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Incidence, aetiology, and serotype spectrum analysis of adult hand, foot, and mouth disease patients: A retrospective observational cohort study in northern Zhejiang, China

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ABSTRACT

Background: Hand, foot, and mouth disease (HFMD) in adults has rarely been reported in the literature, although its clinical significance is underestimated. This study was performed to systematically elucidate the epidemiological characteristics of adult HFMD.
Methods: A total of 266 adult patients with HFMD were recruited. The control group comprised 40 healthy adults. Swabs and serum samples were collected. Enterovirus strains were tested by RT-PCR, and cytokine expression was examined using commercial kits. Socio-demographic data were collected through follow-up telephone calls. Daily meteorological data were obtained from the China Meteorological Data Sharing Service System. Socio-economic data were collected from the statistical bureau.
Results: This study identified several unique spatiotemporal patterns in adult HFMD. Having a child recently diagnosed with HFMD was a risk factor for HFMD, whereas keeping pets was a protective factor against HFMD. The results of this study indicate the existence of subclinical carriers or misdiagnosed patients who might be the latent infectious source of HFMD. Further, this study also indicated that adults may act as the main infectious source of trans-regional spread of HFMD.
Conclusions: This study revealed the potential hazards of adult HFMD and is a reminder of the vital clinical significance of further research into adult HFMD.

Introduction

Hand, foot, and mouth disease (HFMD) is a common infectious disease caused by viruses of the genus Enterovirus (Xing et al., 2014; Gao et al., 2018; Huang et al., 2018). Enteroviruses are primarily transmitted via faecal–oral route or close contact with an infected individual (McMinn, 2002; Sun et al., 2016). The major causative agents of HFMD are coxsackie virus A16 (CA16), which usually leads to a self-limiting infection with mild symptoms, and enterovirus 71 (EV71), which can cause severe complications (Zhao et al., 2011; Hyeon et al., 2013; Solomon et al., 2010; Ooi et al., 2010; Chong et al., 2015). Furthermore, coxsackie virus A6 (CA6)-associated HFMD cases have become more prevalent in recent years (Anh et al., 2018; Fujimoto et al., 2012).

HFMD mostly occurs in infants and children under 5 years of age (Zhu et al., 2013; Li et al., 2014). Sporadic cases of adult HFMD have been reported (Murase and Akiyama, 2018; Harris et al., 2014; Ben-Chetrit et al., 2014; Drago et al., 2017). Since adult HFMD is widely seen as a mild self-limiting infection, its potential hazards have been underestimated.

This study was performed to systematically analyze the epidemiological characteristics of adult patients with HFMD. A total of 266 adult patients with HFMD were recruited into this study. Forty healthy volunteers served as the control group. The enteroviral strain was confirmed by laboratory testing. Demographic features, socio-economic and meteorological data, and clinical characteristics were collected. This study illustrated several unique spatiotemporal patterns of adult HFMD. All data were further analyzed according to the infecting enteroviral strain.

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The results of the study revealed the potential hazards of adult HFMD and serve as a reminder of the vital clinical significance of further research into adult HFMD.

Materials and methods

Ethics statement

This study was approved by the Ethics Committee of the First Affiliated Hospital of Jiaxing College (reference number 2014096). All individual-level data were anonymized. Written informed consent was obtained from all participants.

Study design

This study collected the demographic features, socio-economic data, and clinical characteristics of adult patients with HFMD, as well as meteorological data. Their correlations were evaluated and their associations with the enteroviral strain and inflammatory cytokines were analyzed. The purpose of this study was to elucidate the characteristics of adult HFMD and illustrate the potential hazards of adults acting as enterovirus reservoirs.

Case definition

Clinical criteria for the diagnosis of HFMD were published by the Chinese Ministry of Health in 2010 (Ministry of Health of the People's Republic of China, 2010). Patients with the following symptoms were defined as having HFMD: fever, oral ulcers, and a vesicular rash on the hands, feet, or buttocks.

Study population

The inclusion criteria for enrolment into this study were the following: (1) diagnosed as an HFMD case; (2) positive for enterovirus by laboratory testing; (3) adult patient defined as ≥16 years of age; (4) volunteered to provide a swab or serum sample; (5) could be tracked through follow-up telephone calls.

A total of 43 635 HFMD cases were diagnosed in Jiaxing from November 2014 to June 2018. Among these, 299 cases involved adult patients, of which 266 cases were identified as positive for enterovirus by laboratory testing. Thus, this study recruited 266 adult patients with HFMD. Forty healthy adults served as the control group. The socio-demographic data of the adult HFMD patients were collected through follow-up telephone calls.

