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Epidemiological and genetic characterizations of hand, foot, and mouth disease and acute respiratory infections due to CV-A6 infection in Henan Province, China between 2021 and 2022

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Abstract

Coxsackievirus (CV) A6 has been widely considered as the main cause of global hand, foot, and mouth disease (HFMD) outbreaks. Despite the serious threat to children's health posed by the emerging CV-A6, our knowledge of the epidemiological features and etiology of HFMD caused by the new CV-A6 strains remains limited. In the present study, we aimed to investigate the epidemiological and genetic characterizations of CV-A6-associated HFMD outbreaks in Henan Province, China between 2021 and 2022. Clinical data and biospecimens of 407 children with mild and severe CV-A6 infection from Henan Children's Hospital (Children's Hospital Affiliated to Zhengzhou University) were collected for this prevalence study. Logistic regression analysis was employed to assess potential risk factors for severe illness. We also sequenced the VP1 gene of 4 CV-A6 strains, and a phylogenetic tree was conducted to characterize the evolutionary features of these CV-A6 strains. The majority of patients were 1 ~ 2 years old (236/407, 62.93%). Rash (364/407, 89.43%) and increase of lung markings in both lungs (224/407, 55.04%) were found to account for the highest percentage of clinical manifestations and clinical examination. Logistic regression analysis showed that boys were more likely to develop critical illness (OR: 1.970; 95% CI: 1.220 ~ 3.180), and that persistent high fever (OR: 2.066; 95% CI: 1.375 ~ 3.105), and elevated procalcitonin (PCT) levels (OR: 2.931; 95% CI: 1.590 ~ 5.405) would increase the risk of developing a critical illness ($P < 0.01$). The phylogenetic tree indicated that the genotype of CV-A6 strains in Henan Province was the D3 subtype. Collectively, in addition to the rash, acute respiratory infections due to CV-A6 infection are becoming increasingly common. Male sex, persistent high fever, and elevated PCT levels are associated with an increased risk of critical illness in patients infected with the D3 subtype of CV-A6. These findings may provide a scientific basis for guiding the prevention of HFMD and increase clinicians' awareness of CV-A6 infection.

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Introduction

Hand, foot, and mouth disease (HFMD) is a common infectious disease in children, characterized by the appearance of rash on the hands, feet and mouth, and mainly affects young children under the age of five [1]. The disease is self-limiting and its severity varies among individuals, with complications such as meningitis, myocarditis, and pulmonary edema occurring in a small number of patients [2]. Human enteroviruses are the main pathogens of HFMD, of which the most common enteroviruses are coxsackievirus (CV) A16 and enterovirus (EV) A71 [3]. However, after 2016, the number of EV-A71 cases declined year by year, and even tended to disappear during the coronavirus disease 2019 (COVID-19) pandemic [4]. Instead, CV-A6 and CV-A10 have become the major prevalent serotypes, with the detection rate of CV-A6 reaching 71.1% [5]. Large-scale CV-A6 outbreaks have been reported globally, such as Brazil, Vietnam, and France [6–8]. In recent years, some Provinces in China have also reported HFMD outbreaks associated with CV-A6 [9, 10]. Patients affected by CV-A6 tend to endure a higher fever, have a more prolonged disease course, and display more severe skin manifestations than typically associated with HFMD [11]. In addition, the atypical manifestations of HFMD caused by CV-A6 have increased significantly, including Gianotti Rossi-like rash, Coxsackie eczema, petechiae/purpura rash, onychomadesis [12], and blister. Due to their skin manifestations, similar to those of other serious skin diseases, it is difficult to accurately and timely diagnose them in clinical practice [13]. Severely ill patients infected with CV-A6 will exhibit neurologic symptoms such as vomiting and convulsions [14, 15]. In severe cases, acute myocardial injury and left ventricular dysfunction may also occur [15]. Animal studies have shown that CV-A6 infection induces brain and spinal cord damage in mice, accompanied by neuronal reduction, apoptosis, and astrocyte activation. This cardiophilic and neurophilic nature of CV-A6 places a tremendous burden on society and families [16].

In this study, we aimed to analyze the epidemiological and genetic characterizations of CV-A6 infection and explore the risk factors for severe disease, which will provide a reference for related medical workers and a scientific basis for the prevention of CV-A6.

Materials and methods

Case definition

A clinical case of HFMD was defined as a patient with maculopapular or vesicular rash on hands, feet, mouth, or buttocks, with or without fever, according to the guidelines of the National Health Commission of the People's Republic of China. The determination of mild and severe HFMD is based on the 'Diagnosis and Treatment Guidelines for Hand, Foot, and Mouth Disease (2018 Edition)' [17]. When patients experienced certain neurological complications such as convulsions, vomiting, and muscle weakness, as well as heart and lung failure, a diagnosis of severe cases can be established.

