Association of clinical severity with family-affluence-based socioeconomic status among hospitalized pediatric hand, foot, and mouth disease in Henan, China: a single hospital-based case-series study

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Summary of main points:

The clinical severity of HMFD inpatients was significantly associated with family-affluence-based SES. Severe HFMD inpatients were more likely to have lower SES and suffered heavy economic burden. Medical subsidy and reimbursement policies should offer severe HFMD inpatients sufficient monetary support.
Abstract

Background

The association between the clinical severity of HFMD inpatients and socioeconomic status (SES) is important for quantifying SES inequality in HFMD disease burden and informing decision-makers regarding medical subsidy and reimbursement policies. Here, this association was investigated using a quantitative SES measurement.

Methods

Laboratory-confirmed HFMD cases hospitalized at Henan Children’s Hospital from February 15, 2017 to February 15, 2018 were invited. We utilized the revised Family Affluence Scale for family-affluence-based SES measurement. Clinical severity was diagnosed based on central nervous system (CNS) complications, treatments and length of stay. We applied logistic regression for association analyses and multiple imputation for missing data.

Results

A total of 1229 laboratory-confirmed HFMD inpatients responded. Adjusted by age, sex, rural residence, EV-A71 infection and health-seeking behavior, CNS complications (OR=2.72, 95%CI: 1.41-5.31), ICU admission (OR=7.30, 95%CI: 2.21-25.97) and prolonged hospitalization (OR=4.28, 95%CI: 2.44-7.58) were significantly associated with lower family-affluence-based SES. These associations increased as SES category descended. For EV-A71-infected inpatients, severe HFMD was significantly associated with low and intermediate SES. For non-EV-A71-infected inpatients, only the association of prolonged hospitalization with low SES increased significantly. Also, severe HFMD inpatients, especially those admitted to ICU, incurred high hospitalization costs.
Conclusions

The clinical severity of HFMD inpatients was significantly associated with family-affluence-based SES. Severe HFMD inpatients were more likely to have lower SES than non-severe inpatients and suffered heavy economic burden. Therefore, medical subsidy and reimbursement policies should offer sufficient monetary support to severe HFMD inpatients, to alleviate economic burden of low-SES populations and reduce potential SES inequality.

Key words: Hand, foot, and mouth disease; Clinical severity; Socioeconomic status; Family affluence scale; Hospitalization cost
Introduction

Hand, foot, and mouth disease (HFMD) is a self-limiting pediatric contagious disease caused by enteroviruses (EVs), and it is common in children under the age of five years. However, some patients may progress to severe HFMD accompanied with neurological involvements, cardiopulmonary dysfunction and death, for which EV-A71 is the most associated pathogen. Since the 1990s, EV-A71-related severe HFMD has created a substantial disease burden in Asian-Pacific countries. From 2008 to 2018, mainland China suffered greater than 157,000 accumulated severe HFMD cases. Several factors are associated with HFMD clinical severity, including EV-A71 infection, younger age, health-seeking behavior, like delayed diagnosis, clinical symptoms, like fever over 39 °C, and laboratory indicators, like elevated blood glucose.

Socioeconomic status (SES) is a social determinant, that causes unequal illness and death of infectious diseases via various pathways, such as affecting exposure, susceptibility and medical resources accessibility. However, only limited studies investigated the association between HFMD clinical severity and SES. Some previous evidence suggested that severe HFMD was associated with socioeconomically disadvantaged populations, such as rural residents and floating populations, and traditional SES indicators, such as lower parental or caregiver education level, lower household income and smaller per capita living space. However, there were also conflicting findings on above associations, and meta-analysis studies revealed considerable inter-study heterogeneity. In the existing evidence, the involved SES indicators were categorical or semi-quantitative measurements, which were inconsistently defined or classified in different studies. Therefore, the association between HFMD clinical severity and SES requires further study, especially using quantitative SES measurements that have unified definitions, consistent classifications and good performance.
Information on the association between HFMD clinical severity and SES is important for quantifying the SES inequality in HFMD disease burden and informing the decision-makers regarding medical subsidy and reimbursement policies for HFMD inpatients. Therefore, we conducted a single hospital-based case-series study in which we quantitatively measured the family-affluence-based SES of HFMD inpatients and investigated its association with clinical severity.

Methods

Study design, participants and data collection

This single hospital-based case-series study was performed at Henan Children's Hospital, which is a tertiary hospital located in Zhengzhou, Henan, a typical highly populated and developing region in China. From February 15, 2017 to February 15, 2018, all hospitalized HFMD cases in the acute stage were invited to participate. HFMD was defined as papulovesicular/maculopapular rash on the hands, feet, mouth or buttocks, with or without vesicles/ulcers in the mouth and fever. Once informed consent was obtained, demographic characteristics, clinical records, laboratory test results, medical history, health-seeking behavior and socioeconomic information were collected by our uniformly trained staff using structured questionnaires during hospitalization. Biological specimens, including throat swabs, stool and rectal swabs, were collected and tested for EV, with details described elsewhere.18

