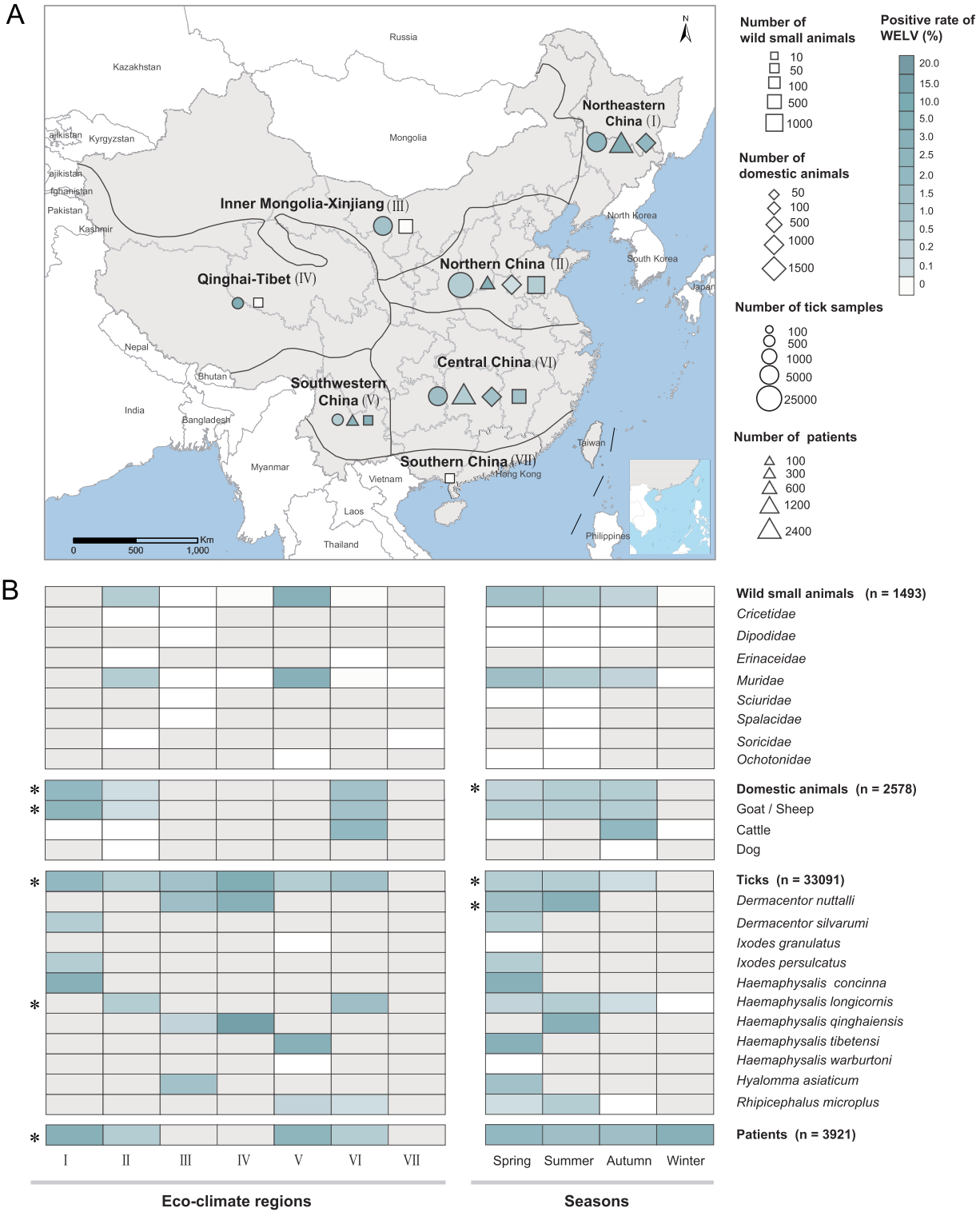

Figure 1. Detection of Wetland virus in ticks, wild and domestic animals, and patients in the mainland of China. (A) Distribution of WELV in seven eco-climate regions in China. The circle, triangle, square, and rhombus represent the ticks, patients, wild and domestic animals, respectively. The colour indicates positive rate. (B) Positive rate of WELV-RNA detected in seven eco-climate regions and four seasons. Comparisons among eco-climate regions or seasons were carried out using Chi-squared test, Chi-squared test (Yate's correction) or Fisher's Exact test where it is appropriate. * $P < 0.05$.

with written informed consent obtained from all participants prior to enrolment.

Molecular detection of WELV-RNA

Molecular screening for WELV-RNA was performed according to our established protocols [12]. Specifically, total RNA was extracted from three sample types: (1) pooled tick specimens, (2) homogenized tissue composites (liver, spleen, lung, kidney) from wild small animals, (3) serum samples from domestic animals and human patients, using the QIAamp Viral RNA Mini Kit (Qiagen, Germany). Primary viral detection employed qRT-PCR targeting

conserved regions of the L and S genomic segments [12]. The screen for WELV was performed by qRT-PCR targeting the L and S segments using cut-off cycle threshold (CT) values for positive and negative of ≤35 and >35, respectively. The qRT-PCR-positive specimens underwent further genetic characterization through amplification of a 407-bp L gene fragment, a 454-bp S gene fragment, or a 444-bp M gene fragment using the PCR System 9700 (Applied Biosystems) (Table S3) [15]. Amplicons were purified and subjected to bidirectional Sanger sequencing. All nucleic acid extraction and amplification incorporated parallel processing of positive controls (WELV strain) and negative controls (nuclease-free water) to ensure accuracy and reliability.

Whole genome sequencing of WELV

Next-generation sequencing of WELV positive samples was performed according to a previously published protocol [12]. Briefly, sequencing library was constructed using MGIEasy RNA Library Prep Kit (Beijing macro&micro-test Bio-Tech, China). Paired end (2 × 150 bp) sequencing of the RNA library was conducted on MGI2000 platform (Beijing macro&micro-test Bio-Tech). The sequencing reads were de novo assembled using MEGAHIT (version 1.2.9).