Data collection

Henan Children's Hospital (Children's Hospital Affiliated to Zhengzhou University) is equipped with 2,200 beds and is the province's premier referral destination for dealing with severe HFMD. It serves as both the National Children's Regional Medical Center and the Children's Medical Center of Henan Province. Our study specifically focused on this hospital, patients with HFMD caused by CV-A6 virus admitted between 2021 and 2022, and collected demographic information, laboratory indicators, and fecal samples from the patients.

Specimen testing

Viral RNA was extracted using commercial kits. The RNA extracts from each specimen were tested using a pan-enteroviral assay with specific oligonucleotide primers and probes that targeted EV-A71, CV-A16, CV-A6, and CV-A10 in separate assays. The test results were classified into six categories: enterovirus negative, EV-A71 positive, CV-A16 positive, CV-A6 positive, CV-A10 positive or other enterovirus positive without further serotype identification.

Sequencing and phylogenetic analysis

Four samples were randomly selected from those determined to contain CV-A6 to sequence the entire VP1 gene. The specific methods of sample preparation, RNA extraction and full-length CV-A6 sequencing were referred to Chen et al.[11]. Perform phylogenetic analysis of 78 strains (74 strains from the GenBank database and 4 strains from patients) of CV-A6 viruses using the molecular evolutionary genetics analysis software MEGA 11.0. The sequences of 4 CV-A6 strains reported in this study have been uploaded to the NCBI database with the GenBank accession numbers PP964015-PP964018.

Statistical analysis

Data analysis was carried out using SPSS 26.0 (IBM Corp., Armonk, NY, USA). Quantitative data were presented as mean ± standard deviation or as median with a 25–75% interquartile range, depending on whether they were normally distributed. After testing for