Socioeconomic status measurement

The Family Affluence Scale (FAS) II, which reflects family affluence, was utilized to measure the SES of children and adolescents in the Health Behaviour in School-Aged Children (HBSC) study.19 The original FAS II has four items, including family holidays and ownership of cars, computers and bedrooms. The FAS II reduces report bias and non-response because of the insensitivity and simplicity.19,20 Although its reliability and validity were verified in many
countries, including China, it still needs development and revision for use in different contexts. Because most HFMD cases occur in children under the age of five years who likely share a bedroom with their parents, we revised the FAS II by replacing ownership of bedrooms with ownership of household real estate. Therefore, the items, response categories and corresponding scores of the revised FAS were as follows:

1) Does your family own a car, van or truck? None=0, one=1, two=2, three or more=3;

2) Over the past 12 months, how many times did the family travel for a vacation (with an overnight stay) at their own expense? No=0, once=1, twice=2, three times or more=3;

3) Does your family own a computer? None=0, one=1, two=2, three or more=3; and

4) Does your family own real estate? None=0, one=1, two=2, three or more=3, housing demolition and relocation=4.

We treated the item “housing demolition and relocation” as missing. Referring to the HBSC study, we combined the highest two response categories of each item and assigned the score of 2. Then, we summed the scores and obtained the revised FAS score, which ranged from 0-8.

For easier interpretation, we first converted the crude score into the material deprivation score based on ridit transformation (Supplementary material Part 1). The material deprivation score had a range of 0-1, where 0 represented inpatients from the most affluent families and 1 represented inpatients from the least affluent families. We also obtained the revised FAS category following the HBSC protocol, where the low category represented inpatients in the lowest 20% (material deprivation score >0.8), the intermediate category represented inpatients in the middle 60% (material deprivation score within 0.2-0.8), and the high category represented inpatients in the highest 20% (material deprivation score <0.2).
**Definitions of clinical severity of the HFMD inpatients**

We defined four criteria for severe HFMD and prospectively collected the clinical records of HFMD inpatients. The first criterion was based on central nervous system (CNS) complications, which included aseptic meningitis, encephalitis, brainstem encephalitis, encephalomyelitis, acute flaccid paralysis and other possible CNS involvements. The detailed diagnostic criteria referred to WHO guidance documents. The second criterion was receiving special treatments during hospitalization, which included systemic corticosteroids or intravenous human immunoglobulin (IVIG). The third criterion was intensive care unit (ICU) admission during hospitalization. The fourth criterion was length of stay (LOS) over 5 days.

**Statistical analyses**

The material deprivation score and the revised FAS category were proxies of family-affluence-based SES and its category. EV-A71-vaccinated inpatients represented children who received at least one dose of EV-A71 vaccines before the current hospitalization. Laboratory-confirmed HFMD cases were defined as clinically diagnosed HFMD inpatients with positive EV detection. Health-seeking behavior referred to the behavior since illness onset, which included the time intervals from illness onset to the first medical consultation, to the first diagnosis of HFMD and to hospitalization at the study hospital. It also included the misdiagnosis of HFMD at the first medical consultation and institutional rank of the first medical consultation. The hospitalization cost referred to the medical cost during hospitalization at Henan Children's Hospital.

We used median and interquartile range (IQR) to describe continuous variables and applied the Wilcoxon rank sum test or Kruskal-Wallis test for comparisons. We used count and proportion to describe categorical variables, and we applied the Chi-square test or Fisher's exact test for comparisons of unordered variables and Kruskal-Wallis test for comparisons of ordered
variables. We also applied the Cochran-Armitage Trend Test to test the trends of proportions between groups. A two-sided P value < 0.05 was considered statistically significant, and for pairwise comparisons, the Bonferroni corrected P value < 0.05 was deemed statistically significant.

For the revised FAS, we first performed an analysis to verify its performance in the HFMD study of a hospital-based context (Supplementary Material Part 2). Only laboratory-confirmed HFMD inpatients were included in the main analysis. We applied multivariate logistic regression to examine the association between the clinical severity of HFMD inpatients and the material deprivation score. The odds ratio (OR) for the material deprivation score was interpreted as follows: the risk of severe HFMD for inpatients with the lowest SES compared with inpatients with the highest SES. In model 1, we controlled for age, sex, rural residence and EV-A71 infection due to their associations with severe HFMD (Table S2-5), and in models 2 and 3, we further adjusted health-seeking behavior. The selection of the health-seeking behavior was based on their associations with severe HFMD and family-affluence-based SES (Supplementary Material Part 1). What's more, we used revised FAS category to detect if above-mentioned association followed certain SES gradients. Although EV-A71 vaccines could prevent EV-A71-related severe HFMD, only 4 EV-A71-infected inpatients received vaccines in this study and all of these inpatients had mild severity. Therefore, it was not appropriate to include EV-A71 vaccination in the models. In the sensitivity analysis, we adopted multiple imputation to deal with the missing response of the revised FAS to check the robustness of our results (Supplementary Material Part 1). All of the above analyses were performed in R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria, https://www.r-project.org) and Mplus version 7 (MUTHEN & MUTHEN, http://www.statmodel.com).
Results

SES distribution and other characteristics of the included HFMD inpatients

From February 15, 2017, to February 15, 2018, 1840 clinically diagnosed HFMD inpatients were enrolled, including 1768 (96.1%) laboratory-confirmed HFMD cases. Finally, 1229 laboratory-confirmed HFMD inpatients (69.5%, 1229/1768) whose families completed the revised FAS were included in the analysis (Figure 1). The included HFMD inpatients had a significantly lower proportion of EV-A71 vaccination \((P=0.0020)\) compared with the excluded, but demographic characteristics, medical history, EV serotypes and clinical severity were roughly comparable between them (Table S1). Among the 266 EV-A71-vaccinated HFMD inpatients, there were 10 (3.8%) inpatients infected with EV-A71, 51 (19.1%) with CV-A16, 108 (40.6%) with CV-A6 and 97 (36.5%) with other EVs, respectively (Table S1).