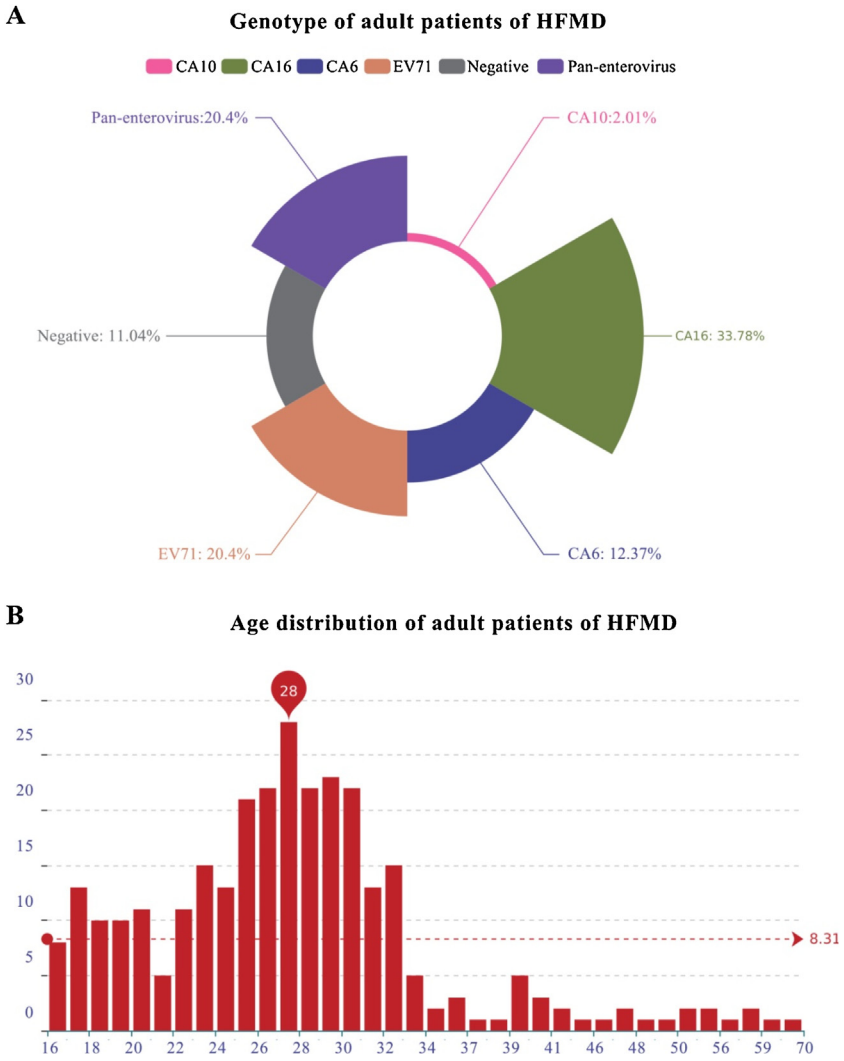

Figure 1. Adult hand, foot, and mouth disease (HFMD) morbidity according to enteroviral strain and age. (A) Distribution of adult HFMD patients by strain. The most prevalent enteroviral strain was CA16, followed by EV71, pan-enterovirus, CA6, negative, and CA10. (B) Age distribution of adult HFMD. Most of the adult patients with HFMD were younger than 34 years old; age 27 years had the maximum patient count.

Meteorological and socio-economic data

Meteorological factors investigated in this study included average temperature, maximum temperature, minimum temperature, and precipitation. Daily meteorological data were obtained from the China Meteorological Data Sharing Service System (http://data.cma.cn). Socio-economic data were collected from the Jiaxing Statistical Yearbook (http://www.jxstats.gov.cn) for the years 2014–2017.

Sample collection

Throat swab specimens were collected from all 266 adult HFMD patients by trained medical personnel. Serum samples were obtained from 60 of the adult HFMD patients. Plasma was obtained at 37 °C from ethylenediaminetetraacetic acid (EDTA)-anticoagulated serum samples. Samples were preserved at −80 °C.

Enterovirus strain

RNA was extracted from the specimens using TRIzol reagent (Invitrogen, CA, USA). The cDNA sample was synthesized using the PrimeScript RT kit (Takara, Dalian, China). One-step RT-PCR assays were performed to detect enterovirus RNA using EV71/CA16/pan-enterovirus commercial kits (the pan-enterovirus kit detects HFMD viruses excluding EV71, CA16, CA6, and CA10) and CA6/CA10 commercial kits (Da An Gene Co. Ltd, China).

Cytokine assays

The expression of cytokines was examined using the Bio-Plex Pro Human Cytokine 27-plex assay kit and Bio-Plex Pro Human Cytokine 23-plex assay kit (Bio-Rad Laboratories, CA, USA) according to the manufacturer's instructions. The data were processed with Bio-Plex Manager software version 6.0 (Bio-Rad Laboratories, CA, USA).

Correlation analysis

Correlations between cytokines and clinical characteristics were tested only for cytokines expressed differentially between HFMD patients and controls (p-value <0.05) using Spearman's Rho analysis (Best and Roberts, 1975).

Statistical analysis

Proportional data were analyzed using the Chi-square test or Fisher's exact test. Continuous data were tested by Student t-test. HFMD patients with different serotypes were compared using the Kruskal–Wallis non-parametric test. Data were pre-processed using Python 3.6 and statistical analyses were performed using R

Table 1
Socio-demographic characteristics of HFMD patients.