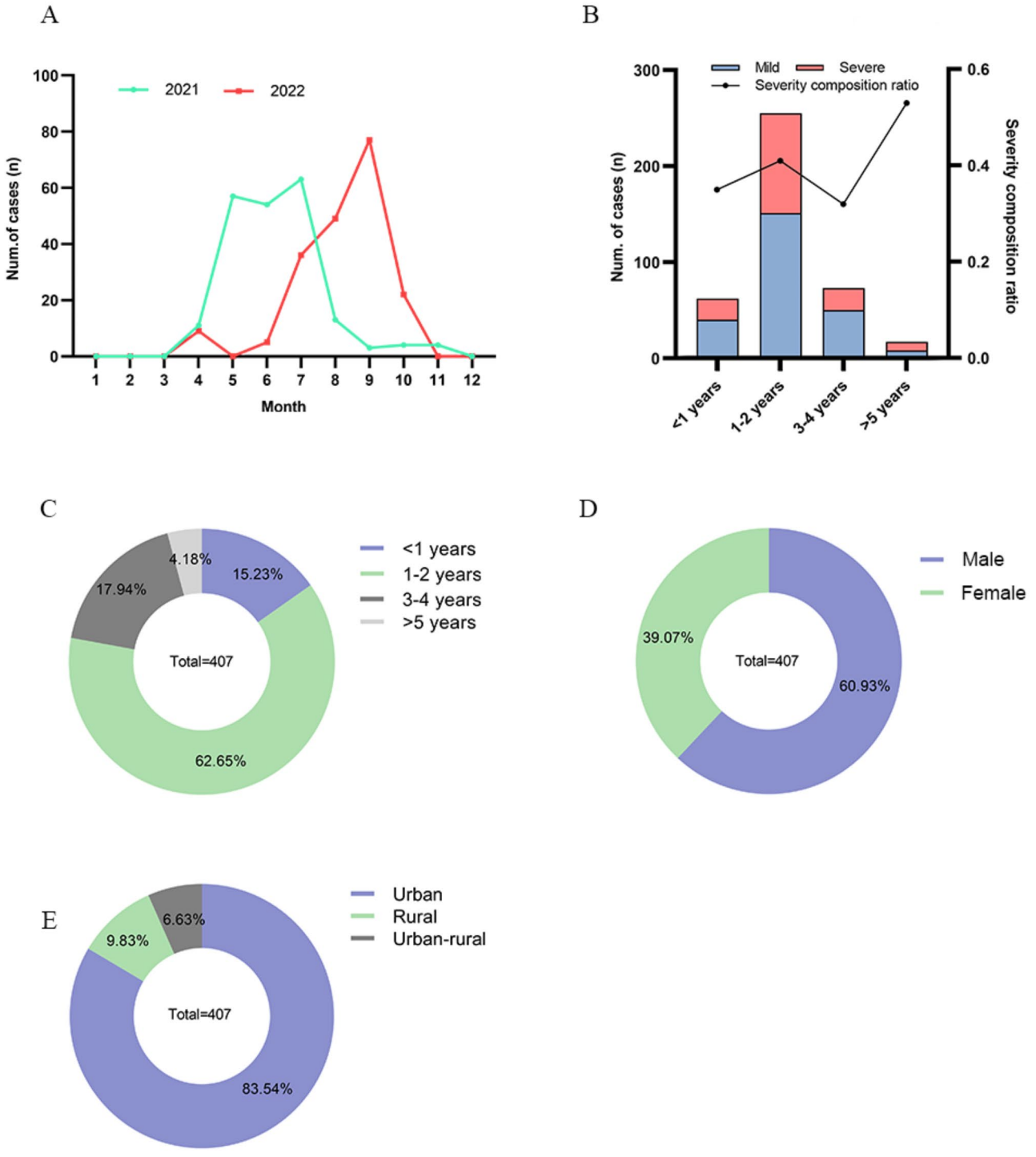

Fig. 1 Epidemiological characteristics of patients with CV-A6 infection in Henan Province, China. (**A**) From 2021 to 2022, the monthly distribution of HFMD patients in Henan Province, China. (**B**) Distribution of mild and severe illnesses and the ratio of the composition of severe illnesses among different age subgroups. (**C**) Age composition of HFMD cases caused by CV-A6. (**D**) Sex composition of HFMD cases caused by CV-A6. (**E**) Regional composition of HFMD cases caused by CV-A6

normality using the Shapiro-Wilk test, Student's t-test was employed to analyze normally distributed continuous data, while the Mann-Whitney U test was employed for data with non-normal distributions. In contrast, data for categorical variables were presented as frequencies and percentages and compared using Chi-square or Fisher's exact test. Multivariate logistic regression analysis was used to identify risk factors for CV-A6-associated

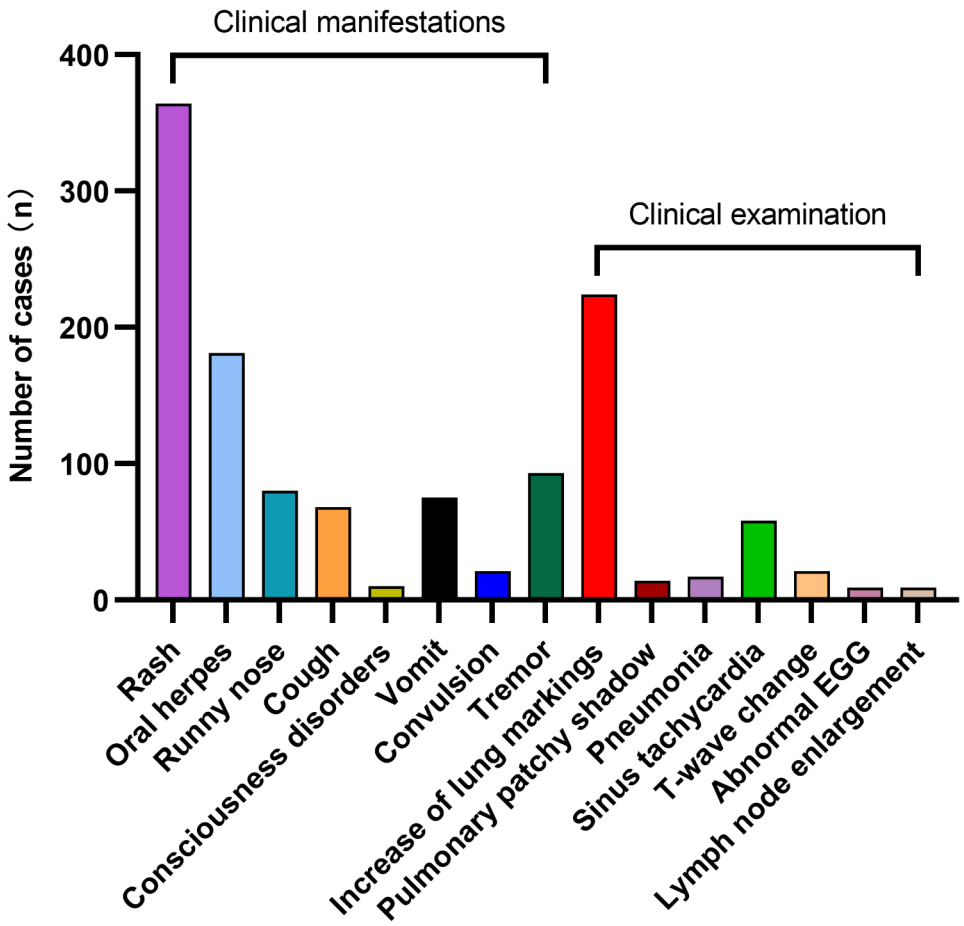

Fig. 2 Clinical manifestations of patients with CV-A6 infection in Henan Province, China

severe HFMD. A two-sided *P*value < 0.05 was considered statistically significant in all the statistical analyses.

