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Association of Clinical Severity With Family Affluence–Based Socioeconomic Status Among Hospitalized Pediatric Hand, Foot, and Mouth Disease Patients in Henan, China: A Single Hospital-Based Case Series Study

Kai Wang,[1,a] Fang Wang,[2,a] Yu Li,[3,4,a] Lu Liang,[5] Peng Cui,[1] Shujuan Han,[2] Yonghong Zhou,[1] Qi Qiu,[1] Yibing Cheng,[2] Chun Guo,[6] Mengyao Zeng,[1,7] Lu Long,[5] Tianchen Zhang,[3] and Hongjie Yu[1]

[1]School of Public Health, Fudan University, Key Laboratory of Public Health Safety, Ministry of Education, Shanghai, China, [2]Children's Hospital Affiliated to Zhengzhou University, Henan Children's Hospital, Zhengzhou, China, [3]Division of Infectious Disease, Key Laboratory of Surveillance and Early Warning on Infectious Disease, Chinese Center for Disease Control and Prevention, Beijing, China, [4]WHO Collaborating Centre for Infectious Disease Epidemiology and Control, School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China, [5]West China School of Public Health and West China Fourth Hospital, Sichuan University, Chengdu, China, [6]School of Public Health, Huazhong University of Science and Technology, Wuhan, China, and [7]NHC Key Lab of Reproduction Regulation (Shanghai Institute of Planned Parenthood Research), Medical School, Fudan University, Shanghai, China

Background. The association between the clinical severity of hand, foot, and mouth disease (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 (odds ratio [OR], 2.72; 95% CI, 1.41–5.31), intensive care unit (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 the 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 the ICU, incurred high hospitalization costs.

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

Keywords. clinical severity; family affluence scale; hand, foot, and mouth disease; hospitalization cost; socioeconomic status.

Hand, foot, and mouth disease (HFMD) is a self-limiting pediatric contagious disease caused by enteroviruses (EVs), and it is common in children age <5 years [1, 2]. However, some patients may progress to severe HFMD accompanied by neurological involvements, cardiopulmonary dysfunction, and death, for which EV-A71 is the most associated pathogen [1, 2]. Since the 1990s, EV-A71-related severe HFMD has created a substantial disease burden in Asian-Pacific countries [1, 3–5]. From 2008 to 2018, mainland China suffered >157 000 accumulated severe HFMD cases [6]. Several factors are associated with HFMD clinical severity, including EV-A71 infection, younger age, health-seeking behavior like delayed diagnosis, clinical symptoms like fever >39°C, and laboratory indicators like elevated blood glucose [1–3].

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 resource accessibility [7–10]. However, few studies have investigated the association between HFMD

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[a]Equal contribution

Correspondence: Hongjie Yu, PhD, School of Public Health, Fudan University, Key Laboratory of Public Health, Safety, Ministry of Education, Shanghai, China, No. 130, Dong An Road, Xuhui District, Shanghai 200032, China (yhj@fudan.edu.cn).

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clinical severity and SES [3, 11–15]. Some previous evidence has suggested that severe HFMD is associated with socioeconomically disadvantaged populations, such as rural residents [3, 11] and floating populations [12], and traditional SES indicators, such as lower parental or caregiver education level [11, 13], lower household income [14], and smaller per capita living space [13]. However, there are also conflicting findings on the above associations [12–15], and meta-analysis studies have revealed considerable interstudy heterogeneity [16, 17]. In the existing evidence, the SES indicators used were categorical or semiquantitative measurements, which were inconsistently defined [12, 15] or classified [13, 14] 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 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 4 items, including family holidays and ownership of cars, computers, and bedrooms. The FAS II reduces report bias and nonresponse because of its insensitivity and simplicity [19, 20]. Although its reliability and validity have been verified in many countries, including China, the FAS II still needs development and revision for use in different contexts [19, 21]. Because most HFMD cases occur in children under the age of 5 years [3] 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, 1 = 1, 2 = 2, 3 or more = 3;
2) Over the past 12 months, how many times has the family traveled for a vacation (with an overnight stay) at their own expense? No = 0, once = 1, twice = 2, 3 times or more = 3;
3) Does your family own a computer? None = 0, 1 = 1, 1 = 2, 3 or more = 3; and
4) Does your family own real estate? None = 0, 1 = 1, 2 = 2, 3 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 2 response categories of each item and assigned them a score of 2 [19]. Then, we summed the scores and obtained the revised FAS score, which ranged from 0 to 8. For easier interpretation, we first converted the crude score into the material deprivation score based on ridit transformation (Supplementary Data) [22]. 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 [22]. We also obtained the revised FAS categories 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 between 0.2 and 0.8), and the high category represented inpatients in the highest 20% (material deprivation score <0.2) [23].

Definitions of Clinical Severity of the HFMD Inpatients

We defined 4 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 World Health Organization guidance documents [1]. The second criterion was receiving special treatments during hospitalization, which included systemic corticosteroids or intravenous human immunoglobulin. The third criterion was intensive care unit (ICU) admission during hospitalization. The fourth criterion was length of stay (LOS) >5 days [24].

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 1 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 behavior since illness onset, which included the time intervals from illness onset to the first medical consultation, from illness onset to the first diagnosis of HFMD, and from illness onset to hospitalization at the study hospital. It also included the misdiagnosis of HFMD at the first medical consultation and the institutional rank of the first medical consultation. 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 exact test for comparisons of unordered variables and the 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 2-sided P value <.05 was considered statistically significant.