Socio-demographic characteristics	HFMD (n = 266)	Control (n = 40)	Chi-square	p-Value	OR (95% CI)
Sex			1.56	0.21	
Male	125	14			
Female	141	26			
Age (years)	27.5 ± 7.8	27.9 ± 3.6		0.65[a]	
Residence			2.31	0.13	
Urban	115	23			
Rural	151	17			
Occupation				0.06[b]	
Civil servant	17	2			
Farmer	36	2			
Household	62	11			
Medical staff	5	5			
Student	33	3			
Teacher	32	4			
Service	24	6			
Labour worker	57	7			
Education			0.51	0.48	
High school or below	185	25			
College	81	15			
Family size			4.08	0.04	2.10 (1.07–4.10)
≥4 persons	168	18			
<4 persons	98	22			
Per capita living space			0.07	0.79	
<10 m^2/person	69	9			
≥10 m^2/person	197	31			
Having child under 5 years old			6.93	<0.01	2.57 (1.31–5.04)
Yes	186	19			
No	80	21			
Having child diagnosed with HFMD			7.06	<0.01	3.76 (1.43–9.93)
Yes	93	5			
No	173	35			
Child with recurrent HFMD				0.34[b]	
Yes	12	0			
No	254	40			
Keeping pets			14.83	<0.01	0.24 (0.11–0.50)
Yes	103	29			
No	163	11			

HFMD, hand, foot, and mouth disease; OR, odds ratio; CI, confidence interval.
[a] Student t-test.
[b] Fisher's exact test.

3.5.1. Differences with a p-value of <0.05 were considered statistically significant.

Results

Demographic characteristics of the study participants

A total of 299 adult patients were identified from 47 383 reported HFMD cases from August 2014 to June 2018. Among these, 33 patients (11.04%) were negative for enterovirus by laboratory testing. The most prevalent enterovirus strain was CA16 (33.78%, 101/299), followed by EV71 (20.4%, 61/299), pan-enterovirus (20.4%, 61/299), CA6 (12.37%, 37/299), and CA10 (2.01%, 6/299) (Figure 1A). Thus, 266 adult patients were recruited according to the study inclusion criteria.

The 266 patients ranged in age from 16 to 70 years (mean 27.5 ± 7.8 years) (Figure 1B). Female patients outnumbered male patients, with a female to male ratio of 1.13:1. Most of the adult patients were housewives or labour workers who lived in a rural area (Table 1).

This study found several epidemiological characteristics that differed significantly between adult HFMD patients and controls, including family size ($p = 0.04$), having a child under 5 years old ($p < 0.01$), having a child diagnosed with HFMD ($p < 0.01$), and keeping pets ($p < 0.01$) (Table 1). A comparison of these epidemiological characteristics between enteroviral strains identified keeping pets to differ significantly between strains ($p = 0.01$) (Table 2).

Seasonality of adult HFMD epidemics

In this study, adult HFMD was found to be prevalent throughout the year, presenting a distinct two-peak pattern (Figure 2A). The incidence rate of adult HFMD increased between May and August with a peak in July (53 patients). Another small epidemic wave of adult HFMD was observed from October to December.

Impact of meteorological factors on adult HFMD

Daily meteorological data were analyzed to determine the impact on morbidity associated with adult HFMD. This study found that a temperature between 12 °C and 27 °C was favourable for the epidemic of adult HFMD (Figure 2A). In agreement with previous studies (Wei et al., 2015; Cheng et al., 2014), the incidence rate of adult HFMD increased with the rising average temperature and dropped dramatically when the average temperature was higher than 27 °C. The morbidity of adult HFMD appeared to follow a weak relationship with the level of precipitation (Figure 2A). There were several peaks of precipitation in this study, which also corresponded to increases in morbidity associated with adult HFMD in June and October.

Temporal distribution of enteroviral strains

The predominant strain in adult HFMD cases was CA16, followed by EV-A71, pan-enterovirus, CA6, and CA10. The total incidence rate of adult HFMD fell in the year 2017 and increased dramatically in the year 2018 (Figure 2B). No pan-enterovirus-associated HFMD case was reported from August 2015 to August 2017. Although sporadic cases of CA6 occurred after August 2014, the epidemic of CA6-associated HFMD started in October 2016. This study included only six CA10-associated HFMD cases. CA10-associated adult HFMD was first reported in the year 2016 and more cases were observed in the year 2018.

Spatial pattern of adult HFMD

This study also analyzed the geographical distribution of adult patients with HFMD. The addresses of patients were displayed on a map with a heat map representing the density of adult HFMD patients. Most of the adult HFMD cases resided in one district (Nanhu) and no case was reported in the district of Haining (Figure 3A). This study further analyzed the geographical distribution of the various enterovirus strains (Figure 3B–E). The results presented a similar spatial pattern to the epidemic, with the various enteroviruses mainly occurring in the district of Nanhu.

The socio-economic data were also reflected on the map. The similarity between the population density (Figure 3F) and morbidity of adult HFMD (Figure 3A–E) was remarkable. The area with the highest population density (Nanhu District) had the highest morbidity of adult HFMD. Interestingly, no adult HFMD case was reported in Haining District, which had the highest GDP (Figure 3G).