Results

Epidemiological characteristics of patients with CV-A6 infection in Henan Province, China

From March 2021 to November 2022, a total of 407 HFMD cases with CV-A6 infection were admitted to Henan Children's Hospital (Children's Hospital Affiliated to Zhengzhou University). Among them, 249 (61.18%) were mild cases and 158 (38.82%) were severe cases. The incidence of HFMD was seasonal, with the peak period from May to September each year (Fig. 1A). Most of patients were younger than 5 years (390/407, 95.82%), especially children aged 1 ~ 2 years (260/407, 63.88%) (Fig. 1B and C). A larger proportion of male patients (248/407, 60.93%) were found in cases (Fig. 1D). Patients were most prevalent in urban areas (340/407, 83.54%), followed by rural areas (40/407, 10.07%) (Fig. 1E).

Clinical manifestations of patients with CV-A6 infection in Henan Province, China

The mean duration of hospitalization of patients was (3.92 ± 2.61) days, mean duration of fever was (1.71 ± 1.25) days and mean maximum temperature was (39.19 ± 1.86) °C. During the initial phase of the illness, a significant majority of patients (364/407, 89.43%) developed a rash, with the most prevalent occurrence observed on the hands, feet, mouth, and buttocks simultaneously (143/407, 35.14%). Furthermore, a subset of patients also exhibited oral herpes (181/407, 44.47%). In several cases, the rash spread to the face (7/407, 1.87%), perianal (4/407, 0.98%) and perineum (5/407, 1.33%). Other clinical manifestations among the patients included runny nose (80/407, 19.66%), cough (68/407, 16.71%), vomiting (75/407, 18.43%), convulsions (21/407, 5.16%), tremors (93/407, 22.85%), increase of lung markings (224/407, 55.04%), sinus tachycardia (58/407, 14.25%), and abnormal electrocardiogram (9/407, 2.40%) (Fig. 2).

Risk factors of CV-A6-related critical illness

A risk factor analysis was conducted on 375 patients after excluding 32 patients with incomplete clinical data,

Table 1 Demographic characteristics, clinical manifestations, and biochemical examinations of mild and severe HFMD caused by CVA6 in Henan Province

Characteristics	Mild ($n=231$)	Severe ($n=144$)	*P*-value
Age	38 (16.45%)	19 (13.19%)	0.166
< 1 year	138 (59.74%)	98 (68.06%)	
1–2 years	47 (20.35%)	19 (13.19%)	
3–4 years	8 (3.46%)	8 (3.46%)	
> 5 years			
Sex	126 (54.55%)	103 (71.53%)	**0.001**
Male	105 (45.45%)	41 (28.47%)	
Female			
Rash	21 (93.07%)	134 (93.06%)	0.995
Oral herpes	126 (54.55%)	60 (41.67%)	**0.019**
Residence	190 (82.25%)	119 (82.64%)	0.992
Urban	25 (10.82%)	15 (10.42%)	
Rural	16 (6.93%)	10 (6.94%)	
Urban-rural			
Birth weight (kg)	3.36 ± 0.49	3.38 ± 0.52	0.634
Body temperature (℃)	39.17 ± 0.63	39.44 ± 0.50	**< 0.001**
Fever days (day)	1.78 ± 1.29	1.62 ± 1.21	0.202
Hospitalization days (day)	3.64 ± 1.01	3.60 ± 1.06	0.738
WBC count ($\times10^9$/L)	12.70 ± 4.43	13.12 ± 4.60	0.366
N%	64.75 ± 16.00	69.65 ± 13.50	**0.002**
L%	26.90 ± 14.19	23.58 ± 12.68	**0.022**
N count ($\times10^9$/L)	5.37 ± 4.00	5.73 ± 4.77	0.608
L count ($\times10^9$/L)	3.89 ± 1.77	3.84 ± 2.06	0.885
Hb (g/L)	121.35 ± 13.63	122.74 ± 11.26	0.777
PLT ($\times10^9$/L)	292.19 ± 88.13	289.10 ± 91.93	0.745
CRP (mg/L)	16.67 ± 21.70	16.37 ± 17.90	0.889
PCT (ng/mL)	0.26 ± 0.34	0.51 ± 0.76	**< 0.001**
IL-6 (pg/mL)	34.08 (9.34,701.90)	33.40 (12.21,243.3)	0.752
IgE (ng/mL)	176.35 (56.50,493.03)	128 (43.06,428.05)	0.141
CD3%	58.80 ± 9.70	57.64 ± 9.47	0.495
CD8%	19.17 ± 6.07	18.94 ± 6.99	0.802
CD4%	34.72 ± 9.37	33.63 ± 9.05	0.400
CD4/CD8	2.14 ± 1.12	2.09 ± 0.89	0.719
ALT (U/L)	23.25 ± 10.51	23.34 ± 14.74	0.953
AST (U/L)	38.28 ± 9.09	40.80 ± 30.03	0.334
LDH (U/L)	341.49 ± 71.59	335.25 ± 66.99	0.475
CK-MB (U/L)	20.93 ± 10.25	21.41 ± 8.10	0.703