Serological test of WELV antibody

WELV-specific antibody was detected by ELISA as previously described [12]. For IgG detection, 96-well plates were coated with 10 ng/well WELV-nucleocapsid protein (NP), followed by incubation with serum samples diluted 1:200 in Western Antibody Dilution Buffer (Cwbio, China). Species-specific detection systems were implemented: horseradish peroxidase (HRP)-conjugated goat anti-human IgG (1:8,000; Jackson ImmunoResearch, USA) for human samples, complemented by rabbit anti-bovine IgG (Bioss, China) and rabbit anti-canine IgG (Bioss) for domestic animal specimens. After TMB substrate development, optical density (OD) at 450 nm was measured using a microplate reader. IgM detection followed analogous protocols with modifications: serum dilution at 1:80 and HRP-conjugated goat anti-human IgM (1:6,000; Jackson) for human samples. All assays included in-plate reference sera and negative controls. Samples were analysed in duplicate, with positivity defined as mean OD450 exceeding twice the negative control mean.

Pathogen screening

To investigate potential co-infections in human patients, serum and whole blood samples were systematically screened for other 10 tick-borne pathogens using PCR or real-time RT–PCR assays. Bacterial targets included *Anaplasma phagocytophilum* [16], *A. capra* [16], *Ehrlichia chaffeensis* [17], spotted fever group rickettsia (SFGR) [18], *Borrelia burgdorferi* sensu lato [19]. Viral screening encompassed YEZV [9], tick-borne encephalitis virus (TBEV) [20], ALSV [21], SGLV [9], and severe fever with thrombocytopenia syndrome virus (SFTSV) [15].

Phylogenetic reconstruction of WELV

Amino acid and nucleotide sequences of WELV obtained in this study were aligned with reference strains from the *Nairoviridae* family downloaded from GenBank (Table S4 and S5) using ClustalW (v2.1) in MEGA (v11). Phylogenetic trees were constructed using the maximum-likelihood method with the best-fitting model determined by the ModelFinder program implemented in IQ-TREE (v1.6.12), and bootstrap values were calculated based on 1,000 replicates. The resulting phylogenetic trees were visualized and refined using the Interactive Tree of Life (iTOL) (http://itol.embl.de/personal_page.cgi). The sequences generated in this study have been deposited in GenBank under accession numbers PV470891-PV470909 (full-length genome sequence), PQ757393-PQ757547, PQ849658-PQ849659, PV470879-PV470882 (partial L gene), PQ757339-PQ757392 (partial S gene), and PV4708867-PV470878 (partial M gene). The viral metagenomic data are available through the NCBI sequence reads archive (SRA) under accession number PRJNA1251011.

Statistical analysis

The WELV-RNA prevalence (95% confidence intervals) in ticks was calculated by maxim likelihood estimation (MLE) using the PooledInfRate (www.cdc.gov/mosquitoes/php/toolkit/mosquito-surveillance-software.html; accessed on 29 May 2024). Geospatial mapping of sampling locations was performed using Google Maps coordinates. Statistical comparisons of categorical variables employed Pearson's χ^2 or Fisher's exact tests, as appropriate, with two-tailed significance thresholds set at $P < 0.05$. All analyses were conducted in R (V 4.0.5), ensuring reproducibility through script-based workflows.

Results

Detection of WELV in questing and feeding ticks

A total of 33,091 questing and feeding ticks, representing 5 genera and 11 species, were tested in 5,333 pools based on their species and collection locations. WELV-RNA was determined in 0.86% (275/5,333) (95% CI: 0.77-0.97%) of the tick pools representing 9 species, including 3.45% of *Haemaphysalis tibetensi*,

3.43% of *Haemaphysalis qinghaiensis*, 3.07% of *Ha. concinna*, 2.08% of *Dermacentor nuttalli*, 1.17% of *Hyalomma asiaticum*, 0.63% of *Ixodes persulcatus*, 0.58% of *Haemaphysalis longicornis,* 0.56% of *Dermacentor silvarum*, and 0.25% of *Rhipicephalus microplus* (Table 1 and Table S6). Positive detections were recorded in all six sampled eco-climate regions, with significant geographical heterogeneity: *Ha. qinghaiensis* that dominated in Qinghai-Tibet had high prevalence of 15.65%; followed by *Ha. concinna* (3.07%) in northeastern China, *Ha. longicornis* in central China (1.59%), and *Ha. tibetensi* (3.45%) in southwestern China (Figure 1 and Table S6). WELV-RNA positive rate exhibited marked seasonality (χ^2 test, $P <$ 0.001), peaking in summer (0.99%), followed by spring (0.82%), autumn (0.09%), with no positive in winter (Figure 1 and Table 2).

Comparative analysis of five tick species (*De. nuttalli*, *De. silvarum*, *Ha. concinna*, *Rh. microplus*, *Ha. longicornis*) among 18,524 questing and 12,585 engorged ticks (10,027 collected from goats; 1190 from dogs; 700 from cattle; 324 from yak; 307 from hedgehogs; 22 from chicken; and 15 from rabbits), revealed distinct ecological patterns. Feeding ticks exhibited higher WELV prevalence than questing ticks across four species (*De. nuttalli*, *De. silvarum*, *Ha. concinna*, *Ha. longicornis*), with statistical significance in *De. nuttalli* (χ^2 test, $P = 0.01$) (Table S7). Notably, ticks collected from WELV IgG-positive goats demonstrated trend towards higher positive rate than those collected from WELV IgG-negative goats (2.82% vs. 0.66%), however with no statistical significance (Fisher's Exact test, $P = 0.14$).

Two tick species (*Ha. qinghaiensis* and *Ha. longicornis*) collected at the same location were examined across all three life stages (adult, nymph and larval). Life-stage comparison in *Ha. qinghaiensis* showed comparable prevalence, whereas *Ha. longicornis* displayed stage-dependent infection difference: highest for adult (0.90%), followed by nymph (0.21%) and larval (0.05%) (χ^2 test with Yate's correction, $P = 0.03$) (Table S8).