Migration status of adult patients with HFMD

This study collected mobile telephone numbers and identity card numbers from the adult patients with HFMD. Their original addresses were extracted from the mobile numbers and identity card numbers. Migration patients were defined as those whose original addresses were not located in Jiaxing. It was found that 21.8% (58/266) of the study subjects were migration patients and most of them had come from eastern or southern China (Figure 4A). Of note, the migration path was highly matched with the distribution of HFMD morbidity in China (Figure 4). Almost all the migration patients had come from areas with a high incidence rate of HFMD.

Table 2
Socio-demographic characteristics according to enteroviral strain.

Socio-demographic characteristics	EV71 ($n = 61$)	CA16 ($n = 101$)	CA6 ($n = 37$)	CA10 ($n = 6$)	Pan[a] ($n = 61$)	p-Value
Family size						0.74
≥4 persons	38	63	21	5	41	
<4 persons	23	38	16	1	20	
Having child under 5 years old						0.16
Yes	37	72	24	4	49	
No	24	29	13	2	12	
Having child diagnosed with HFMD						0.76
Yes	23	34	11	1	24	
No	38	67	26	5	37	
Keeping pets						0.01
Yes	22	48	6	3	24	
No	39	53	31	3	37	

HFMD, hand, foot, and mouth disease; EV, enterovirus; CA, coxsackie virus.
[a] Pan-enterovirus.

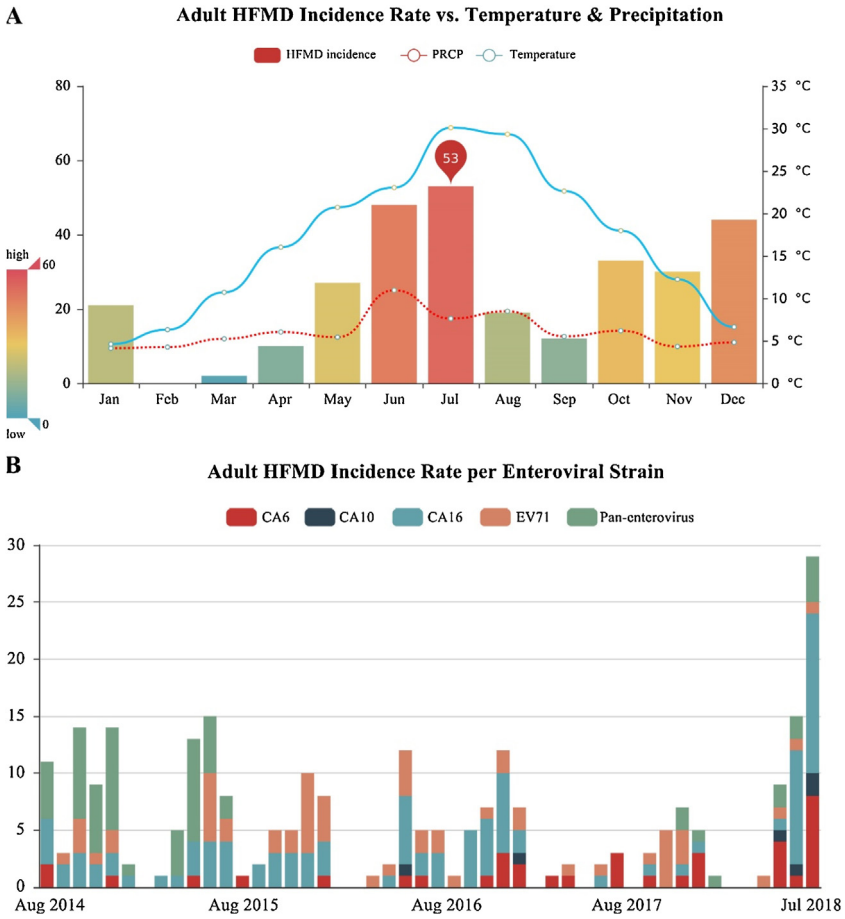

Figure 2. Incidence rate of adult hand, foot, and mouth disease (HFMD) and factors impacting the rate. (A) Relationship between the incidence rate and meteorological factors. The temperature favouring the spread of enterovirus was 12 °C to 27 °C. The incidence rate of adult HFMD increased with the average temperature and fell at 27 °C. The incidence rate also increased with increasing precipitation. (B) Distribution of the incidence rate according to the enteroviral strain from August 2014 to June 2018. CA6-associated HFMD cases increased starting in the year 2016.

Clinical characteristics of adult HFMD

This study compared the severity of illness of adult patients with the various enteroviral strains (Table 3). No severe case was reported in this study. Most of the patients presented mild symptoms (98.1%, 261/266). There was a significant difference in the severity of the illness in adult patients according to the strain ($p = 0.02$). No hospitalized patient had strains CA16, CA10, or pan-enterovirus. Notably, the rate of admission to the hospital was significantly higher for CA6-associated HFMD than for HFMD caused by the other strains.