The median of the revised FAS score of the 1229 included HFMD inpatients was 3 \([IQR:2-5]\) (Figure S1). Inpatients with scores between 0-2, 3-5, and 6-8 were grouped into the low, intermediate and high category of the revised FAS, respectively, and accounted for 26.9%, 57.7% and 15.4% of the included inpatients, respectively. Table 1 shows the characteristics of the 1229 included HFMD inpatients by the revised FAS category, and no statistically significant difference in sex or age was detected. However, HFMD inpatients in lower categories of the revised FAS were more likely to come from rural areas \((P<0.0001)\) and be unvaccinated against EV-A71 \((P=0.0133, \text{Table 1})\).

The distribution of EV serotypes was significantly different between the revised FAS categories \((P=0.0075, \text{Table 1})\), and more EV-A71 infections were found in lower categories of the revised FAS. Similarly, passive health-seeking behavior was more common in lower categories of the revised FAS, such as misdiagnosis of HFMD at the first medical consultation \((P=0.0094)\), delayed
diagnosis ($P=0.0281$) and delayed hospitalization ($P=0.0004$, Table 1). We also observed that there were significantly fewer severe HFMD inpatients in higher categories of the revised FAS (Table 1), and the proportions of severe HFMD significantly increased as the revised FAS category descended (Figure S2, Cochran-Armitage Trend Test).

In terms of economic burden, severe HFMD inpatients had significantly higher hospitalization costs than mild inpatients for all four severity criteria (Table 2). Among severe HFMD inpatients, those with ICU admission incurred the most hospitalization costs, which were followed by CNS complications, receiving special treatments and prolonged hospitalization (Table 2).

**SES and the clinical severity of HFMD inpatients**

Severe HFMD inpatients had significantly lower revised FAS scores and categories than mild inpatients (Figure S2 and Table 2). Univariate analysis showed that severe HFMD was significantly associated with a lower material deprivation score and the lower category of revised FAS, and these associations increased as the revised FAS category descended (Table 2 and Table 3).

Table 3 shows the results of multivariate logistic regression. Considering the higher proportion of EV-A71 infection among HFMD inpatients in the lower categories of the revised FAS, we first adjusted age, sex, rural residence and EV-A71 infection in model 1. The results showed that severe HFMD was significantly associated with a lower material deprivation score for all four severity criteria. Giving the associations of passive health-seeking behavior with the revised FAS and severe HFMD (Table S6&7), we further adjusted health-seeking behavior in models 2 and 3.
We found that these associations remained statistically significant, except for receiving special treatments (OR=1.80, 95%CI: 0.99-3.26, \( P=0.0509 \)). We did not detect any meaningful interaction between the material deprivation score and EV-A71 infection.

Figure 2 shows the adjusted associations of severe HFMD with EV-A71 infection and revised FAS category, with non-EV-A71-infected HFMD inpatients in the high category of the revised FAS as the reference. Overall, stronger associations of severe HFMD were found in inpatients with EV-A71 infection and inpatients in lower categories of the revised FAS. Specifically, among EV-A71-infected HFMD inpatients, the associations of severe HFMD with the low and intermediate categories of the revised FAS were statistically significant for all four criteria. But for the high category of the revised FAS, only its associations with CNS complications significantly increased (OR=5.49, 95%CI: 1.65-17.34, Figure 2.a). For HFMD inpatients with non-EV-A71 infection, only the association of prolonged hospitalization with the low category of the revised FAS was statistically significant (OR=2.75, 95%CI: 1.50-5.35, Figure 2.d).

**Sensitivity analysis**

After filling in the missing response of the revised FAS using multiple imputation, the association of the clinical severity of HFMD inpatients with family-affluence-based SES was reanalyzed. The results showed that although the point estimations generally decreased, the pattern and statistical significance of these associations remained, which indicated the robustness of our results (Table 3 and Figure 2).

**Discussion**

To the best of our knowledge, this report is the first study to quantitatively measure the family-affluence-based SES of HFMD inpatients and investigate its association with clinical severity. In the both of univariate and multivariate analyses, severe HFMD inpatients, especially those with CNS complications, ICU admission and prolonged hospitalization, were significantly associated
with lower family-affluence-based SES. Also, severe HFMD inpatients incurred high hospitalization costs, which were at least more than 5000 yuan (740 US dollars).

The quantitative SES measurement used in this study was derived from FAS II, which has characteristics of insensitivity, simplicity and high response rate.\textsuperscript{19,20} Based on the younger age of HFMD inpatients, we revised the FAS II by replacing ownership of bedrooms with ownership of household real estate, which made our SES measurement more scientific. Besides, the verification analysis (Supplementary Material Part 2) showed that the revised FAS was an acceptable measurement with moderate response rate (Figure S3 and Table S8) and internal reliability (Table S9&10) and adequate external (Table S11) and structural validity (Figure S4). Most importantly, we identified that our revision was reasonable and helped improve the reliability and validity.