Detection of WELV in wild small animals and domestic animals

Molecular screening of 1,493 wild small mammals (32 species, 8 families) identified WELV-RNA in 0.54% (8/1,493) of them, exclusively in *Muridae* family: *Apodemus chevrieri* (4.08%, 2/49) and *Rattus norvegicus* (1.00%, 6/602) (Table 3 and Table S9). No obvious histomorphological abnormalities were observed from the WELV-positive rodents during their dissection. Spatial clustering emerged in southwestern China (4.00%) and northern China (0.73%) (Fisher's exact test, $P = 0.05$), with seasonal positive detections limited to spring through autumn, while not in winter (Figure 1 and Tables 1 and 2).

Table 1. Positive rate of Wetland virus in patients, ticks, wild small and domestic animals by seven eco-climate regions.

	Eco-climate regions								
	Northeastern China	Inner Mongolia-Xinjiang	Northern China	Central China	Southwestern China	Qinghai-Tibet	Southern China	Total	*P*-value
WELV-RNA									
Wild animal	–	0/335 (0)	6/822 (0.73)	0/229 (0)	2/50 (4)	0/44 (0)	0/13 (0)	8/1493 (0.54)	0.05[a]
Domestic animal	17/900 (1.89)	–	1/682 (0.15)	11/996 (1.10)	–	–	–	29/2578 (1.12)	0.005[b]
Goat/sheep	17/800 (2.13)	–	1/558 (0.18)	10/949 (1.05)	–	–	–	28/2307 (1.21)	0.005[b]
Cattle	0/100 (0)	–	0/100 (0)	1/47 (2.13)	–	–	–	1/247 (0.40)	0.19[a]
Dog	–	–	0/24 (0)	–	–	–	–	0/24 (0)	–
Tick[c]	84/324/4576 (2.12)	23/300/1909 (1.25)	125/3826/24198 (0.53)	22/511/1839 (1.20)	2/215/375 (0.53)	19/157/194 (9.83)	–	275/5333/33091 (0.86)	< 0.001[d]
Patient	45/1131 (3.98)	–	4/547 (0.73)	17/2065 (0.82)	5/178 (2.81)	–	–	71/3921 (1.81)	< 0.001[d]
WELV IgG									
Domestic animal	29/900(3.22)	–	6/682 (0.88)	28/996 (2.81)	–	–	–	63/2578 (2.44)	0.007[b]
Goat/sheep	29/800 (3.63)	–	6/558 (1.08)	28/949 (2.95)	–	–	–	63/2307 (2.73)	0.015[b]
Cattle	0/100 (0)	–	0/100 (0)	0/47 (0)	–	–	–	0/247 (0)	–
Dog	–	–	0/24 (0)	–	–	–	–	0/24 (0)	–
Patient	95/1131 (8.40)	–	19/547 (3.47)	48/2065 (2.32)	2/178 (1.12)	–	–	164/3921 (4.18)	< 0.001[b]

Note: Data are No. of positive samples/ No. of total tested samples (%).
[a]Fisher's Exact test.
[b]Chi-squared test.
[c]Data are No. of positive pools/No. of tested tick pools/No of tested ticks. The WELV-RNA prevalence in ticks was calculated by maximum likelihood estimation (MLE) using the program PooledInfRate.
[d]Chi-squared test (Yate's correction).

Table 2. Positive rate of Wetland virus in patients, ticks, wild small and domestic animals by seasons.

	Seasons					
	Spring	Summer	Autumn	Winter	Total	*P*-value
WELV-RNA						
Wild animal	4/294 (1.36)	3/588 (0.51)	1/399 (0.25)	0/212 (0)	8/1493 (0.54)	0.18[a]
Domestic animal	3/751 (0.40)	22/1318 (1.67)	4/509 (0.79)	–	29/2578 (1.12)	0.02[b]
Goat/Sheep	3/551 (0.54)	22/1318 (1.67)	3/438 (0.68)	–	28/2307 (1.21)	0.07[b]
Cattle	0/200 (0)	–	1/47 (2.13)	–	1/247 (0.40)	0.19[a]
Dog	–	–	0/24 (0)	–	0/24 (0)	–
Tick[c]	128/1367/16677 (0.82)	146/3678/14955 (0.99)	1/203/1053 (0.09)	0/85/406 (0)	275/5333/33091 (0.86)	< 0.001[b]
Patient	29/1357 (2.14)	30/1868 (1.61)	11/662 (1.66)	1/34 (2.94)	71/3921 (1.81)	0.49[a]
WELV IgG						
Domestic animal	12/751 (1.60)	37/1318 (2.81)	14/509 (2.75)	–	63/2578 (2.44)	0.20[b]
Goat/sheep	12/551 (0.54)	37/1318 (2.81)	14/438 (3.20)	–	63/2307 (2.73)	0.60[b]
Cattle	0/200 (0)	–	0/47 (0)	–	0/247 (0)	–
Dog	–	–	0/24 (0)	–	0/24 (0)	–
Patient	70/1357 (5.16)	79/1868 (4.23)	12/662(1.81)	3/34 (8.82)	164/3921 (4.18)	< 0.001[a]

Note: Data are No. of positive samples/ No. of total tested samples (%).
[a]Fisher's Exact test.
[b]Chi-squared test.
[c]Data are No. of positive pools/No. of tested tick pools/No of tested ticks. The WELV-RNA prevalence in ticks was calculated by maximum likelihood estimation (MLE) using the program PooledInfRate.

Domestic animal surveillance revealed WELV-RNA in 1.12% (29/2,578) of apparently healthy livestock, including 1.21% (28/2,307) of goats/sheep, 0.40% (1/247) of cattle, and none of the 24 dogs (Table 3). Positive detection was observed in all three sampled eco-climate regions, with a higher prevalence in northeast China (1.89%, 17/900) compared to central China (1.10%, 11/996) and northern China (0.15%, 1/682) (χ^2 test, $P = 0.005$) (Table 1). A significant difference was observed in WELV-RNA prevalence among domestic animal types (Fisher exact test, $P < 0.001$), with goats/sheep having a higher WELV-RNA positive rate compared to all other animals (1.21% vs. 0.37%; χ^2 test with Yate's correction, $P = 0.35$) (Figure 1 and Table 1). A seasonal pattern of WELV infection was also determined (χ^2 test, $P = 0.02$), with the highest prevalence determined in summer (1.67%), followed by autumn (0.79%) and spring (0.40%) (Figure 1 and Table 2).