This study also examined the clinical characteristics of the adult patients with the various enteroviral strains (Table 4). There was no statistically significant difference in most of the clinical characteristics between the enteroviral strains (white blood cell count, creatine kinase-muscle/brain, lactate dehydrogenase, alanine aminotransferase, aspartate aminotransferase, C-reactive protein, glucose, peak temperature, and fever) ($p > 0.05$). However, the results showed a significant difference in the incidence of rash ($p = 0.04$) and oral ulcers ($p = 0.02$) between enteroviral strains. Consistent with previous reports (Bian et al., 2015), most of the adult patients infected with enterovirus CA6 presented with a rash and oral ulcers. All of the CA10-associated HFMD patients presented with oral ulcers.

Correlation between cytokine expression and enteroviral strain

Previous studies have shown that the pathogenesis and progression of HFMD are related to elevated levels of cytokines (Zeng et al., 2013; Lin et al., 2002). Thus, this study tried to identify the association between cytokine expression and the infecting enteroviral strain in these adult patients. A total of 50 cytokines were examined in this study. Since the study only recruited six patients with CA10-associated HFMD, CA10 was excluded from the correlation analysis. The results showed that each enteroviral strain presented a unique pattern of correlation with cytokine expression (Figure 5).

Risk factors for adult HFMD

Epidemiological characteristics of participants were analyzed by single-factor analysis ($\alpha = 0.1$) to determine the risk factors for adult HFMD (Table 1). When compared with the controls, single-factor analysis showed that a family size of ≥ 4 (odds ratio (OR) 2.10, 95% confidence interval (CI) 1.07–4.10), having a child under 5 years old (OR 2.57, 95% CI 1.31–5.04), and having a child recently diagnosed with HFMD (OR 3.76, 95% CI 1.43–9.93) were risk factors for adult HFMD. Interestingly, this study revealed that keeping pets was a protective factor for adult HFMD (OR 0.24, 95% CI 0.11–0.50).

The results of the single-factor analysis were further examined by unconditional logistic regression analysis (likelihood ratio test) (Table 5). The results confirmed that having a child recently diagnosed with HFMD (OR 3.31, 95% CI 1.22–19.66) was a risk factor for adult HFMD, whereas keeping pets (OR 0.25, 95% CI 0.11–0.56) was a protective factor against HFMD.

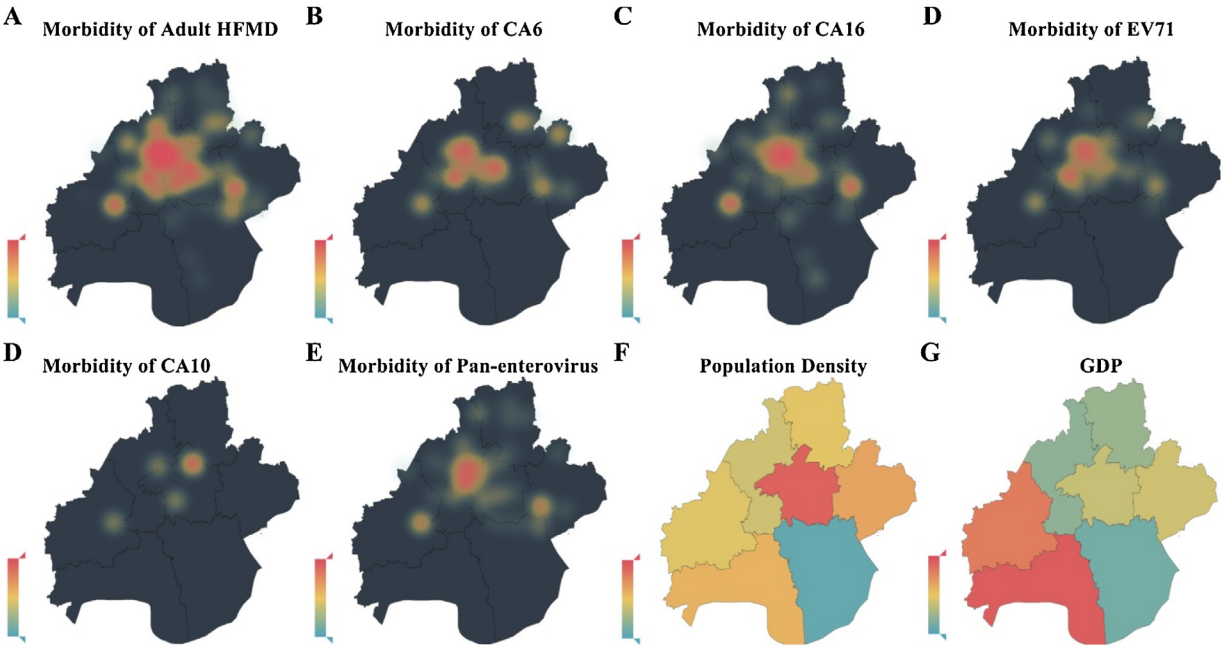

Figure 3. Spatial distribution of adult hand, foot, and mouth disease (HFMD) morbidity. (A) Overall morbidity distribution of adult HFMD. The incidence rate of adult HFMD was clearly higher in several areas compared with others. (B)–(E) Morbidity of enterovirus CA6, CA16, EV71, CA10, and pan-enterovirus, respectively. The spatial distribution of the various enteroviruses differed, although they shared a common pattern, with a majority of the adult patients located in particular areas. (F) Population density of Jiaxing. The distribution of adult patients was highly similar to the population density, indicating that a high population density may be a risk factor. (G) GDP distribution of Jiaxing. There was no adult HFMD case reported in the area with the highest GDP.