In this case-series of HFMD inpatients, we noticed that EV-A71 infection was more common among lower-SES HFMD inpatients. This result was consistent with another hospital-based study, which found an association between EV-A71 infection and HFMD cases from rural-to-urban migrant families.\textsuperscript{12} According to the conceptual framework of the association between SES and pandemic influenza, SES may result in unequal levels of illness and death by affecting the accessibility and utilization of medical resources after illness onset.\textsuperscript{8,9} Similarly, we noticed that passive health-seeking behavior after illness onset was more common among lower-SES HFMD inpatients. And some of above behavior was also found significantly associated with severe HFMD (Table S6), which was consistent with previous risk-factor studies of severe HFMD.\textsuperscript{3,11,13,15}
The present study demonstrated the SES inequality in the clinical severity of HFMD inpatients, especially in CNS complications, ICU admission and prolonged hospitalization. However, previous findings on associations between HFMD clinical severity and SES were inconsistent. One of the reasons may be that the involved traditional SES indicators were categorical or semi-quantitative measurements that lacked unified definitions and consistent classifications. For example, Zeng et al.\textsuperscript{12} and Pan et al.\textsuperscript{15} used different definitions of floating population in their studies, and they reached contradictory results on the association between floating population and severe HFMD. Similarly, Huang et al.\textsuperscript{13} and Cao et al.\textsuperscript{14} used inconsistent income classifications in their studies, and their results about the effect of household income on HFMD clinical severity were conflicting. Additionally, the ecological indicators, like rural residents and floating populations, may lead to the misclassification of SES,\textsuperscript{25} because urban residents may not always have higher SES than rural residents. In contrast, the revised FAS used in this study was based on family-level and also had quantitative features, unified definitions, consistent classifications and acceptable reliability and validity, which supported the credibility of our results.

Besides, we also observed that these associations followed an increasing trend as the SES category descended, which was similar to a previous study that found the association between caregiver education level and severe HFMD decreased as education level increased.\textsuperscript{11} We further demonstrated that severe HFMD had the strongest association with EV-A71-infected HFMD inpatients of low and intermediate SES. This is because that EV-A71 is a neurotrophic virus which accounted for most of severe HFMD in many years.\textsuperscript{1-6} It's also worth noting that the association of prolonged hospitalization with low SES was also remarkable for non-EV-A71-infected HFMD inpatients. The reason could be that doctors may postpone the discharge out of concerns on incompetent parental monitoring of lower-SES families and their limited medical resource accessibility, which was irrespective of EV serotypes.\textsuperscript{26}
In this study, we also found that the above-mentioned associations remained statistically significant after we adjusted for health-seeking behavior. Therefore, we hypothesized that family-affluence-based SES would be associated with the clinical severity of HFMD inpatients via other pathways. One possible explanation is the lack of medical literacy on HFMD, which has been reported to be associated with lower parental education level, household income and floating population.\textsuperscript{8,27} Many clinical signs and symptoms were identified as predictors of severe HFMD,\textsuperscript{1,2,16} and an unawareness of these predictors may lead to missed opportunities to prevent disease progression at an early stage.\textsuperscript{1,2} In addition, specific antiviral drugs are still unavailable, and mainstream strategies for clinical management are limited to supportive therapies.\textsuperscript{1,2,5} Therefore, another possible explanation is improper care. For example, children from less affluent families may face problems of malnutrition, which may affect the antiviral immune response.\textsuperscript{7-9,28}

Notably, we found that severe HFMD inpatients incurred high hospitalization costs, which accounted for a non-negligible proportion of the per capital annual disposal income of Henan province in 2017 (20,170 yuan/2987 US dollars), ranging from 25.9\% for prolonged hospitalization to 93.8\% for ICU admission.\textsuperscript{29} In contrast, above proportion for mild HFMD inpatients was about 13.9\%, which was only half of the prolonged hospitalization. Given the heavy economic burden for severe HFMD inpatients, SES inequality in the clinical severity of HFMD inpatients could further incur SES inequality in economic burden, since socioeconomically disadvantaged populations themselves are vulnerable to heavy economic burden. Therefore, our findings added evidence to offering sufficient monetary support to severe HFMD inpatients via medical subsidy and reimbursement policies. This intervention could help alleviate HFMD economic burden of low-SES populations and then reduce potential SES inequality.
There are some limitations in this study. Firstly, our participants were enrolled from a single HFMD-designated hospital in Zhengzhou, which has different criteria for admission, treatment and discharge compared with medical institutions of other levels. Therefore, our samples may not well represent the overall population of HFMD inpatients, and extrapolation should be conducted with caution. In the future, multi-center studies or HFMD surveillance systems that include SES information are needed to verify our findings. Secondly, socioeconomic information was self-reported without external validation in this study, and reporting bias inevitably existed. However, the items of the revised FAS is deemed simple and insensitive,\textsuperscript{19,20} therefore this bias should not be a major concern. Finally, the non-response rate of the revised FAS reached 30.5\% in this study, which may bring selection bias to the results. However, the comparisons between the included and excluded inpatients did not detect any statistically significant difference in clinical severity. Besides, we also utilized multiple imputation to fill in the missing responses of the revised FAS in the sensitivity analysis, which further verified the robustness of our results.

