Factors related to the mortality risk of severe hand, foot, and mouth diseases (HFMD)：a 5-year hospital-based survey in Guangxi, Southern China

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Research Article

Keywords: Hand, foot, and mouth disease; Severe cases; Outcome; Influencing factors; EV-A71 vaccination

Posted Date: August 29th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1974794/v1

Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at BMC Infectious Diseases on March 8th, 2023. See the published version at https://doi.org/10.1186/s12879-023-08109-y.

Abstract

Background: To understand the factors influencing clinical outcomes of severe hand, foot, and mouth diseases (HFMD), and to provide scientific evidence for reducing the mortality risk of severe HFMD.

Methods: From 2014 to 2018, children diagnosed with severe HFMD cases in Guangxi, China, were enrolled in this hospital-based study. The epidemiological data obtained through face-to-face interviews with the parents and guardians. Univariate and multivariate logistics regression models were used to analyze the factors influencing the clinical outcomes of severe HFMD. Survival analysis was performed by the Kaplan-Meier method. The impact of the EV-A71 vaccination on inpatient mortality was analyzed by a comparison approach. Stratified analysis and propensity score matching (PSM) analysis were performed to eliminate the influence of potential confounding factors.

Results: A total of 1,565 severe HFMD cases were enrolled in this survey, including 1474 (94.19%) survival cases and 91 (5.81%) death cases. The multivariate logistic analysis demonstrated that males, HFMD history of playmates in the last three months, first visit to the village hospital, time from the first visit to admission less than two days, critical illness, and having no rash symptoms were the independent risk factors for severe HFMD cases (all $P<0.05$). While EV-A71 vaccination was a protective factor ($P<0.05$). Stratified analysis and Kaplan-Meier survival analysis further confirmed the result of the multivariate regression. The 1:1 PSM of the EV-A71 vaccination group versus the non-vaccination group showed 2.34% of death in the vaccination group and 7.01% of death in the non- vaccination group. The EV-A71 vaccination protected 66.62% of the death of severe HFMD cases, with an effective index of 3.00.

Conclusions: The mortality risk of severe HFMD in Guangxi was related to gender, hospital grade, clinical severity at admission, EV-A71 vaccination, and rash symptom. EV-A71 vaccination can significantly reduce mortality among severe HFMD. The findings are of great significance for the effective prevention and control of HFMD in Guangxi, southern China.

Background

Hand, foot, and mouth disease (HFMD) is an acute contagious disease caused by human enteroviruses (EVs), which mostly affects children under five years old. The transmission of HFMD is mainly through direct contact with saliva, faces, vesicular fluid, respiratory droplets of the infected individual, or indirect contact with contaminated objects. Generally, HFMD is a self-limited disease. However, some patients may also develop neurologic complications such as neurogenic pulmonary edema, aseptic meningitis, acute flaccid paralysis, and encephalitis, and even die [1]. Guangxi Zhuang Autonomous Region, located in Southern China, is one of the worst-hit provinces for HFMD. The average morbidity and mortality have consistently ranked first among all provinces in mainland China over the decade. There were about 9,000 severe HFMD cases in Guangxi from 2012 to 2015 [3]. In recent years, the severe cases and fatal cases were on the rise, hundreds of cases with central nervous system complications were emerged, resulting in nearly 100 deaths. This poses a serious public health challenge for local health systems[2–3]. In addition to a higher risk of death, severe HFMD patients have sequelae such as dysfunctional aerodigestive tract, neurological sequelae, delayed neurodevelopment, impaired

cognition even after treatment[4]. The sequelae can greatly reduce the life quality of the patients, increase the burden on families, and cause over-expenditure on the social economy. Enterovirus A71 (EV-A71) was the dominant etiological agent of severe HFMD in Southern China. Since 2016, Guangxi has launched a universal vaccination campaign against EV-A71 for children under five years old. As of December 31, 2019, EV-A71 vaccination cumulative coverage in Guangxi was 32.8%, and 27.3% of children under five years of age had completed the 2-dose vaccination, and the proportion of HFMD cases aged 0–12 months decreased from 23.0–15.3% between 2013–2015 and 2017–2019[5].To the best of our knowledge, few studies have assessed the impact and effectiveness of the vaccination in reducing mortality of HFMD hospitalized patients in real-world settings. Therefore, the aim of this study was to analyze the influencing factors of clinical outcomes of severe HFMD cases in southern China, and to further evaluate the effect of the monovalent inactivated EV-A71 vaccination as a protective factor in reducing mortality.