Statistically significant values are identified in boldface

Abbreviations: leukocyte, WBC; neutrophil percentage, N%; lymphocyte percentage, L%; neutrophil, N; lymphocyte, L; hemoglobin, Hb; platelet, PLT; C-reactive protein, CRP; interleukin-6, IL-6; immunoglobulin E, IgE; alanine transaminase, ALT; aspartate aminotransferase, AST; lactic dehydrogenase, LDH; creatine kinase-MB, CK-MB

with the study consisting of 231 mild cases and 144 severe cases. In terms of age, there was no statistical difference between the mild and severe groups ($P=0.392$). The proportion of male patients in the severe group was higher than that of patients in the mild group (71.53% vs. 54.54%, $P=0.001$). No significant difference was observed between the mild and severe group in terms of days of hospitalization, birth weight, place of residence and rash. Oral herpes was statistically different between the mild and severe group (54.55% vs. 41.67%, $P=0.019$). The mean body temperature of patients in the severe group (39.44 ± 0.50) was higher than that of the mild group (39.17 ± 0.63) and the difference was statistically significant ($P<0.001$). The severe group had higher percentage neutrophils (NEUT), and increased level of procalcitonin (PCT), and lower percentage of lymphocytes (LYM), as compared to the mild group, and the differences were statistically significant ($P<0.05$) (Table 1).

We further conducted multiple regression analyses to recognize the risk factors of CV-A6-related critical illness (Fig. 3). Our results showed that male sex (OR: 1.970; 95% CI: 1.220 ~ 3.180), persistent high fever (OR: 2.066; 95% CI: 1.375 ~ 3.105), and increased level of PCT (OR: 2.931;

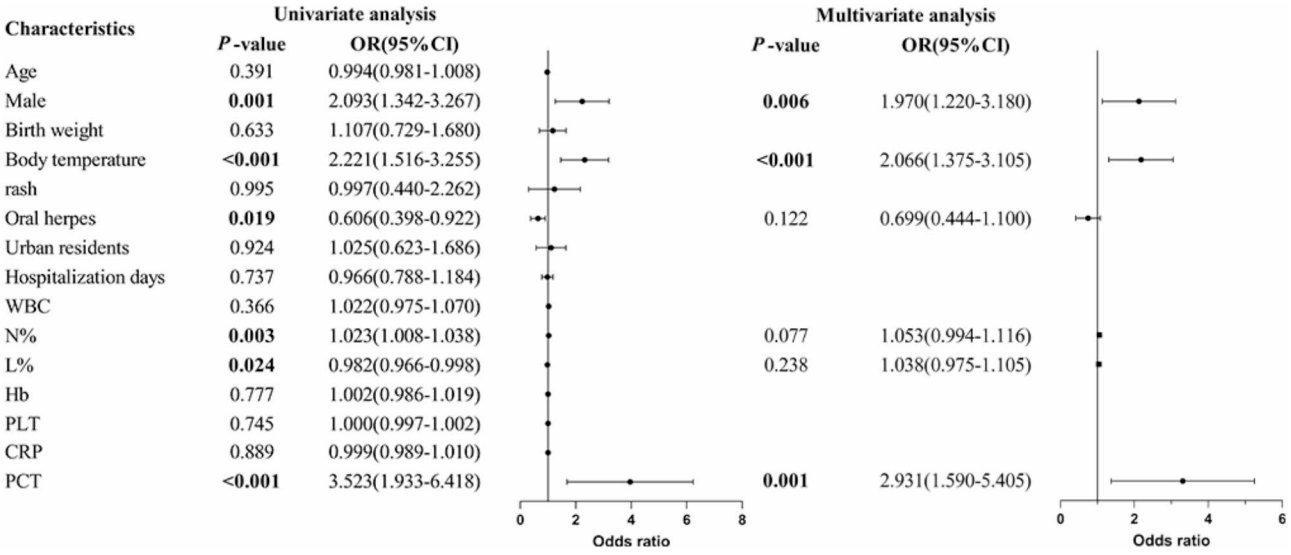

Fig. 3 Forest plot of a logistic regression model for identifying CV-A6-related serious illness

95% CI: 1.590 ~ 5.405) were associated with an increased risk of critical illness.