In conclusion, the clinical severity of HFMD inpatients was significantly associated with family-affluence-based SES, and severe HFMD inpatients were more likely to have lower SES than non-severe inpatients. Also, severe HFMD inpatients suffered heavy economic burden. Therefore, medical subsidy and reimbursement policies should offer sufficient monetary support to severe HFMD inpatients to help alleviate the economic burden of low-SES populations and reduce potential SES inequality.
Patient Consent Statement

The Institutional Review Boards of Henan Children’s Hospital (IRB#YZ-17-006), Chinese Centre for Disease Prevention and Control (IRB#201624), and Public Health School of Fudan University (IRB#2017-12-0654) have approved the study protocol. Written informed consent was provided by parents or legal guardians of study participants on enrollment.

Contributors

HJY and YL designed the study. HJY supervised the study. FW, YL, LL, PC, SJJH, YBC, CG, MYZ LL and TCZ collected data and specimens. YHZ and QQ performed virologic testing. YL, LL, PC, YHZ, QQ, CG, MZY, LL and TCZ cleaned data. KW analyzed the data and wrote the drafts of the manuscript. HJY, KW and YL interpreted the findings. FW, SJJH and YBC commented on and revised drafts of the manuscript. All authors have verified the underlying data. All authors read and approved the final report.

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Conflicts of Interest

HJY has received research funding from Sanofi Pasteur, GlaxoSmithKline, Yichang HEC Changjiang Pharmaceutical Company and Shanghai Roche Pharmaceutical Company, outside the submitted work. All other authors declare no competing interests.
References

1. World Health Organization. A Guide to Clinical Management and Public Health Response for Hand, Foot and Mouth Disease (HFMD). Manila, Malaysia: World Health Organization Western Pacific Region; 2011. https://apps.who.int/iris/handle/10665/207490 (accessed Sep 25, 2020).

2. Li XW, Ni X, Qian SY, et al. Chinese guidelines for the diagnosis and treatment of hand, foot and mouth disease (2018 edition). World J Pediatr 2018; 14: 437-47.

3. Xing W, Liao Q, Viboud C, et al. Hand, foot, and mouth disease in China, 2008-12: an epidemiological study. Lancet Infect Dis 2014; 14: 308-18.

4. Solomon T, Lewthwaite P, Perera D, Cardosa MJ, McMinn P, Ooi MH. Virology, epidemiology, pathogenesis, and control of enterovirus 71. The Lancet Infectious diseases. 2010;10(11):778-90.

5. Yu H, Cowling BJ. Remaining challenges for prevention and control of hand, foot, and mouth disease. Lancet Child Adolesc Health 2019; 3: 373-4.

6. Ren M, Cui J, Nie T, Liu F, Sun J, Zhang Y, et al. [Epidemiological characteristics of severe cases of hand, foot, and mouth disease in China, 2008-2018]. Chin J of Epidemiol. 2020;41(11):1802-7.

7. Quinn SC, Kumar S. Health inequalities and infectious disease epidemics: a challenge for global health security. Biosecur Bioterror 2014; 12: 263-73.

8. Kumar S, Quinn SC. Existing health inequalities in India: informing preparedness planning for an influenza pandemic. Health Policy Plan 2012; 27: 516-26.

9. Blumenshine P, Reingold A, Egerter S, Mockenhaupt R, Braveman P, Marks J. Pandemic influenza planning in the United States from a health disparities perspective. Emerg Infect Dis 2008; 14: 709-15.

10. Munday JD, van Hoek AJ, Edmunds WJ, Atkins KE. Quantifying the impact of social groups and vaccination on inequalities in infectious diseases using a mathematical model. BMC
11. Chen SM, Du JW, Jin YM, et al. Risk Factors for Severe Hand-Foot-Mouth Disease in Children in Hainan, China, 2011-2012. Asia Pac J Public Health 2015; 27: 715-22.

12. Zeng M, Pu D, Mo X, et al. Children of rural-to-urban migrant workers in China are at a higher risk of contracting severe hand, foot and mouth disease and EV71 infection: a hospital-based study. Emerg Microbes Infect 2013; 2: e72.

13. Huang T, Li Q, Shen X, Fu X, Cun J. [Analysis of the risk factors for severe hand-foot-and-mouth disease (HFMD) in Yunnan Province]. Modern Preventive Medicine 2017; 44: 1115-9.

14. Cao M, Liu H, Wan J, Zhu I. [An case-control study of severe case of Hand-Foot-and-mouth disease (EV71) in Fuyang City, Anhui Province]. Anhui J Prev Med 2010; 16: 19-20.

15. Pan H, Zheng Y, Mao S, et al. [A case-control study on risk factors that associated with severe hand-foot-mouth disease in Shanghai]. Chin J of Epidemiol 2012; 33: 763-7.

16. Sun BJ, Chen HJ, Chen Y, An XD, Zhou BS. The Risk Factors of Acquiring Severe Hand, Foot, and Mouth Disease: A Meta-Analysis. Can J Infect Dis Med Microbiol. 2018; 2018: 2751457.

17. Li J, Gu Y. [Meta-analysis of the risk factors on severe hand-foot-mouth disease]. Modern Preventive Medicine 2016; 43: 2703-6.