Methods

Study design and study population

A hospital-based epidemiological survey was conducted in Guangxi, a province in southern China where HFMD is prevalent. Cases of severe HFMD from 2014 to 2018 were collected from Guangxi Zhuang Autonomous Region Center for Disease Prevention and Control (CDC) system. The definition of severe HFMD was referred to the “diagnosis and treatment guidelines for HFMD” (2010)”[6], and the diagnosis criteria are as follow: (1) frequent convulsions, coma and cerebral hernia; (2) breathing difficulties, cyanosis, bloody frothy sputum and pulmonary rales; and (3) shock and circulatory insufficiency. In our study, subjects were included if : 1) Severe HFMD case: A severe case was defined as a clinical case with any central nervous system (CNS) complications, cardiopulmonary dysfunction, or both [7]. 2) Patient’s parents approved of participation; 3) Individuals with completed investigation data. Subjects were excluded if: 1) The neurological dysfunction was caused by non-HFMD; 2) Patients with incomplete investigation data. All participants understood the purpose of the study and signed the informed consent forms. Investigation was performed in accordance with the relevant guidelines and regulations.

Data Collection

Detailed clinical data of the severe HFMD patients were collected by reviewing the medical records. Socio-demographic characteristics of the patients were collected via face-to-face interviews with patients and guardians using a structured questionnaire [8]. The collected information included demographic characteristics (gender, age, EV-A71 vaccination, the patient was hospitalized for other reasons previously, HFMD history of patient’s daily playmates prior to the onset of the current illness, etc), disease characteristics, diagnosis, and treatment (date of the illness onset, first diagnosis and admission, severe HFMD diagnosis, clinical severity at admission, hospital grade of initial and severe HFMD diagnosis, rash symptoms, etc).

Definitions

(1) Vaccine protection against death. The percentage of death among vaccinated patients was protected compared with that among unvaccinated patients. The following formula was used to calculate the vaccine protection against death:

$$\mathrm{Vaccineprotectionagainstdeath} = \frac{(\mathrm{ratioofdeathsintheunvaccinatedgroup} - \mathrm{ratioofdeathsinthevaccinatedgroup})}{\mathrm{ratioofdeathsintheunvaccinatedgroup}}$$

(2) Index of effectiveness against death. It is defined as the number of death in the unvaccinated group divided by the number of deaths in the vaccinated group.

Statistical Analyses

All statistical analyses were performed using R software (version 4.04) and IBM SPSS Statistics (version 26). Univariate and multivariate logistics regression models were used to analyze the factors influencing the clinical outcomes of severe HFMD. The influencing factors of clinical outcomes of severe HFMD cases were firstly analyzed by the univariate analysis, and then the variables with differences ($P < 0.1$) were included in the multivariate logistic regression model. The OR and 95%CI were compared between the survival group and the death groups. All the comparisons were two-sided, and the P-value of < 0.05 was considered significant. Kaplan-Meier analysis with log-rank test was applied for survival analysis. Because most severe HFMD patients recovered within one week after treatment, and the duration of hospitalization was inconsistent. Therefore, in the study, the date of patients' first admission was taken as the start time of follow-up, and the time of longest hospitalization was taken as the end time of follow-up. In addition, a 1:1 ratio propensity score matching (PSM) analysis was applied to match socio-demographic characteristics such as gender, age, residence, etc. between vaccinated and unvaccinated groups to eliminate the influence of confounding factors.

Results

Demographics Characteristics

As shown in Table 1, a total of 1565 patients with severe HFMD were enrolled in this study, including 998 males (63.77%) and 567 females (36.23%), with a male-to-female ratio of 1.76:1. The median age of the patients was 1.83 years old (0- 11.69 years). Severe HFMD occurred mainly in children under 3 years old (80.57%). There were 1288 severe HFMD cases in rural areas, accounting for 82.30%, and the ratio of rural to urban was 4.75:1. Among all 1565 severe HFMD cases, 91 cases died (5.81%, 91/1565). Univariate analysis indicated that, between the survival group and death group, there was no significant difference in the distribution of gender, age, area, registered residence, group classification, etc. (Table 1) (all $P > 0.05$). While there was a significant difference ($P < 0.05$) in EV-A71 vaccination, visiting hospital previously, HFMD history of playmates in the last 3 months, hospital grade of first visit, correct diagnosis at first visit, time interval from first visit to diagnosis of severe HFMD, clinical severity at admission and rash symptoms (Table 1).