Discussion

Adult HFMD is generally seen as a sporadic mild viral infection that spontaneously resolves in a short time (Murase and Akiyama, 2018; Harris et al., 2014; Ben-Chetrit et al., 2014; Drago et al., 2017). However, this study revealed the potential epidemic hazard of adult HFMD. Among the adult patients with HFMD, females outnumbered males, with a female to male ratio of 1.13:1, and most of them were housewives (62/266), students (33/266), or teachers (32/266). Of the 266 adult patients with HFMD, 186 had a child under 5 years of age, 93 had a child who had been diagnosed with HFMD in the family, and 12 had a child who had been diagnosed with recurrent HFMD. These findings suggest that adult patients who have close contact with children become a latent infectious source of HFMD.

Consistent with previous reports, this study showed CA16 and EV71 to be the major causative agents of adult HFMD, followed by pan-enterovirus, CA6, and CA10 (Gao et al., 2018; Hyeon et al., 2013). Previous studies have reported that EV71 may cause severe symptoms, and CA6-associated HFMD has become more prevalent in recent years (Solomon et al., 2010; Ooi et al., 2010; Chong et al., 2015; Anh et al., 2018; Fujimoto et al., 2012). The present study examined the temporal distribution of adult HFMD caused by various enteroviral strains. It was found that the morbidity of adult HFMD fell in the year 2017 and increased dramatically in the year 2018. This study also demonstrated that the incidence rate of CA6-associated adult HFMD increased starting in the year 2016. This finding is in accordance with that of a previous study, which reported CA6 as having high morbidity in adults (Bian et al., 2015). Together, these findings serve as a warning of the difficult situation in HFMD prevention.

This study showed the seasonality characteristics of adult HFMD epidemics. The incidence rate of adult HFMD presented two peaks, a large one from May to August and a small one from October to December. Previous studies have shown that the activities and spread of enterovirus are associated with meteorological factors, such as temperature and humidity (Wei et al., 2015; Cheng et al., 2014). The present study analyzed the impact of meteorological factors on the morbidity of adult HFMD. The results indicated that warmth and high humidity may be the conditions favouring the activities and spread of enterovirus. The weather in Jiaxing is generally warm and rainy from May to June and the temperature is generally very high in July and August. Prior studies have reported that HFMD morbidity lags 1 week behind the change in temperature and humidity (Huang et al., 2013; Chen et al., 2014). This would explain the first peak in the incidence rate that occurred in July. Similarly, this could explain the other small epidemic wave in October and November as well. Unfortunately, this could not explain the elevated adult HFMD morbidity in December, which requires further study.

This study compared the geographical distribution of adult HFMD caused by various enteroviruses. The results clearly demonstrated that the epidemics of adult HFMD were positively correlated with the population density and negatively correlated with economic growth. High population density increases the risk of contagion, whereas economic development might improve hygiene conditions, thereby eliminating the potential spread of enterovirus. By comparing the original address and the current address of the patients, it was found that many of these adult patients had migrated from areas with a high incidence rate of HFMD. This finding suggests that adults may act as the main infectious source of trans-regional spread of HFMD.

No participants in this study had severe complications. Most of the patients presented mild symptoms and the prognosis was generally good. These findings imply the possibility of a large number of subclinical carriers of enterovirus or patients with mild symptoms who would not visit the hospital. Remarkably, this study found that the admission rate for CA6-associated HFMD was significantly higher than that for the other strains. This observation is in agreement with those of previous studies that have shown CA6-associated HFMD to have become more prevalent in recent years and to have high morbidity in adults (Gao et al., 2018; Bian