18. Li Y, Zhou Y, Cheng Y, et al. Effectiveness of EV-A71 vaccination in prevention of paediatric hand, foot, and mouth disease associated with EV-A71 virus infection requiring hospitalisation in Henan, China, 2017–18: a test-negative case-control study. Lancet Child Adolesc Health 2019; 3: 697-704.

19. Currie C, Molcho M, Boyce W, Holstein B, Torsheim T, Richter M. Researching health inequalities in adolescents: the development of the Health Behaviour in School-Aged Children (HBSC) family affluence scale. Soc Sci Med 2008; 66: 1429-36.

20. Currie CE, Elton RA, Todd J, Platt S. Indicators of socioeconomic status for adolescents: the WHO Health Behaviour in School-aged Children Survey. Health Educ Res 1997; 12: 385-97.
21. Liu Y, Wang M, Villberg J, et al. Reliability and Validity of Family Affluence Scale (FAS II) among Adolescents in Beijing, China. *Child Indicators Research* 2011; 5: 235-51.

22. Torsheim T, Currie C, Boyce W, Kalnins I, Overpeck M, Haugland S. Material deprivation and self-rated health: a multilevel study of adolescents from 22 European and North American countries. *Soc Sci Med* 2004; 59: 1-12.

23. World Health Organization. Growing up unequal: gender and socioeconomic differences in young people’s health and well-being. Copenhagen, Denmark: World Health Organization Regional Office for Europe; 2016. [https://apps.who.int/iris/handle/10665/326320](https://apps.who.int/iris/handle/10665/326320) (accessed Sep 25, 2020).

24. Nhan LNT, Turner HC, Khanh TH, et al. Economic Burden Attributed to Children Presenting to Hospitals With Hand, Foot, and Mouth Disease in Vietnam. *Open Forum Infect Dis* 2019; 6: ofz284.

25. Finkelstein MM. Ecologic proxies for household income: how well do they work for the analysis of health and health care utilization? Canadian journal of public health. 2004;95(2):90-4.

26. Dionne A, Bucholz EM, Gauvreau K, et al. Impact of Socioeconomic Status on Outcomes of Patients with Kawasaki Disease. *J Pediatr* 2019; 212: 87-92.

27. Xu X, Li E, Zhou Z, Wang J, Wu C. [Survey on Awareness of Hand-Foot-Mouth Disease Among Parents of Kindergarten Children in Zhabei District of Shanghai]. *Health Education and Health Promotion* 2015; 10: 369-71.

28. Chen S, Yang Y, Yan X, Chen J, Yu H, Wang W. Influence of vitamin A status on the antiviral immunity of children with hand, foot and mouth disease. *Clinical Nutrition*. 2012;31(4):543-8.

29. 2018 Henan statistical year book. [http://oss.henan.gov.cn/sbgt-wztipt/attachment/hntj/hntj/lib/tjnj/2018/zk/indexch.htm](http://oss.henan.gov.cn/sbgt-wztipt/attachment/hntj/hntj/lib/tjnj/2018/zk/indexch.htm) (accessed Feb 5, 2021).
Table 1. Characteristics of the included HFMD inpatients by the revised FAS category.

| Characteristics                        | Overall (N=1229) | Revised FAS category | P value |
|----------------------------------------|------------------|----------------------|---------|
|                                        |                  | Low (N=343)          | Intermediate (N=708) | High (N=178) |         |
| Male                                   | 793 (64.5)       | 227 (66.2)           | 451 (63.4)          | 115 (64.6)  | 0.733   |
| Age group                              |                  |                      |                     |             | 0.172   |
| < 1 year                               | 172 (14.0)       | 54 (15.7)            | 96 (13.6)           | 22 (12.4)   |         |
| 1 year                                 | 558 (45.4)       | 140 (40.8)           | 341 (48.2)          | 77 (43.3)   |         |
| 2-14 years                             | 499 (40.6)       | 149 (43.5)           | 271 (38.2)          | 79 (44.3)   |         |
| Rural residence                        | 395 (32.1)       | 172 (50.1)           | 200 (28.2)          | 23 (12.9)   | <0.0001 |
| EV-A71 Vaccinated                      | 163 (13.3)       | 31 (9.0)             | 110 (15.5)          | 24 (12.4)   | 0.0133  |
| EV serotypes                           |                  | 189 (15.4)           | 73 (21.3)           | 97 (13.7)   | 0.0075  |
| EV-A71                                 |                  | 251 (20.4)           | 62 (18.1)           | 142 (20.1)  |         |
| CV-A16                                 |                  | 383 (31.2)           | 96 (28.0)           | 231 (32.6)  |         |
| CV-A6                                  |                  | 406 (33.0)           | 112 (32.6)          | 238 (33.6)  |         |
| Health-seeking behavior                |                  |                      |                     |             |         |
| Time of the first medical consultation | 1.00 [0.00, 1.00] | 0.00 [0.00, 1.00]    | 1.00 [0.00, 1.00]   | 1.00 [0.00, 1.00] | 0.310   |
| Institutional rank of the first medical consultation |          |                     |                     |             | 0.0603 †|
| Tertiary or secondary hospitals        | 868 (70.6)       | 228 (66.5)           | 506 (71.5)          | 134 (75.3)  |         |
| Primary hospitals or private clinics   | 343 (27.9)       | 111 (32.4)           | 191 (27.0)          | 41 (23.0)   |         |
| Unknown                                | 18 (1.5)         | 4 (1.1)              | 11 (1.5)            | 3 (1.7)     |         |
| Misdiagnosis of HFMD at the first medical consultation | 455 (37.0)       | 147 (42.9)           | 255 (36.0)          | 53 (29.8)   | 0.0094  |
| Time of the first diagnosis of HFMD after illness onset | 1.00 [0.00, 1.00] | 1.00 [0.00, 1.00]    | 1.00 [0.00, 1.00]   | 1.00 [0.00, 1.00] | 0.0281  |
| Time of hospitalization at Henan Children's Hospital after illness onset (day) | 2.00 [1.00, 2.00] | 2.00 [1.00, 2.00]    | 2.00 [1.00, 2.00]   | 1.50 [1.00, 3.00] | 0.0004  |
CNS complications *