Table 1
Epidemiological characteristics of severe HFMD cases in Guangxi, 2014–2018, grouped by survival and death.

Characteristics	Total n	Survival n (%)	Death n (%)	χ^2	*P*
Gender					
male	998	948(94.99)	50(5.01)	3.257	0.071
female	567	526(92.77)	41(7.23)		
Age(years)					
0–1 years	160	144(90.00)	16(10.00)	7.355	0.061
1–2 years	687	656(95.49)	31(4.51)		
2–3 years	414	389(93.96)	25(6.04)		
3 years or older	298	280(93.96)	18(6.04)		
Area					
urban	271	256(94.46)	15(5.54)		
rural	1 288	1 213(94.18)	75(5.82)	0.034	0.853
Registered residence					
long-term	1 527	1 441(94.37)	86(5.63)		
migrant	30	27(90.00)	3(10.00)	1.042	0.307
Group classification					
kindergarten children	204	193(94.61)	11(5.39)	0.339	0.896
scattered children	1 341	1 263(94.18)	78(5.82)		
school student	15	14(93.33)	1(6.67)		
No. of children 0–5 years old in the family					
≤ 1	678	638(94.10)	40(5.90)		
2–3	555	525(94.59)	30(5.41)		
≥ 4	125	120(96.00)	5(4.00)	0.755	0.686
Milk feeding way					
breast milk	1 151	1 090(94.70)	61(5.30)	0.484	0.785
milk powder	84	81(96.43)	3(3.57)		
mix feeding	296	281(94.93)	15(5.07)		
EV-A71 vaccination					
yes	628	614(97.77)	14(2.23)		
no	925	858(92.76)	67(7.24)	19.021	< 0.001
Visiting hospital previously					
yes	38	33(86.84)	5(13.16)		
no	1 514	1 430(94.45)	84(5.55)	3.971	0.046
HFMD history of playmates in the last 3 months					

Characteristics	Total n	Survival n (%)	Death n (%)	χ^2	*P*
yes	231	208(90.04)	23(9.96)		
no	1 318	1 253(95.07)	65(4.93)	9.262	0.002
History of chicken pox, eczema, etc. in the last month					
yes	115	112(97.39)	3(2.61)		
no	1 433	1 349(94.14)	84(5.86)	2.124	0.145
Time interval from disease onset to first visit to hospital					
≤ 1 day	1321	1245(94.27)	76(5.75)	0.806	0.668
1–2 days	134	127(94.78)	7(5.22)		
≥ 3 days	103	95(92.23)	8(7.77)		
Hospital grade of first visit					
village	429	390(90.91)	39(9.09)	18.444	< 0.001
township	211	195(92.42)	16(7.58)		
county	573	546(95.29)	27(4.71)		
city	341	333(97.65)	8(2.35)		
Correct diagnosis at first visit					
yes	1066	1024(96.06)	42(3.94)		
no	490	442(90.20)	48(9.80)	21.124	< 0.001
Time interval from first visit to diagnosis of severe HFMD					
≤ 1 day	740	691(93.38)	49(6.62)	6.909	0.032
1–2 days	361	336(93.07)	25(6.93)		
≥ 3 days	452	437(96.68)	15(3.32)		
Hospital grade of severe HFMD diagnosis					
county grade or below	607	566	41	1.947	0.163
city grade	947	899	48		
Time interval from first visit to admission					
≤ 1day	882	829(93.99)	53(6.01)	0.947	0.623
1-2days	328	307(93.60)	21(6.40)		
≥ 3days	336	320(95.24)	16(4.76)		
Clinical severity at admission					
mild	316	300(94.94)	16(5.06)		
severe	1137	1094(96.22)	43(3.79)		
critical	92	61(66.30)	31(33.70)	139.253	< 0.001
Fever					
yes	1514	1428(94.32)	86(5.68)	0.252	0.616