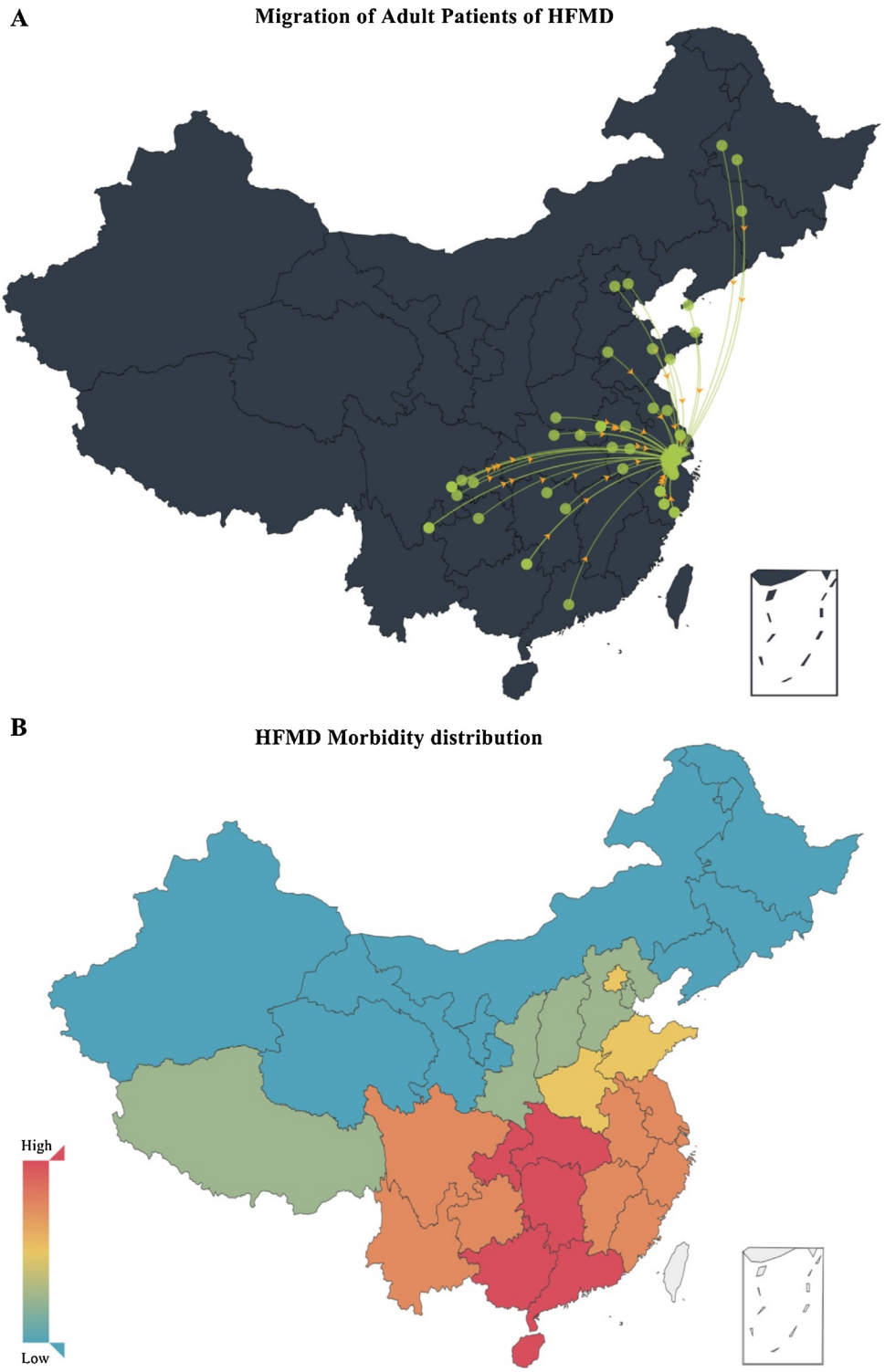

Figure 4. Adult patients may cause the trans-regional spread of hand, foot, and mouth disease (HFMD). (A) Migration of adult patients with HFMD. Most of the adult patients with HFMD had come from eastern and southern China. (B) Morbidity distribution of HFMD in China. Eastern and southern China had a high incidence rate of HFMD.

et al., 2015). By examining the clinical characteristics of adult patients with various enteroviral strains, this study revealed that CA6-associated HFMD presents atypical clinical features. Consistent with previous reports, most of the CA6-associated HFMD patients had a rash over the face, neck, or trunk (Bian et al., 2015). Thus, a clinician might misdiagnose CA6-associated HFMD as another exanthema illness. In summary, the findings mentioned above suggest the existence of subclinical carriers or misdiagnosed patients who might be the latent infectious source of HFMD.

Cytokines are important in the occurrence, development, and prevalence of infectious disease (Hotamisligil, 2017; Strowig et al., 2012; Rathinam and Fitzgerald, 2016; Lamkanfi and Dixit, 2014). This study showed that each enteroviral strain presented a unique pattern of correlation with cytokine expression. Cytokine

Table 3
Severity of disease in adult patients with HFMD.[a]

Severity	EV71 ($n=61$)	CA16 ($n=101$)	CA6 ($n=37$)	CA10 ($n=6$)	Pan[b] ($n=61$)	p-Value
Mild	59	101	34	6	61	0.02
Hospitalized	2	0	3	0	0	

HFMD, hand, foot, and mouth disease.
[a] No severe case was found in this study.
[b] Pan-enterovirus.

Table 4
Clinical characteristics of adult patients of HFMD.