Serological profiling detected WELV-IgG exclusively in goats/sheep (2.73%, 63/2,307), which showed significant regional trends (northeastern China: 3.63%, 29/800 > central China: 2.95%, 28/949 > northern China: 1.08%, 6/558; χ^2 test, $P = 0.015$), while no seasonal difference (χ^2 test, $P > 0.05$) (Figure 1 and Tables 1–3). No antibodies were detected in cattle or dogs.

WELV infection in human patients

Between April 2015 and October 2024, a total of 3,921 febrile patients (median age 59 years, range 3–89 years; 53.00% female) were recruited from four eco-climate regions (Figure 1, Table S10). WELV-RNA was determined in 1.81% (71/3,921) of the patients, across all four sampled regions, with the highest prevalence observed in northeastern China (3.98%, 45/1,131), followed by southwestern China (2.81%, 5/178), central China (0.82%, 17/2,065), and northern China (0.73%, 4/547) (Figure 1 and Table 1). Seasonal distribution was observed, with 83.10% (59/71) of human WELV infections occurring between May and September and 60.56% (43/71) reported a history of tick bites. WELV specific IgM and IgG antibodies were present in 60.56% (43/71) and 59.15% (42/71) of these patients, respectively.

Table 3. Detection of Wetland virus RNA and IgG antibodies in human patients and animals.

Hosts	No. of tested	No. (%) RNA positive	No. (%) IgG positive
Patients	3921	71 (1.81)	164 (4.18)
Domestic animals	2578	29 (1.12)	63 (2.44)
Goat/sheep	2307	28 (1.21)	63 (2.73)
Cattle	247	1 (0.40)	0 (0)
Dog	24	0 (0)	0 (0)
Wild animals	1493	8 (0.54)	–

Fifty-five patients with WELV-RNA monoinfection (median age: 54 years old; range 10-82; 63.64% female) exhibited a median treatment delay of 5 days (range: 2-31) from symptom onset. Among these patients, 36.36% (20/55) required hospitalization. The most common clinical manifestations at the time of hospital admission included fever (100%, 20/20), malaise (55%, 11/20), gastrointestinal manifestations (50%, 10/20), myalgia (35%, 7/20), headache (30%, 6/20), dizziness (15%, 3/20), arthritis (10%, 2/20), and back pain (5%, 1/20) (Table 4). Petechiae and localized lymphadenopathy were displayed among 5% (1/20) of the patients; and neurological symptoms such as dysphoria, lethargy, and coma were reported in seven patients. Laboratory profiling revealed haematologic dysregulation at admission (lymphopenia in 65% of patients; thrombocytopenia in 75%; leukopenia in 85%); alongside elevated level of high-sensitivity C-reactive protein (hs-CRP, 80%), d-dimer (45%), lactate dehydrogenase (LDH, 20%), fibrinogen (15%), alanine aminotransferase (ALT, 55%), aspartate aminotransferase (AST, 35%). Despite the viral aetiology, 95% (19/20) received empiric antibiotics, while 65% (13/20) underwent ribavirin therapy (Table 4).

Table 4. Clinical characteristics and treatments of patients with Wetland virus infection.

Characteristic	Monoinfected patients ($N = 55$)	Coinfected patients ($N = 16$)[a]
Age, years	54 (10-82)	62 (9-78)
<60	38 (69.09)	7 (43.75)
≥60	17 (30.91)	9 (56.25)
Sex, female	35 (63.64)	11 (68.75)
Occupation		
Farmer	28 (50.91)	10 (62.50)
Worker	5 (9.09)	2 (12.50)
Unknown	22 (40)	4 (25.00)
Clinical signs[b]		
Fever	20 (100.00)	14 (100.00)
Malaise	11 (55.00)	12 (85.71)
Myalgia	7 (35.00)	9 (64.29)
Headache	6 (30.00)	3 (21.43)
Dizziness	3 (15.00)	1 (7.14)
Arthritis	2 (10.00)	0 (0)
Back pain	1 (5.00)	0 (0)
Gastrointestinal manifestations	10 (50.00)	9 (64.29)
Petechiae	1 (5.00)	2 (14.29)
Lymphadenopathy	1 (5.00)	7 (50.00)[c]
Neurological symptoms	7 (35.00)	4 (28.57)
Laboratory abnormalities on admission[b]		
Leukopaenia	17 (85.00)	9 (64.29)
Thrombocytopenia	15 (75.00)	12 (85.71)
Lymphopenia	13 (65.00)	11 (78.57)
Hs-CRP >3 mg/liter	16 (80.00)	12 (85.71)
Fibrinogen >4.0 g/liter	3 (15.00)	3 (21.43)
D-dimer >0.55 mg/liter	9 (45.00)	7 (50.00)
LDH >245 U/liter	4 (20.00)	6 (42.86)
AST levels, > 40 U/liter	7 (35.00)	9 (64.29)
ALT levels, > 40 U/liter	11 (55.00)	10 (71.43)
Treatments[b]		
Antibiotics	19 (95.00)	13 (92.86)
Ribavirin	13 (65.00)	6 (42.86)
Mortality rate	3 (5.45)	2 (12.50)

Note: Data are median (range) or n (%).

[a]Coinfection involved SFTSV (13 patients), TBEV (two patient) and spotted fever group *Rickettsia* (one patient). LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Hs-CRP, high-sensitivity C-reactive protein.

[b]Shown are collected clinical characteristics, laboratory abnormalities on admission and treatments of hospitalized patients with WELV-RNA positive and complete medical records.

[c]$P = 0.004$. Fisher's exact test.

Sixteen patients presented with co-infection involving WELV-RNA and other tick-borne pathogens, predominantly SFTSV (13 cases), TBEV (two cases), spotted fever group *Rickettsia* (one case). Comparative analysis revealed significantly higher prevalence of lymphadenopathy (50.00% vs. 5.00%, Fisher's Exact test, $P = 0.004$) and hospitalization rate (87.50% vs.36.36%, χ^2 test, $P < 0.001$) compared to those with WELV monoinfection (Table 4). Mortality was recorded in 7.04% (5/71) of WELV-RNA positive patients, comprising three cases of monoinfection and two cases of co-infections with SFTSV. The survived patients did not exhibit any significant sequelae during prospective follow-up observations.