Characteristics	Total n	Survival n (%)	Death n (%)	χ^2	*P*
no	47	43(91.49)	4(8.51)		
Rash symptoms					
yes	1517	1434(94.53)	83(5.47)	13.266	< 0.001
no	31	24(77.42)	7(22.58)		

Multivariate Logistic Analysis

To further determine the factors influencing the clinical outcomes of severe HFMD, multivariate logistics regression analysis was performed, and the variables with differences ($P < 0.1$) in univariate analysis (Table 1) were included in the multivariate logistic regression model. The status (survival and death) at the end of the follow-up was set as the outcome variable (survival = 0, death = 1). Among the independence variables, we set female, no HFMD history of playmates in last 3 months, EV-A71 vaccination, no history of chicken pox, eczema, etc. in last month, first visit to the city hospital, time interval from first visit to diagnosis of severe HFMD ≥ 3days, mild HFMD, having rash symptoms as the reference, respectively, to calculate internal OR values (Table 2). The multivariate logistics regression analysis showed that male (OR: 2.074, 95%CI: 1.154–3.726), playmates had HFMD history in last 3 months (OR: 2.327, 95%CI: 1.164–4.652), no EV-A71 vaccination (OR: 5.373, 95%CI: 2.590-11.145), first visit to village hospital (OR: 9.883, 95%CI: 3.408–28.659), time interval from first visit to diagnosis of severe HFMD ≤ 1day (OR: 5.249, 95%CI: 2.242–12.288) or 1–2 days (OR: 3.131, 95%CI: 1.295–7.570), critical clinical severity at admission (OR: 16.380, 95%CI: 6.095–44.503), having no rash symptoms (OR: 6.802, 95%CI: 1.873–24.702) were the promoting factors for death risk among severe HFMD cases (Table 2).

Table 2
Multivariate logistic analysis of potential risk factors for death in severe HFMD patients

Characteristics	Total(n)	β	SE	Wald χ^2	*P*	OR	95% CI
Gender							
male	791	0.729	0.299	5.952	0.015	2.074	1.154–3.726
female	444					1	
HFMD history of playmates in last 3 months							
yes	183	0.845	0.353	5.711	0.017	2.327	1.164–4.652
no	1052					1	
EV-A71 vaccination							
yes	548					1	
no	687	1.681	0.372	20.398	0.000	5.373	2.590-11.145
History of chicken pox, eczema, etc. in last month							
yes	102	-1.292	0.668	3.738	0.053	0.275	0.074–1.018
no	1133					1	
Hospital grade of first visit							
village	378	2.291	0.543	17.784	< 0.001	9.883	3.408–28.659
township	167	1.203	0.614	3.839	0.050	3.332	1.000-11.104
county	418	0.955	0.545	3.068	0.080	2.598	0.893–7.563
city	272					1	
Time interval from first visit to diagnosis of severe HFMD							
≤ 1day	577	1.658	0.434	14.597	< 0.001	5.249	2.242–12.288
1-2days	297	1.141	0.450	6.419	0.011	3.131	1.295–7.570
≥ 3days	361					1	
Clinical severity at admission							
mild	271					1	
severe	889	0.091	0.440	0.043	0.837	1.095	0.462–2.595
critical	75	2.796	0.505	30.716	0.000	16.380	6.095–44.053
Rash symptoms							
yes	1211					1	
no	244	1.917	0.658	8.489	0.004	6.802	1.873–24.702

Note: OR odds ratio, CI confidence interval, HFMD hand, foot and mouth disease, EV-A71 enterovirus A71