Phylogenetic analysis of complete VP1 gene sequences of CV-A6

Phylogenetic analysis was performed on entire VP1 sequences of 78 CV-A6 strains (74 strains from the GenBank database and 4 strains from this study) using the software MEGA 11.0. As shown in Fig. 4, these 4 CV-A6 strains from clinical patients in Henan Province were the D3 subtype.

Discussion

Compared to other enteroviruses associated with HFMD, CV-A6 causes a longer disease duration and more severe symptoms, affecting both children and adults. Recently, the increasing morbidity of HFMD associated with CV-A6 has become an important public health issue. In this study, a total of 407 CV-A6 infections were collected in Henan Children's Hospital (Children's Hospital Affiliated to Zhengzhou University) from March 2021 to November 2022. We found a severe rate of 38.4% in hospitalized CV-A6 cases. The specific manifestations of neurological involvement include vomiting (75/407, 18.43%), convulsions (21/407, 5.16%), tremors (93/407, 22.85%), consciousness disorders (10/407, 2.46%), limb weakness (2/407, 0.49%), and drowsiness (1/407, 0.25%). According to infectious disease surveillance data from 2011 to 2012 in Japan, the reported rates of cases of encephalitis or encephalopathy associated with EV-A71 and CV-A16 were 0.93% and 0.31% [2], respectively, and a recent study has shown that the proportion of HFMD cases caused by CV-A6 with central nervous system (CNS) involvement ranges from 3.6 to 18.2% of patients [18]. This may be due to the fact that the sample in this study was from one hospital, and Berkson's bias cannot be avoided. It is also possible that we underestimated the ability of CV-A6 to damage the CNS [19].

There were 95.82% patients under the age of 5 years, especially children aged 1 ~ 2 years, suggesting that children aged 1 ~ 2 years were the main susceptible population for HFMD [20]. On the one hand, this is because children under the age of 5 have immature humoral and cellular immune functions, making them susceptible to virus invasion. On the other hand, the close contact in childcare facilities also accelerates the rate of disease outbreaks [21]. Urban children accounted for 83.54% of the total cases, which may be related to the high population density and increased opportunities for children to come into contact with each other, resulting in a corresponding increase in the probability of virus transmission [22]. As with previous research findings, this study also concluded that the prevalence of HFMD is seasonal, with a peak incidence from May to September each year [23]. As for the difference between the two epidemic peaks in 2021 and 2022, it is mainly related to non-pharmaceutical intervention measures during the COVID-19 pandemic. Related study has shown that hot and humid weather is very conducive to the spread of enteroviruses in the population, which just supports our findings [23]. We found that 89.43% of patients developed rashes, mostly on the hands, feet, mouth, and buttocks. Notably, some of the rashes appear in atypical areas such as the face, anus and perineum. These atypical clinical presentations result in patients who may be misdiagnosed, which in turn leads to inappropriate and unnecessary investigations, hospitalization and treatment. As described in our recent