Phylogenetic analysis of WELV

We performed meta-transcriptomic sequencing on WELV-positive samples, yielding six complete WELV genomes (L, M, and S segments; GenBank: PV470891-PV470908) from *Ha. concinna* ticks and a full-length S segment from the sheep (GenBank: PV470909). Phylogenetic reconstruction using Tofla virus (TFLV) as the outgroup revealed that WELV strains cluster within the Hazara genogroup of the *Orthonairovirus* genus, forming a distinct monophyletic lineage separate from other Hazara orthonairoviruses (Figure 2(A)–(C)).

The L protein-based phylogeny resolved two major WELV clades: Clade I includes the 2019 human-derived strain (GenBank: XH033407) and our *Ha. concinna*-derived strains from Inner Mongolia (2019–2023); Clade II comprises one *Ha. concinna*-derived sequence from this study, two *Ha. concinna*-derived sequences from Heilongjiang/Inner Mongolia (GenBank: XJP49237, XJP49240), and two *De. nuttalli*-derived sequences from Inner Mongolia (GenBank: XJP49238-39) (Figure 2(D)). The human derived sequence exhibited 99.36-100% and 99.22-99.34% amino acid similarity of L protein to tick-derived sequences in Clade I and II, respectively.

Our genomic characterization identified four conserved functional domains across all WELV isolates: an ovarian tumour domain–like cysteine protease (vOTU, aa35-161), a topoisomerase-like domain (KLXXY), a C2H2-type zinc-finger domain (aa 601-624), and a leucine zipper motif. However, critical amino acid substitutions differentiated the clades in both the vOTU and RNA-dependent RNA polymerase (RdRp) domains. Within the N-terminal vOTU region, Clade I strains predominantly exhibited Lys at aa70 and aa85, contrasting with Glu at aa70 and invariant Arg at aa85 in Clade II. The RdRp domain (aa2042-2774) showed further divergence, with Clade I maintaining Lys at aa2130 and Thr at aa2341 versus Glu and Ala at these positions in clade II (Figure 2(E)).

To resolve broader evolutionary relationships, we performed comparative phylogenetic analyses using partial gene sequences from diverse hosts (Figures S1-S3). By examining 407-bp L gene fragments (n = 161), 444-bp M gene regions (n = 12), and 454-bp S gene segments (n = 54) obtained from ticks (n = 194), rodents (n = 5), goats (n = 2), and patients (n = 26), we observed remarkable sequence stability. Tick-derived WELV strains in this study maintained 99.73-100% (L gene), 98.65-100% (M), and 99.55-100% (S) nucleotide identity with the *Ha. concinna*-associated WELV strains (GenBank: OR860403, OR860413 and OR860397) from our previous study [12]. Human-derived sequences showed comparable conservation, exhibiting 98.92-100% (L), 99.76-99.77% (M), and 99.54-99.85% (S) identity to prior human-associated references (GenBank: OR860402, OR860408 and OR860396) [12].

Cross-species comparisons uncovered minimal divergence thresholds of 97.31% (L) and 99.32% (S)