Survival Hazard Risk Among Different Stratifications Of Severe Hfmd Cases

Since several factors have been identified as influencing factors for death risk among severe HFMD cases, including time interval from the first visit to diagnosis of severe HFMD, hospital grade of first visit, rash symptoms, etc. (Table 2), we further analyzed the impact of these factors on survival rate using stratified analysis. During the follow-up, 91 deaths were recorded. We found that the survivals changed mainly in the first ten days after the admission and remained stable thereafter (Fig. 1A-D). The survival rates of severe HFMD cases decreased from city hospitals, county hospitals, township health service centers to village health service centers (Fig. 1A). The survival rates of city hospitals and county hospitals were significantly higher than those of township and village health service centers ($P = 0.0017$) (Fig. 1A). Compared with the mild and severe patients, the survival rate of critical patients decreased rapidly to 30% in the first 7 days after admission, and there was a significant difference between the critical and the other groups ($P < 0.001$) (Fig. 1B). Consistent with the results of multivariate logistic analysis, the shorter time from the first visit to diagnosis of severe HFMD, the higher risk of death (Fig. 1C). Nevertheless, high survival rates (> 75%) were observed among all the stratifications, although significant difference were observed between different stratifications ($P = 0.00068$) (Fig. 1C). In addition, the survival rate in patients without rash symptoms decreased to 30% on the 9th day after admission, whereas the survival rate in patients with rash symptoms remained above 85% ($P = 0.00011$) (Fig. 1D). Overall, the results of the Kaplan-Meier survival analysis with different stratifications were consistent with those of the multivariate logistic regression analysis.

Psm Analysis Of Impact Of Ev-a71 Vaccination On Death In Severe Hfmd Patients

To investigate the impact of inactivated monovalent EV-A71 vaccination on death in severe HFMD patients, a 1:1 PSM of the vaccinated and unvaccinated groups was performed to eliminate the influence of potential confounding factors. A total of 942 severe HFMD cases were successfully matched, including 471 cases in the vaccinated group and 471 cases in the unvaccinated group. The matching results showed that PSM scores in the two groups were consistent, and socio-demographic characteristics of the two groups were comparable (caliper value was 0.01, supplementary 1). The PSM analysis indicated that 2.34% of the patients died in the vaccinated group and 7.01% in the unvaccinated group ($p < 0.01$). The inactivated monovalent EV-A71 vaccine can protect 66.62% of death among severe HFMD cases, and the effectiveness index against death was 3.00 (Table 3). In addition, we found that the survival rate had decreased to about 75 percent in the unvaccinated group, while it was maintained at above 90 percent in the vaccinated group; the difference was significant between the two groups ($P < 0.01$)(Fig. 2).

Table 3
PSM analysis of protective effect of EV-A71 vaccination on death of severe HFMD cases

	EV-A71 vaccination		protection rate(%)	effect index	χ^2	*P*
outcome	yes n(%)	no n(%)				
survival	460(97.66)	438(92.99)	66.62	3.00	11.539	0.001
death	11(2.34)	33(7.01)				

Discussion

HFMD has become a serious public health problem in the Asia-Pacific region due to the large number of severe and fatal cases in a short period, and has been listed as a mandatory notifiable infectious disease in mainland China in 2008[9–10]. Our study showed that the majority of severe and dead HFMD cases occurred in children under 3 years of age, which was consistent with the previous studies in Guangxi and other provinces in China[10–12]. Most severe HFMD cases occur in children under 3-year-old, possibly due to the poor immune system of the young children. There was a higher prevalence among males than in females, which may be related to boys' frequent exposure to enterovirus-contaminated environments or toys, where poor hygiene may increase the chance of infection[13–14]. However, our study showed that there was no significant difference in clinical outcomes among different gender groups (Table 1), suggesting that gender had little effect on the disease progression.

In this study, we found that children who lived in the rural areas were more likely to develop severe HFMD, which is in line with previous studies in Guangxi [15]. Previous studies have found that poor medical conditions and poor guardian awareness of HFMD treatment are the influencing factors for the development of severe HFMD and mortality in rural areas in China[16–18]. Meanwhile, rural patients are more willing to seek medical treatment nearby, which is a possible reason for the higher mortality of HFMD in rural areas. Rural village or township health service centers often do not have adequate conditions for HFMD diagnosis and treatment. Because some HFMD cases have hidden or asymptomatic symptoms in the early stage, the inadequate capacity of village or township health service centers for diagnosis and treatment may lead to prolonged and inappropriate treatment. In addition, due to the limitations of medical resources and economic conditions, the mortality of HFMD is high in some regions in China, especially in the underdeveloped Guangxi[19–20]. Given the fact that HFMD cases in Guangxi are most concentrated in rural areas, primary medical centers, including village and township health service centers, need to improve the ability of precision diagnosis and treatment, such as introducing new diagnostic technologies or instruments to make rapid and accurate diagnosis, so that HFMD patients can receive timely treatment.