| Condition                       | Group 1 | Group 2 | Group 3 | Group 4 | p-value |
|---------------------------------|---------|---------|---------|---------|---------|
| Brainstem encephalitis          | 123 (10.0) | 49 (14.3) | 62 (8.8) | 12 (6.7) | 0.0058  |
| Encephalitis                    | 26 (2.1) | 10 (2.9) | 12 (1.7) | 4 (2.2)  | 0.391   |
| Encephalomyelitis               | 14 (1.1) | 7 (2.0)  | 6 (0.8)  | 1 (0.6)  | 0.204   |
| Meningitis                      | 4 (0.3)  | 1 (0.3)  | 3 (0.4)  | 0 (0.0)  | 1.000   |
| Epilepsy attack                 | 2 (0.2)  | 2 (0.6)  | 0 (0.0)  | 0 (0.0)  | 0.0986  |
| Acute flaccid paralysis         | 2 (0.2)  | 2 (0.6)  | 0 (0.0)  | 0 (0.0)  | 0.0986  |

Special treatments

| Treatment                          | Group 1 | Group 2 | Group 3 | Group 4 | p-value |
|------------------------------------|---------|---------|---------|---------|---------|
| Systemic corticosteroids           | 215 (17.5) | 75 (21.9) | 118 (16.7) | 22 (12.4) | 0.0172  |
| IVIG                               | 81 (6.6)  | 34 (9.9) | 41 (5.8) | 6 (3.4)  | 0.0072  |
| Length of stay (day)               | 4.00 [4.00, 5.00] | 5.00 [4.00, 6.00] | 4.00 [4.00, 5.00] | 4.00 [4.00, 5.00] | <0.0001 |

Data were n (%) or median [IQR].

* The diagnose categories were mutually exclusive.

† The comparison excluded unknown.
Table 2. Crude association between the clinical severity of HFMD inpatients and the revised FAS category, and hospitalization cost distribution of HFMD inpatients by clinical severity.

| Clinical severity | Revised FAS category | Severe | Mild | P value * | Crude OR (95% CI) | P value ** |
|-------------------|----------------------|--------|------|-----------|------------------|-----------|
| CNS complications |                      |        |      |           |                  |           |
| High              | 17 (9.9)             | 161 (15.2) | <0.0001 | Reference | ...             |
| Intermediate      | 83 (48.6)            | 625 (59.1) | 1.26 (0.74, 2.25) | 0.404 |
| Low               | 71 (41.5)            | 272 (25.7) | 2.48 (1.44, 4.47) | 0.0008 |
| Hospitalization cost (Yuan) | [3726.97, 15607.58] | [2528.90, 3399.99] | <0.0001 |
| Receiving special treatments |                 |        |      |           |                  |           |
| High              | 22 (10.2)            | 156 (15.4) | 0.0044 | Reference | ...             |
| Intermediate      | 118 (54.9)           | 590 (58.2) | 1.42 (0.89, 2.36) | 0.149 |
| Low               | 75 (34.9)            | 268 (26.4) | 1.98 (1.20, 3.39) | 0.0066 |
| Hospitalization cost (Yuan) | [3634.86, 12907.10] | [2502.92, 3336.41] | <0.0001 |
| ICU admission     | 49 (4.0)             | 1180 (96.0) | <0.0001 | Reference | ...             |
| High              | 1 (2.0)              | 177 (15.0) | <0.0001 | Reference | ...             |
| Intermediate      | 23 (46.9)            | 685 (58.1) | 5.94 (1.24, 106.64) | 0.0211 |
| Low               | 25 (51.1)            | 318 (26.9) | 13.92 (2.91, 249.48) | 0.0001 |
| Hospitalization cost (Yuan) | 18919.72            | 2978.92 | <0.0001 |

* P value for comparing severe vs. mild
** P value for comparing high vs. low
| LOS > 5 days | Reference | \( P \) value of Wilcoxon rank sum test or Kruskal-Wallis test. | \( P \) value of log-likelihood ratio test. |
|--------------|-----------|--------------------------------------------------------------|--------------------------------------------------|
| High         | 237 (19.3)| 992 (80.7)                                                  | <0.0001                                          |
| Intermediate | 15 (6.3)  | 163 (16.4)                                                  | 2.38 (1.39, 4.33)                               | 0.0010                                          |
| Low          | 127 (53.6)| 581 (58.6)                                                  | 248 (25.0)                                      | 4.16 (2.40, 7.70)                               | <0.0001                                          |
| Hospitalization cost (Yuan) | \[15751.26, 26730.58\] | \[2557.43, 3566.37\] | \[3817.30, 11648.80\] | \[2496.86, 3281.87\] | <0.0001                                          |

Data were n (%) or median [IQR].