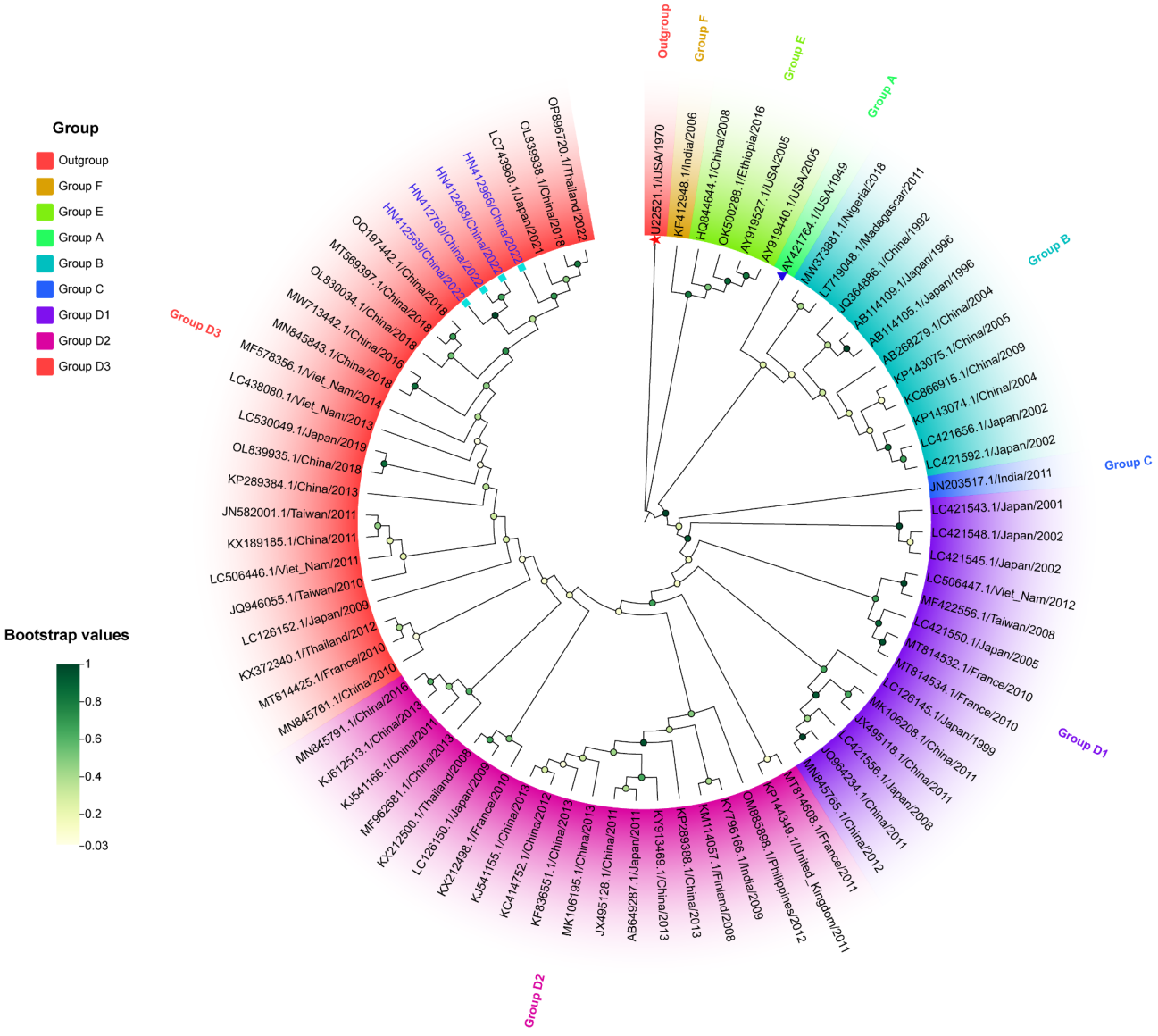

Fig. 4 Phylogenetic analysis of entire VP1 sequences of CV-A6. The prototype strain of EV-A71 was marked with red star. The prototype strain of CV-A6 was marked with blue triangle. The cyan squares represented the strain isolated in this study

studies, there is a need to raise awareness of atypical presentations of HFMD.

CV-A6 not only causes typical symptoms such as rash, but also leads to acute respiratory infections. Some patients showed symptoms of acute respiratory infections such as runny nose and cough. Chest computed tomography (CT) images showed the increase of lung markings in half of the patients and a small number of them had patchy lungs and pneumonia. The above results suggest that the impact of CV-A6 on the respiratory tract should not be underestimated. Previous studies indicated that the relationship between specific viral strains and the nervous system, and the impact of HFMD and the respiratory system has been under-explored, especially the complex impact of CV-A6 [24, 25]. One noteworthy study noted the ability of CV-B4 to cause severe pneumonia infections, suggesting that CV-A6, our fellow enterovirus, may have similar pathogenic potential, especially in attacking the respiratory tract [26]. In addition, a significant increase in lower respiratory infections has been reported in young children with low birth weight who develop HFMD [27]. Of particular concern is the case of a child with symptoms of both HFMD and atypical symptom who was co-infected with enterovirus D68 (EV-D68) and CV-A6, a case that directly supports the possibility of co-infection of CV-A6 with other respiratory viruses [28]. What's more, cases of vertical transmission of CV-A6 leading to severe congenital pneumonia/septicemia have been documented, which not only confirms the diversity of transmission routes for CV-A6, but also suggests that

infection with the virus during pregnancy may have serious respiratory effects on the foetus, further highlighting the potential risk of intergenerational transmission [29].