Our study showed that severe HFMD without skin rash symptoms was a risk factor for death, which is consistent with other studies [21]. Skin rash is an obvious physical sign that may prompt the guardians to take their children to see the doctor, so the patients with skin rash may have more chances to meet the doctor and get timely treatment. On the other hand, HMFD patients without skin rash or other clinical symptoms may miss opportunity to visit the hospital because the guardians were unaware of the occurrence of HMFD, thus increasing the risk of developing severe HFMD and even death. Our study also found that the time interval from the first visit to diagnosis of severe HMFD was a significant risk factor for mortality. In general, a shorter time from the first visit to diagnosis should improve clinical outcomes. However, our results show an opposite trend (Table 2). We speculated that this may be related to insufficient awareness of HFMD among guardians, which often leads to delays in visiting to hospital. The delayed visit of hospital means that some patients will quickly become serious or critical in a shorter time, and these patients are most likely to die of cardiopulmonary failure due to delayed treatment. Therefore, in this sense, it is of particular importance to strengthen the education of guardians on HFMD knowledge and improve their awareness of children seeking medical treatment, which may become an effective strategy to prevent the death of HFMD in rural areas.

It is worth mentioning that an important finding of our study is the protective effect of EV-A71vaccination against death of severe HFMD cases. EV-A71 is the primary pathogen of HFMD and is also the main cause of severe and fatal HFMD cases[22–23]. Previous studies have shown that inactivated monovalent EV-71 vaccine has a protective effect of about 85.4% against EV-71 virus infection[24], however, which also means that some immunized children will still infected with EV-71 virus. This raises the interesting question of whether there is a reduction in mortality in patients who remain infected with EVs after EV-A71 immunization. Our study provides a positive answer that EV-A71vaccination is effective in preventing death of severe HFMD cases, evidenced by the fact that EV-A71 vaccination protected 66.62% of the death of severe HFMD cases (Table 3). The protective effect of EV-A71 vaccination on mortality is of great significance, which is comparable with that of COVID-19 vaccination, although the vaccination has little protective effect on viral infection, it can greatly reduce the mortality [27–29]. In addition, another interesting question is whether EV-71 vaccination protects against death from severe HFMD cases caused by other EVs infections, such as Cox-16. Our data showed that among 27 severe HFMD cases caused by Cox-16 infection, there were 3 deaths in EV-71 unvaccinated group but 0 death in EV-71vaccinated group, preliminarily suggesting that EV-71 vaccination may have a protective effect against death caused by COX-16 infection. Our current data is too few to do statistical analysis, but this is a direction worth focusing on in the future.

Our study has several advantages. First, this is a multicenter study, with samples from almost all medical institutions in Guangxi, covering almost all of severe HFMD cases in Guangxi during 2014–2018. Second, this study is a hospital-based study. Most of the data came from medical records, which are accurate and reliable. Third, the sample size is relatively large, facilitating statistical analysis and PSM analysis. Meanwhile, this study has several limitations. First, the subjects enrolled in this study were hospitalized patients with severe HFMD. Because HFMD is a self-limited disease, not all the severe HFMD cases were hospitalized. Especially in village or township health service centers, a small number of patients were treated by combining outpatient and home medication. Second, although PSM was used to balance the comparability between the vaccinated and unvaccinated groups, its retrospective nature makes it less accurate in assessing the effect of vaccination than prospective clinical trials.

Conclusions

Through a hospital-based epidemiologic study, we found that the mortality risk of severe HFMD in Guangxi was related to gender, hospital grade, clinical severity at admission, EV-A71 vaccination, and rash symptom. More importantly, we found EV-A71 vaccination can significantly reduce mortality among severe HFMD cases. Given the fact that the HFMD epidemic in Guangxi is still serious and the coverage of EV-A71 vaccination is not very high, our findings are of great significance for the effective prevention and control of HFMD in Guangxi, and one of the priorities is to greatly improve the coverage of EV-A71 vaccination.

Abbreviations

HFMD
hand, foot and mouth disease
EV-A71
enterovirus A 71
PSM
propensity score matching.