* \( P \) value of Wilcoxon rank sum test or Kruskal-Wallis test.

** \( P \) value of log-likelihood ratio test.
Table 3. Associations between the clinical severity of HFMD inpatients and family-affluence-based SES (material deprivation score) by clinical severity.

| Model | Clinical severity | Overall (N=1229) | Adjusted OR (95% CI) | P value * | P value for inter-action between EV-A71 and SES * |
|-------|------------------|------------------|----------------------|-----------|-----------------------------------------------|
|       |                  |                  |                      |           |                                               |
| **Univariate** |                   |                  |                      |           |                                               |
|         | CNS complications | 3.43 (1.99, 5.98) | <0.0001              | -         |                                               |
|         | Receiving special treatments | 2.18 (1.35, 3.53) | 0.0013               | -         |                                               |
|         | ICU admission     | 10.34 (3.51, 33.00) | <0.0001              | -         |                                               |
|         | LOS > 5 days      | 3.86 (2.43, 6.21)  | <0.0001              | -         |                                               |
| **Model 1 †** |                   |                  |                      |           |                                               |
|         | CNS complications | 2.81 (1.46, 5.48) | 0.0019               | 0.392     |                                               |
|         | Receiving special treatments | 1.86 (1.04, 3.34) | 0.0374               | 0.370     |                                               |
|         | ICU admission     | 7.14 (2.17, 25.39) | 0.0010               | 0.570     |                                               |
|         | LOS > 5 days      | 4.09 (2.35, 7.20)  | <0.0001              | 0.968     |                                               |
| **Model 2 ‡** |                   |                  |                      |           |                                               |
|         | CNS complications | -                | -                    | -         |                                               |
|         | Receiving special treatments | 1.89 (1.05, 3.41) | 0.0326               | 0.370     |                                               |
|         | ICU admission     | 7.27 (2.21, 25.78) | 0.0009               | 0.597     |                                               |
|         | LOS > 5 days      | 4.25 (2.43, 7.50)  | <0.0001              | 0.968     |                                               |
| **Model 3 †** |                   |                  |                      |           |                                               |
|         | CNS complications | 2.72 (1.41, 5.31) | 0.0029               | 0.358     |                                               |
|         | Receiving special treatments | 1.80 (0.99, 3.26) | 0.0509               | 0.330     |                                               |
|         | ICU admission     | 7.30 (2.21, 25.97) | 0.0009               | 0.598     |                                               |
|         | LOS > 5 days      | 4.28 (2.44, 7.58)  | <0.0001              | 0.970     |                                               |
| **Sensitivity analysis (multiple imputation)** | | | | | |
| **Model 3 †** |                   |                  |                      |           |                                               |
|         | CNS complications | 1.85 (1.02, 3.34) | 0.0438               | 0.334     |                                               |
|         | Receiving special treatments | 1.45 (0.86, 2.46) | 0.166                | 0.468     |                                               |
|         | ICU admission     | 4.01 (1.23, 13.09) | 0.0223               | 0.483     |                                               |
|         | LOS > 5 days      | 3.19 (1.84, 5.54)  | 0.0001               | 0.612     |                                               |

* P value of log-likelihood ratio test.
†Model 1 was adjusted by age, sex, rural residence and EV-A71 infection.

§Model 2 was further adjusted by time of the first medical consultation based on Model 1.

¶Model 3 was further adjusted by the rest health-seeking behavior based on Model 2. Specifically, we additionally adjusted institutional rank of the first medical consultation, time of the first diagnosis of HFMD and time of hospitalization in the analysis of CNS complications and receiving special treatments; we additionally adjusted time of the first diagnosis of HFMD and time of hospitalization in the analysis of ICU admission and LOS > 5 days.
Figure legends

Figure 1. Flowchart for the inclusion of HFMD inpatients in this study.

Figure 2. Adjusted associations of the clinical severity of HFMD inpatients with EV-A71 infection and the revised FAS category. (a: CNS complications; b: Receiving special treatments; c: ICU admission; d: LOS > 5 days. ORs were adjusted by age, sex, rural residence and health-seeking behavior. Specifically, we adjusted for institutional rank of the first medical consultation, time of the first diagnosis of HFMD and time of hospitalization in the analysis of CNS complications; we adjusted for time and institutional rank of the first medical consultation, time of the first diagnosis of HFMD and time of hospitalization in the analysis of receiving special treatments; we adjusted for time of the first medical consultation, time of the first diagnosis of HFMD and time of hospitalization in the analysis of ICU admission and LOS > 5 days. Abbreviation: Ref, reference)
Figure 1

1840 clinically diagnosed HFMD inpatients enrolled

Excluded
66 EV negative
6 without any samples collected

1768 (96.1%) laboratory-confirmed HFMD inpatients

Excluded 539 (30.5%) inpatients whose families did not complete the revised Family Affluence Scale
217 (40.3%) with four items missing
217 (40.3%) with three items missing
15 (2.7%) with two items missing
90 (16.7%) with one item missing

1229 (69.5%) laboratory-confirmed HFMD inpatients
1040 (84.6%) Non-EV-A71-infected HFMD
189 (15.4%) EV-A71-infected HFMD
Figure 2