Clinical characteristics	EV71 ($n=61$)	CA16 ($n=101$)	CA6 ($n=37$)	CA10 ($n=6$)	Pan[a] ($n=61$)	p-Value[b]
WBC (10^9/l)	6.57 ± 1.17	6.55 ± 1.05	6.68 ± 1.06	6.81 ± 1.12	6.28 ± 1.08	0.37
CK-MB (IU/l)	19.50 ± 6.37	18.61 ± 6.16	18.56 ± 5.78	18.79 ± 5.36	19.34 ± 5.50	0.86
LDH (U/l)	197.63 ± 35.13	194.26 ± 32.04	194.67 ± 29.51	206.92 ± 28.97	185.08 ± 31.12	0.18
ALT (IU/l)	34.99 ± 5.92	35.58 ± 5.98	35.61 ± 5.84	31.75 ± 7.79	34.53 ± 5.99	0.58
AST (IU/l)	25.54 ± 3.77	26.09 ± 3.51	27.03 ± 3.73	28.41 ± 4.59	25.62 ± 3.99	0.16
CRP (mg/l)	27.60 ± 5.96	28.21 ± 6.25	27.68 ± 6.13	28.29 ± 4.54	28.73 ± 6.13	0.92
GLU (mmol/l)	5.06 ± 0.59	4.98 ± 0.61	4.97 ± 0.58	4.79 ± 0.46	4.97 ± 0.63	0.84
Temperature (°C)	37.51 ± 0.44	37.46 ± 0.64	37.35 ± 0.50	37.46 ± 0.56	37.37 ± 0.45	0.42
Fever (%)	19.7	30.7	16.2	0	16.4	0.09
Rash (%)	73.8	88.1	91.9	66.7	77.0	0.04
Oral ulcer (%)	83.6	69.3	91.9	100	72.1	0.02

HFMD, hand, foot, and mouth disease; EV, enterovirus; CA, coxsackievirus; WBC, white blood cell count; CK-MB, creatine kinase-muscle/brain; LDH, lactate dehydrogenase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; GLU, glucose.
[a] Pan-enterovirus.
[b] Kruskal–Wallis non-parametric test.

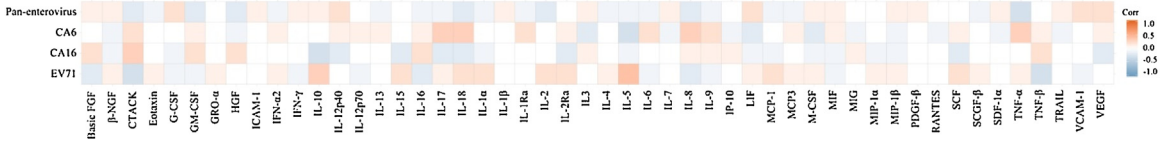

Figure 5. Correlation between enterovirus strains and cytokines. Each enterovirus strain presented a distinct correlation pattern with cytokines, indicating that the cytokine profiles may be used to classify the strain.

Table 5
Risk factors for adult HFMD (logistic regression analysis).

Socio-demographic characteristics	β	p-Value	OR (95% CI)
Family size ≥4 persons	0.13	0.78	1.14 (0.43–2.97)
Having child under 5 years old	−0.04	0.93	0.95 (0.35–2.64)
Having child diagnosed with HFMD	1.20	0.03	3.31 (1.22–19.66)
Keeping pets	−1.37	<0.01	0.25 (0.11–0.56)

HFMD, hand, foot, and mouth disease; OR, odds ratio; CI, confidence interval.

expression might indicate that various enteroviruses could cause a different immune response in the host upon infection. The results revealed that cytokines have the potential to identify enteroviral infection effectively. Cytokines plus machine-learning might help eliminate misdiagnosis in the clinic, but this needs further study. This finding suggests that a combination of cytokines may act as a marker for the differential diagnosis of HFMD caused by the various enteroviral strains.

Finally, this study indicated that having a child recently diagnosed with HFMD is a risk factor for adult HFMD. Having a child HFMD patient in the family would increase the risk of contagion. Considering that a majority of the participants in this study were housewives and teachers, this in turn also raises the possibility of the spread of enterovirus to other children. Intriguingly, the study identified keeping pets as a protective factor for HFMD. Numerous studies have shown that keeping pets increases the diversity and abundance of the gut microbiota, which may act as a protective barrier against bacterial and viral infection (Gupta, 2017; Lax et al., 2014; Song et al., 2013). Moreover, it was found that the protective effects of keeping pets were more obvious in CA6-associated HFMD than in HFMD caused by the other three enteroviruses. It is speculated that there is a particular gut microbe in CA6-associated HFMD patients that causes the difference. In this study, the protective effect of keeping pets might be the result of a healthy gut microbiome, although this requires further study.

In conclusion, this study collected the epidemiological features and socio-economic data of adult patients with HFMD and associated these with the clinical characteristics and strain. The results illustrated the potential hazards of adult HFMD. This study suggests the existence of subclinical carriers or misdiagnosed patients who might be the latent infectious source of HFMD. Further, this study also indicates that adults may act as the main infectious source of trans-regional spread of HFMD. Adult HFMD should gain greater importance for research in order to better control the HFMD epidemic.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Linghua Yu participated in the design, data analysis and interpretation, and drafted the manuscript. Jin He, Linlin Wang, and Huixing Yi participated in the interpretation of data and helped to finalize the manuscript.

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