Declarations

Acknowledgments

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Author contributions

YJP: Data analysis, Methodology, Writing-original draft, Writing-review and editing. WTH, YJ, CZ: Investigation, Data collection, Data entry, Data curation, Formal analysis, Methodology, Writing-review and editing. JW, LNJ: Investigation, Data collection and entry, Writing-review and editing. ZGZ: Data analysis, Methodology, Formal analysis, Writing-review and editing. ZWL: Data collection and entry, writing-review and editing. PJP, YYL, HLW, HL: Formal analysis, Writing-review and editing. MMC: Conceptualization, Formal analysis, Writing-review and editing, Supervision, Project Administration. LY: Conceptualization, Formal analysis, Writing-review and editing. The author(s) read and approved the final manuscript.

Funding

This work was supported by Guangxi Natural Science Foundation Programs (2017GXNSFAA198369).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The data were extracted from the China National HFMD investigation databases and analyzed retrospectively and anonymously. Informed consent forms were also signed by patients' parents as they were interviewed. Written data use consent was also signed by patients during the investigation process. The study was approved by the Ethics and Human Subjects Committee (EHSC) of Guangxi CDC. And Investigation was performed in accordance with the relevant guidelines and regulations.

Consent for publication

Not applicable

Competing interests

The authors have no competing/conflicting interests to declare in this article.

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Figures

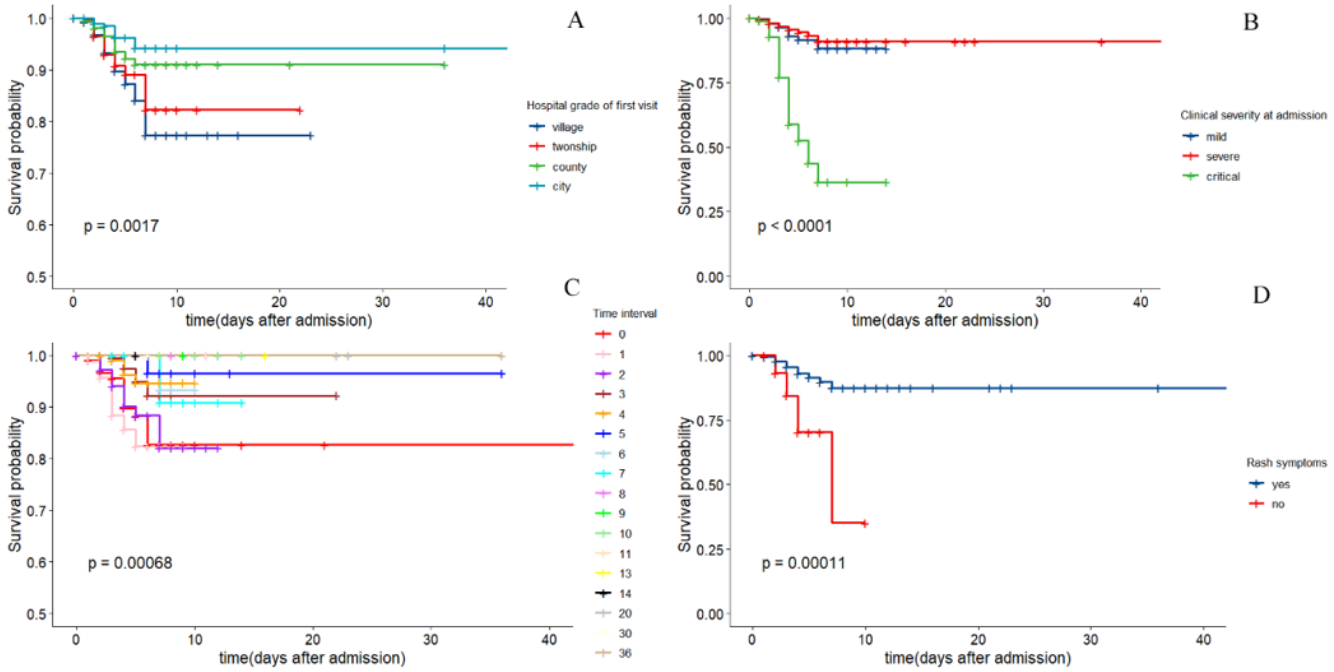

Figure 1

Accumulative survival function for survival hazard risk among different stratifications of severe HFMD cases. Kaplan-Meier survival curves comparing severe HFMD patients' survival in (A) the hospital grade of first visit, village (blue line), township (red line), county (green line), city (light-blue line), (*P*=0.0017), (B) clinical severity at admission, mild (blue line), severe (red line), critical (green line), (*P*<0.0001), (C) different time intervals between the first visit and diagnosis of severe HFMD, (*P*=0.00068), and (D) rash symptoms, yes (blue line), no (red line), (*P*=0.00011).