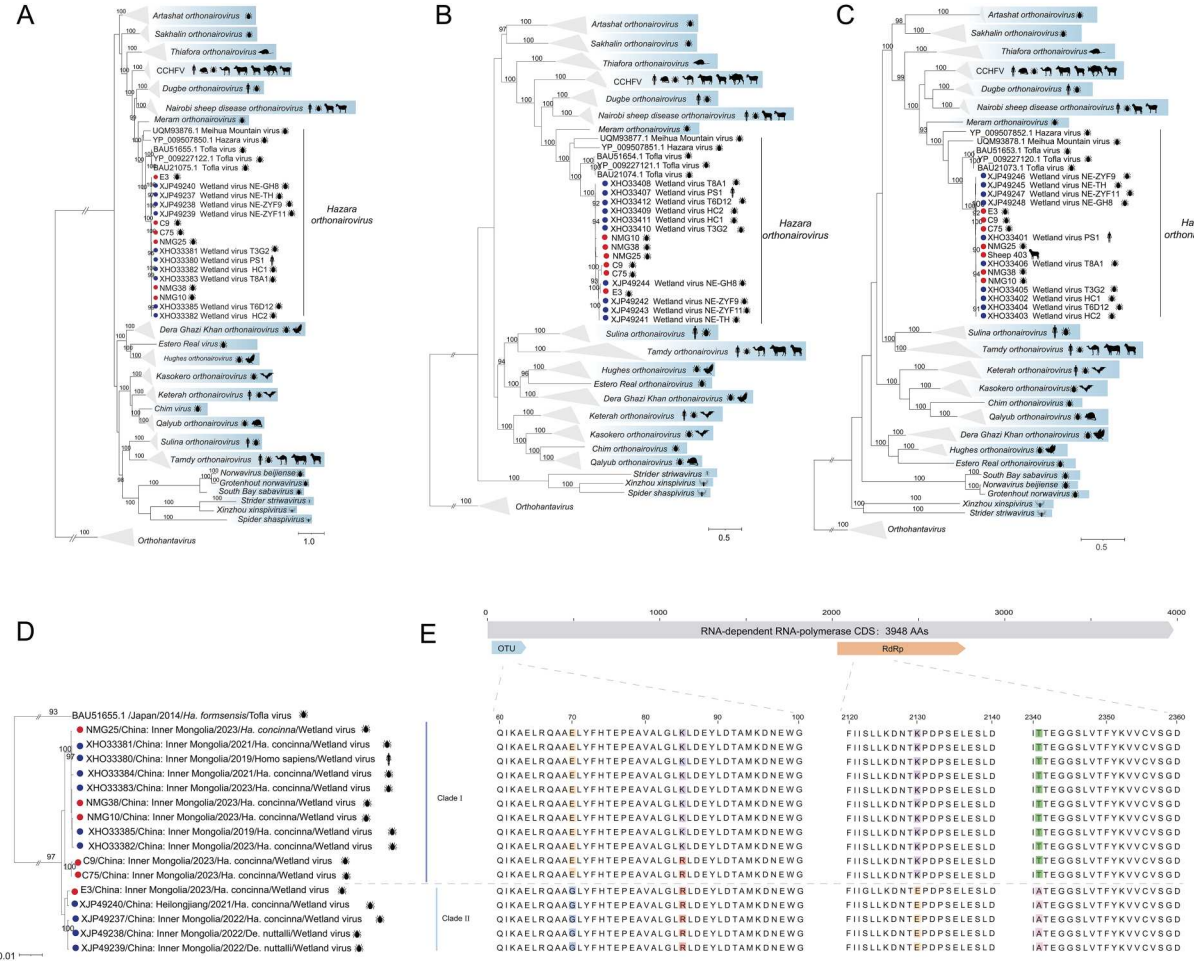

Figure 2. Phylogenetic tree and mutation of Wetland virus. The phylogenetic trees were estimated on the basis of complete AA sequences of L protein (A), GPC (B), and N (C) from WELV strains, as well as other recognized species in the *Nairoviridae* family, with the use of 1000 bootstrap replications. The best-fitting model was determined by the ModelFinder program implemented in IQ-TREE based on the Bayesian information criterion (BIC), the LG + G + F model for the L sequences, the LG + G + I model for the M sequences, the LG + G model for the S sequences. The scale bars denote the number of protein substitutions per site. WELV sequences that were obtained in this study and previous report are marked by red and blue dots, respectively. (D) Phylogenetic tree based on six L protein of tick-derived WELV strains in this study together with sequences of 10 human and tick-derived WELV strains from GenBank. (E) Structure and mutation of WELV RdRP CDS. The CDS contains OTU and RdRP domain. The mutations are highlighted in yellow, blue, purple, red, green, and pink, dependent on the amino acid. CDS = coding sequence. OTU = ovarian tumour protease. RdR*P* = RNA-dependent RNA-polymerase. E = Glu. G = Gly. K = Lys. R = Arg. T = Thr. A = Ala.

among WELV strains from nine tick species (Figure S4, Table S11), demonstrating exceptional sequence preservation across arthropod vectors. Phylogenetic reconstruction incorporating 65 representative sequences (40 partial L, 8 M, 17 S from ticks; all available goat/human sequences) consistently positioned WELV within a monophyletic cluster of *Hazara* orthonairoviruses (Figures S1–S3).

Discussion

The current findings substantially broadens the recognized endemic range of WELV across seven biogeographic regions in China, delineated by distinct climatic and ecological parameters [22,23]. Beyond its initial detection in *Ha. concinna* and four other tick species (*Ha. japonica*, *Ix. persulcatus*, *De. silvarum*, *Ha. longicornis*), we identified five novel WELV tick vectors: *Ha. qinghaiensis* (mainly endemic to western China) [24]; *Ha. tibetensis* (mainly in Tibet and Gansu provinces) [25]; *De. nuttalli* (widely distributed from southern Siberia to northern China) [26]; *Hy. asiaticum* (prevalent across Asia); and *Rh. microplus* (subtropical and tropical cattle tick) [27]. Regional prevalence patterns revealed vector specialization, with *Ha. qinghaiensis* dominating Qinghai-Tibet (WELV-RNA positive rate of 15.65%), *Ha. concinna* in northeastern China (3.07%), and *D. nuttalli* in Inner Mongolia-Xinjiang (1.81%). This geographical partitioning suggests primary and secondary vector roles within local transmission cycles, particularly for *Ha. qinghaiensis*. Despite high natural prevalence, its vector competence requires experimental validation.

The ability of WELV to replicate in various cell types and be positively detected in multiple animal species underscores its capacity to productively infect different

animal hosts [12]. Our study, for the first time revealed that a wide range of domestic (goats, sheep, cattle, dogs, chicken, and yaks) and wildlife (hedgehog) harbour WELV-positive feeding ticks in endemic regions. Serological evidence in goats/sheep (2.73% IgG positivity) and elevated WELV prevalence in ticks feeding on seropositive hosts suggest their role as amplification reservoirs. Spatial congruence in WELV detection among ticks, livestock, and humans across three eco-regions supports an enzootic "tick-wildlife-livestock-human" transmission model. Notably, only 60.56% of WELV infected patients recalled tick exposure, implying alternative routes or unrecognized vector interactions.

Furthermore, an extensive investigation of wild small mammal species across extended regions had identified additional reservoir hosts beyond the known hosts *Myospalax psilurus* in northeastern China. Specifically, WELV prevalence was higher in *Apodemus* genus (4.17%) from southwestern China and *Rattus* genus (1.13%) from northern China, both in the family *Muridae*. However, no correlation was found between WELV-RNA prevalences in wild small mammals and ticks in the same regions (Table 1), suggesting these mammals may maintaining adult tick populations but are not reproductive hosts for WELV transmission.

Human surveillance revealed 1.81% RNA and 4.18% IgG prevalence, peaking in northeastern China (3.98% RNA positivity), followed by southwest China (2.81%), central China (0.82%), and northern China (0.73%). Case distribution followed a bimodal seasonal pattern (April-May and September-October) (Figure S5), which might align with agricultural activities and tick abundance cycles. Phylogenetic clustering of human, tick, and livestock strains confirmed ecological overlap driving spillover risk.

While WELV monoinfection typically mirrors the non-specific febrile presentation of other tick-borne pathogens, including SFTSV [28], YEZV [6,29], ALSV [21], and SGLV [9], our data reveal exacerbated clinical diseases during WELV coinfection with SFTSV, which represents the first report of SFTSV-WELV coinfection. SFTSV, known to induce a clinical spectrum from influenza-like illness to fatal haemorrhagic and neurological complications [28], demonstrated pathogenic synergy when coexisting with WELV. Coinfected patients exhibited amplified severity of overlapping pathologies, with lymphadenopathy incidence increasing tenfold, while LDH elevations – a biomarker of cellular damage – elevated proportionally to viral loads. These synergistic effects likely stem from compounded endothelial dysfunction and immune hyperactivation, mechanisms previously implicated in SFTSV-driven critical illness [33]. This differs from clinical effects of SFTSV interactions with SFGR (delayed recovery, elevated mortality) and Hantaan orthohantavirus (HTNV) (aggravated haemorrhagic manifestations) [30–32]. On the other hand, the overlapping symptom profile between WELV and SFTSV necessitate multiplex molecular testing in endemic regions to prevent misdiagnosis or underdiagnosis. Furthermore, the hospitalization rate in coinfected cohorts than monoinfections underscores the urgency for early empiric antiviral protocols.