Multivariate analysis showed that male sex, persistent hyperthermia, and elevated PCT levels are associated with an increased risk of critical illness in patients infected with the D3 subtype of CV-A6. Boys tend to have higher levels of physical activity, which may result in increased opportunities for viral exposure, contributing to the observed differences [30]. We hypothesize that the sustained high fever in patients may trigger excessive activation of the body's immune system, leading to intensified inflammatory responses and weakened viral clearance, thereby exacerbating the condition. On the other hand, prolonged high fever may also facilitate viral replication and dissemination within the body, further contributing to disease progression [31]. Procalcitonin (PCT) is the precursor of calcitonin. Recent studies have revealed that PCT is not only a biomarker, but may also be directly involved in immunomodulation [32]. The results suggest that procalcitonin is associated with the severity of CV-A6 infection, which is consistent with previous studies [33]. Elevated levels of PCT may inhibit the body's immune function, reduce the body's resistance to the virus, and lead to the deterioration of the disease. At the same time, PCT is an early marker for predicting sepsis and should be given sufficient attention [34, 35].

The phylogenetic tree indicated that the CV-A6 strain circulating in Henan Province was the D3 subtype. As reported previously, the D3 subtype is dominant among CV-A6 subtypes in China; however, the current status of virus virulence and the presence of recombination and mutation need to be investigated in greater depth [36, 37]. The D3 subtype of CV-A6 has demonstrated a sustained epidemiological pattern in specific regions, particularly prominent in the Asia-Pacific region, where epidemiological studies including the Philippines (2012 ~ 2017) [38], Thailand (2000 ~ 2022) [39], and South Korea (2022) [40] confirmed the D3 subtype as the dominant strain. In addition, the global distribution of CV-A6 subtypes showed diversity: in France, subtypes D1 and D3 were the predominant prevalent strains during 2010 ~ 2018 [41]; in Hong Kong, China, in 2018, strains were dominated by subtypes D5 and D4 [42]; Japan witnessed the prevalence of subtypes A3 and A4 during 2013 ~ 2017 [43]; and India reported the presence of strains of sublineage E2 in 2022 [44]. Notably, the geographic distribution of CV-A6 subtypes dynamically adjusts over time, geographic differences, and changes in population immunization status. Therefore, continuous tracking and in-depth investigation of the global distribution of CV-A6 subtypes and the latest scientific research progress will be invaluable for the development of public health strategies, optimization of outbreak early warning systems, and implementation of targeted medical interventions.

This study also had some limitations. First, all the data in this study were obtained from one hospital. Second, the inclusion of risk factors was not comprehensive due to incomplete clinical examination indicators in some patients, which may bring about missing data from some examinations and may have overlooked some factors. Third, we only obtained the full-length VP1 sequences of four CV-A6 strains, which is a limitation for revealing the genetic evolutionary features of CV-A6 in Henan Province. It is hoped that in future study, we will use multicenter studies to further explore the epidemiological features and genetic characterizations of CV-A6 strains.

Conclusions

Collectively, in addition to the rash, acute respiratory infections due to CV-A6 infection are becoming increasingly common. Male sex, persistent high fever, and elevated PCT levels are associated with an increased risk of critical illness in patients infected with the D3 subtype of CV-A6. These findings may provide a scientific basis for guiding the prevention of HFMD and increase clinicians' awareness of CV-A6 infection.

Abbreviations

HFMD	Hand, foot, and mouth disease
CV	Coxsackievirus
PCT	Procalcitonin
EV	Enterovirus
COVID-19	Coronavirus disease 2019
LYM	Lymphocytes
CNS	Central nervous system
CT	Computed tomography

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12887-025-05527-6.

Supplementary Table 1

Acknowledgements

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Author contributions

Yuefei Jin conceptualized and designed the study, and critically reviewed and revised the manuscript for important intellectual content. Jin Zhipeng directed the design of the study and provided funding for it. Shouhang Chen collected the data, and Tianyu Li, Xin Yuan, and Dan Su performed data entry and screening. Xiaolong Li drafted the initial manuscript and critically revised it. Yu Chen, Bowen Dai and Shujie Han directed the experiments. Fang Wang and Zhi Li conducted the formal analysis and investigation. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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Data availability
The datasets generated and/or analyzed during the current study are available in the Supplementary Table 1. The sequences of 4 CV-A6 strains reported in this study have been uploaded to the NCBI database with the GenBank accession numbers PP964015-PP964018. The other data of the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was carried out in accordance with the recommendations of the Declaration of Helsinki, World Medical Association. The protocol was approved by the Ethical Review Board of Zhengzhou University (ZZUIRB2023-180) and written informed consent was obtained from all participants' parents.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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