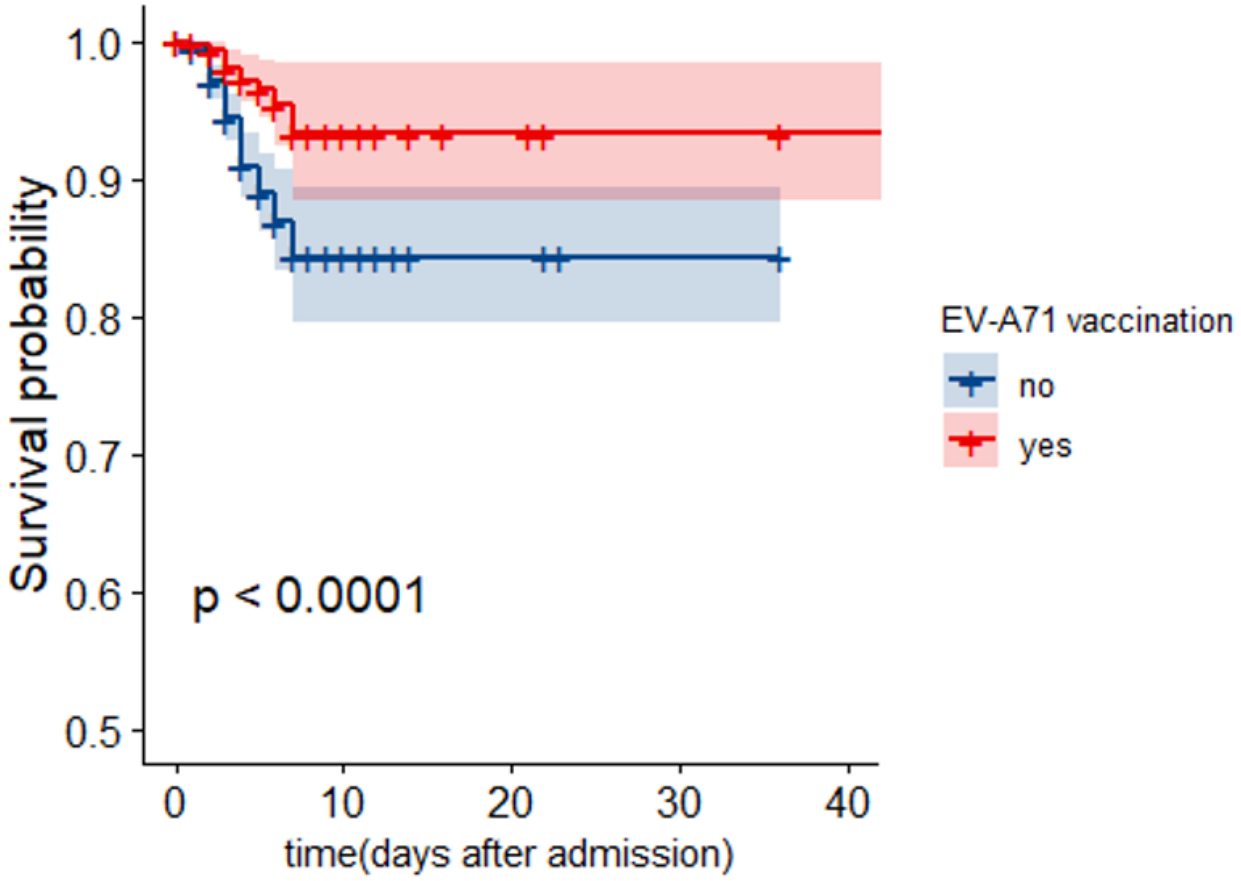

Figure 2

Effects of EV-A71 vaccination on survival rate of severe HFMD cases, with PSM. Kaplan-Meier curves for severe HFMD cases survival from time after admission in patients with EV-A71 vaccinated (red line) and unvaccinated groups (blue line). Difference between groups, *P*<0.0001.

Supplementary Files

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