Within the Hazara orthonairovirus genogroup, only four species have been characterized to date. WELV poses as the sole member with confirmed human infectivity, contrasting with TFLV and Meihua Mountain virus (MHMV), which remain restricted to wild boars and cattle [34,35]. Notably, WELV demonstrates exceptional zoonotic plasticity, been detected across three rodent genera and five livestock species (sheep, goats, pigs, horses, dogs), underscoring its broad host adaptability [12]. While all Hazara orthonairoviruses primarily utilize *Haemaphysalis* ticks as vectors, WELV exhibits exclusive transovarial transmission capability in *Ha. concinna* – a critical adaptation for environmental persistence. Its distinctive pathogenicity is further evidenced by lethal outcomes in diverse murine models and tropism for human cell lines (e.g. hepatocytes, neurons) as well as primate, canine, and rodent-derived cultures [12]. The current comprehensive phylogenetic analyses of WELV strains revealed remarkable genetic conservation patterns across diverse hosts and tick vectors. This conserved evolutionary pattern persisted despite the virus' capacity to infect multiple mammalian hosts, suggesting strong purifying selection pressures maintaining core genomic stability.

In reviewing the results of this study, two potential limitations should be kept in mind. First, wide sampling across regions compounded by sparse temporal data for poultry and livestock species had limited the application of multivariate statistical analysis. Second, the absence of epidemiological linkages among human cases – coupled with low incidence rates – precludes definitive conclusions regarding transmission routes. While current evidence points to sporadic, tick-mediated spillover, the small cohort size cannot exclude potential human-to-human transmission mechanisms observed in other nairoviruses. These gaps highlight the necessity for longitudinal, population-level surveillance to delineate WELV's full transmission potential.

The current findings underscore the imperative for healthcare networks in regions with documented WELV activity (human, vector, or animal) to incorporate WELV screening into differential diagnoses of acute febrile syndromes, particularly where SFTSV or other tick-borne pathogens are endemic. The established co-circulation patterns necessitate the implementation of multiplex diagnostic platforms capable of simultaneous detection of WELV, SFTSV, and associated pathogens – a critical advancement given the synergistic morbidity observed in coinfected patients. Furthermore, the geographical congruence

between human seropositivity, livestock reservoirs, and vector prevalence maps argues for integrated One Health surveillance systems that monitor animal sentinels, tick populations, and human cases through coordinated frameworks.

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Author contribution

Conceptualization: Shu-Zhen Han, Xiao-Ai Zhang and Wei Liu. Gathered data and collected the samples: Zhi-Jun Zhao, Hong-Xia Yuan, Xiao-Long Lv, Xiao-Hu Han, Zhi-Jun Hou, Ning Cui, Xin Yang, Han-Zheng Mu and Peng-Tao Bao. **Laboratory tests**: Guang-Qian Si, LZ, HZM, YDM and CP. **Data analysis**: Mei-Qi Zhang, Guang-Qian Si, Si-Qian Wu, Ming Chen, Lei Zhang, Hao Li, Xiao-Ai Zhang and Wei Liu. **Writing – original draft**: Hong-Xia Yuan, Xiao-Long Lv, Mei-Qi Zhang, Guang-Qian Si, Shu-Zhen Han, Xiao-Ai Zhang and Wei Liu. **Writing – review and editing**: Hong-Xia Yuan, Xiao-Long Lv, Mei-Qi Zhang, Guang-Qian Si, Shu-Zhen Han, Xiao-Ai Zhang and Wei Liu. All authors reviewed the manuscript and agreed with the final version. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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References

[1] Lindquist L, Vapalahti O. Tick-borne encephalitis. Lancet. 2008;371(9627):1861–1871. doi:10.1016/S0140-6736(08)60800-4

[2] Liu Q, He B, Huang S-Y, et al. Severe fever with thrombocytopenia syndrome, an emerging tick-borne zoonosis. Lancet Infect Dis. 2014;14(8):763–772. doi:10.1016/S1473-3099(14)70718-2

[3] Hawman DW, Feldmann H. Crimean-Congo haemorrhagic fever virus. Nat Rev Microbiol. 2023;21(7):463–477. doi:10.1038/s41579-023-00871-9

[4] Zhou H, Xu L, Shi W. The human-infection potential of emerging tick-borne viruses is a global public health concern. Nat Rev Microbiol. 2023;21(4):215–217. doi:10.1038/s41579-022-00845-3

[5] Frank MG, Weaver G, Raabe V. Crimean Congo hemorrhagic fever virus for clinicians-diagnosis, clinical management, and therapeutics. Emerg Infect Dis. 2024;30(5):864–873. doi:10.3201/eid3005.231648

[6] Kodama F, Yamaguchi H, Park E, et al. A novel nairovirus associated with acute febrile illness in hokkaido, Japan. Nat Commun. 2021;12(1):5539. doi:10.1038/s41467-021-25857-0

[7] David-West TS. Dugbe virus: a new tick-borne arbovirus from Nigeria. Trans R Soc Trop Med Hyg. 1973;67(4):438. doi:10.1016/0035-9203(73)90062-X

[8] Liu X, Zhang X, Wang Z, et al. A tentative tamdy orthonairovirus related to febrile illness in northwestern China. Clin Infect Dis. 2020;70(10):2155–5560. doi:10.1093/cid/ciz602

[9] Ma J, Lv XL, Zhang X, et al. Identification of a new orthonairovirus associated with human febrile illness in China. Nat Med. 2021;27(3):434–439. doi:10.1038/s41591-020-01228-y

[10] Zhou H, Ma Z, Hu T, et al. Tamdy virus in ixodid ticks infesting bactrian camels, Xinjiang, China, 2018. Emerg Infect Dis. 2019;25(11):2136–2138. doi:10.3201/eid2511.190512

[11] Marczinke BI, Nichol ST. Nairobi sheep disease virus, an important tick-borne pathogen of sheep and goats in Africa, is also present in Asia. Virology. 2002;303(1):146–151. doi:10.1006/viro.2002.1514

[12] Zhang XA, Ma YD, Zhang YF, et al. A New orthonairovirus associated with human febrile illness. N Engl J Med. 2024;391(9):821–831. doi:10.1056/NEJMoa2313722

[13] Rubel F, Brugger K, Walter M, et al. Geographical distribution, climate adaptation and vector competence of the eurasian hard tick haemaphysalis concinna. Ticks Tick Borne Dis. 2018;9(5):1080–1089. doi:10.1016/j.ttbdis.2018.04.002

[14] Zhao G-P, Wang Y-X, Fan Z-W, et al. Mapping ticks and tick-borne pathogens in China. Nat Commun. 2021;12(1):1075. doi:10.1038/s41467-021-21375-1

[15] Liu W, Lu QB, Cui N, et al. Case-fatality ratio and effectiveness of ribavirin therapy among hospitalized patients in China who had severe fever with thrombocytopenia syndrome. Clin Infect Dis. 2013;57(9):1292–1079. doi:10.1093/cid/cit530

[16] Li H, Zheng YC, Ma L, et al. Human infection with a novel tick-borne anaplasma species in China: a surveillance study. Lancet Infect Dis. 2015;15(6):663–670. doi:10.1016/S1473-3099(15)70051-4

[17] Li H, Jiang JF, Liu W, et al. Human infection with candidatus neoehrlichia mikurensis, China. Emerg Infect Dis. 2012;18(10):1636–1639. doi:10.3201/eid1810.120594

[18] Lu QB, Li H, Jiang FC, et al. The differential characteristics between severe fever with thrombocytopenia syndrome and hemorrhagic fever With renal syndrome in the endemic regions. Open Forum Infect Dis. 2019;6(12):ofz477. doi:10.1093/ofid/ofz477

[19] Ni XB, Jia N, Jiang BG, et al. Lyme borreliosis caused by diverse genospecies of borrelia burgdorferi sensu lato in northeastern China. Clin Microbiol Infect. 2014;20(8):808–814. doi:10.1111/1469-0691.12532

[20] Jia J, Li Y, Wu X, et al. Reverse transcription recombinase polymerase amplification assays for rapid detection of tick-borne encephalitis virus infection. Virol Sin. 2019;34(3):338–341. doi:10.1007/s12250-019-00105-4

[21] Wang ZD, Wang B, Wei F, et al. A New segmented virus associated with human febrile illness in China. N Engl J Med. 2019;380(22):2116–2125. doi:10.1056/NEJMoa1805068

[22] He J, Kreft H, Gao E, et al. Patterns and drivers of zoogeographical regions of terrestrial vertebrates in China. J Biogeogr. 2017;44(5):1172–1184. doi:10.1111/jbi.12892

[23] Zhang R. China animal geography. Beijing: Science Press; 1999
[24] Lu M, Ji Y, Zhao H, et al. Circulation of multiple rickettsiales bacteria in ticks from Sichuan province, southwest China. Microb Pathog. 2023;183:106313. doi:10.1016/j.micpath.2023.106313
[25] Wang R, Li N, Liu J, et al. Symbiont dynamics of the Tibetan tick haemaphysalis tibetensis (acari: ixodidae). Parasit Vectors. 2017;10(1):259. doi:10.1186/s13071-017-2199-0
[26] Ma H, Lao Y, Liu S, et al. The diurnal salivary glands transcriptome of dermacentor nuttalli from the first four days of blood feeding. Ticks Tick Borne Dis. 2023;14(4):102178. doi:10.1016/j.ttbdis.2023.102178
[27] Pereira DFS, Ribeiro HS, Gonçalves AAM, et al. Rhipicephalus microplus: an overview of vaccine antigens against the cattle tick. Ticks Tick Borne Dis. 2022;13(1):101828. doi:10.1016/j.ttbdis.2021.101828
[28] Yu XJ, Liang MF, Zhang SY, et al. Fever with thrombocytopenia associated with a novel bunyavirus in China. N Engl J Med. 2011;364(16):1523–1532. doi:10.1056/NEJMoa1010095
[29] Zhang MZ, Bian C, Ye RZ, et al. A series of patients infected with the emerging tick-borne yezo virus in China: an active surveillance and genomic analysis. Lancet Infect Dis. 2025;25(4):390–398. doi:10.1016/S1473-3099(24)00616-9
[30] Lu QB, Li H, Zhang PH, et al. Severe fever with thrombocytopenia syndrome complicated by Co-infection with spotted fever group rickettsiae, China. Emerg Infect Dis. 2016;22(11):1957–1960. doi:10.3201/eid2211.161021
[31] Jiang F, Zhao Y, Peng R, et al. Clinical and etiological characteristics of severe hemorrhagic fever caused by coinfection of Hantaan orthohantavirus and severe fever with thrombocytopenia syndrome virus. J Med Virol. 2024;96(9):e29931. doi:10.1002/jmv.29931
[32] Xu Q, Wu C, Liu H, et al. A case of brucellosis concomitant with severe fever with thrombocytopenia syndrome – Weifang City, Shandong Province, China, 2023. China CDC Wkly. 2024;6(27):677–680
[33] Li XK, Yang ZD, Du J, et al. Endothelial activation and dysfunction in severe fever with thrombocytopenia syndrome. PLoS Negl Trop Dis. 2017;11(8):e0005746. doi:10.1371/journal.pntd.0005746
[34] Zhang X, Li HY, Shao JW, et al. Genomic characterization and phylogenetic analysis of a novel Nairobi sheep disease genogroup orthonairovirus from ticks, southeastern China. Front Microbiol. 2022;13:977405. doi:10.3389/fmicb.2022.977405
[35] Shimada S, Aoki K, Nabeshima T, et al. Tofla virus: A newly identified nairovirus of the crimean-Congo hemorrhagic fever group isolated from ticks in Japan. Sci Rep. 2016;6:20213. doi:10.1038/srep20213