For the revised FAS, we first performed an analysis to verify its performance in the HFMD study, which was conducted in a hospital-based context (Supplementary Data). 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 [22]. In model 1, we controlled for age, sex, rural residence, and EV-A71 infection due to their associations with severe HFMD (Supplementary Tables 2–5), and in models 2 and 3, we further adjusted for health-seeking behavior. The selection of health-seeking behavior was based on its associations with severe HFMD and family affluence–based SES (Supplementary Data). What's more, we used revised FAS category to detect if the above-mentioned association followed certain SES gradients. Although EV-A71 vaccines could prevent EV-A71-related severe HFMD [18], 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 Data). 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 = .0020) compared with those excluded, but demographic characteristics, medical history, EV serotypes, and clinical severity were roughly comparable between them (Supplementary Table 1). 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 (Supplementary Table 1).

The median revised FAS score of the 1229 included HFMD inpatients (IQR) was 3 (2–5) (Supplementary Figure 1). Inpatients with scores between 0–2, 3–5, and 6–8 were grouped into the low, intermediate, and high categories of the revised FAS and accounted for 26.9%, 57.7%, and 15.4% of the included

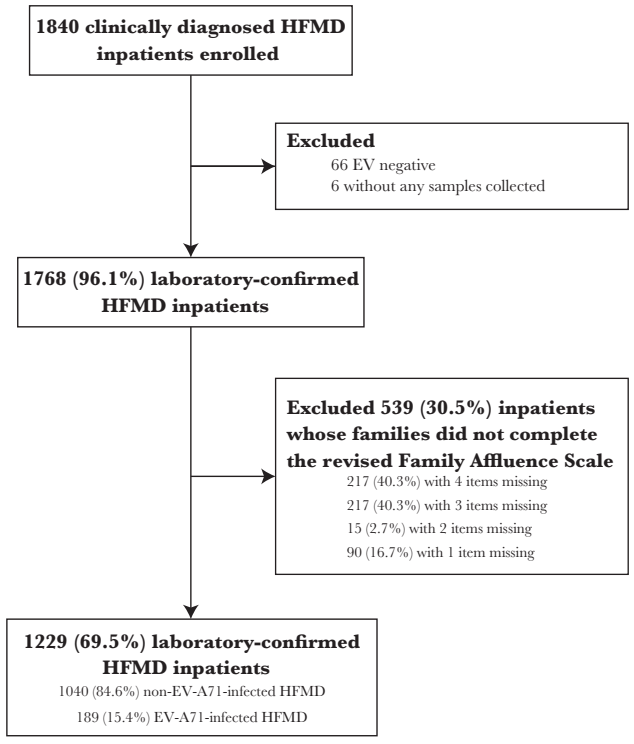

Figure 1. Flowchart for the inclusion of HFMD inpatients in this study. Abbreviation: HFMD, hand, foot, and mouth disease.

inpatients, respectively. Table 1 shows the characteristics of the 1229 included HFMD inpatients by the revised FAS categories, 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 ($P < .0001$) and to be unvaccinated against EV-A71 ($P = .0133$) (Table 1).

The distribution of EV serotypes was significantly different between the revised FAS categories ($P = .0075$) (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 ($P = .0094$), delayed diagnosis ($P = .0281$), and delayed hospitalization ($P = .0004$) (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 (Cochran-Armitage trend test) (Supplementary Figure 2).

In terms of economic burden, severe HFMD inpatients had significantly higher hospitalization costs than mild inpatients for all 4 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 (Table 2; Supplementary Figure 2). Univariate analysis showed that severe HFMD was

Table 1. Characteristics of the Included HFMD Inpatients by Revised FAS Categories

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)	.733
Age group					.172
<1 y	172 (14.0)	54 (15.7)	96 (13.6)	22 (12.4)	
1 y	558 (45.4)	140 (40.8)	341 (48.2)	77 (43.3)	
2–14 y	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)	<.0001
EV-A71 vaccinated	163 (13.3)	31 (9.0)	110 (15.5)	24 (12.4)	.0133
EV serotypes					.0075
EV-A71	189 (15.4)	73 (21.3)	97 (13.7)	19 (10.6)	
CV-A16	251 (20.4)	62 (18.1)	142 (20.1)	47 (26.4)	
CV-A6	383 (31.2)	96 (28.0)	231 (32.6)	56 (31.5)	
Other	406 (33.0)	112 (32.6)	238 (33.6)	56 (31.5)	
Health-seeking behavior					
Time of the first medical consultation after illness onset, d	1.00 [0.00–1.00]	0.00 [0.00–1.00]	1.00 [0.00–1.00]	1.00 [0.00–1.00]	.310
Institutional rank of the first medical consultation					.0603[b]
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)	.0094
Time of the first diagnosis of HFMD after illness onset, d	1.00 [0.00–2.00]	1.00 [0.00–2.00]	1.00 [0.00–2.00]	1.00 [0.00–2.00]	.0281
Time of hospitalization at Henan Children's Hospital after illness onset, d	2.00 [1.00–3.00]	2.00 [1.00–3.00]	2.00 [1.00–3.00]	1.50 [1.00–3.00]	.0004
Clinical characteristics					
CNS complications[a]					
Brainstem encephalitis	123 (10.0)	49 (14.3)	62 (8.8)	12 (6.7)	.0058
Encephalitis	26 (2.1)	10 (2.9)	12 (1.7)	4 (2.2)	.391
Encephalomyelitis	14 (1.1)	7 (2.0)	6 (0.8)	1 (0.6)	.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)	.0986
Acute flaccid paralysis	2 (0.2)	2 (0.6)	0 (0.0)	0 (0.0)	.0986
Special treatments					
Systemic corticosteroids	215 (17.5)	75 (21.9)	118 (16.7)	22 (12.4)	.0172
IVIG	81 (6.6)	34 (9.9)	41 (5.8)	6 (3.4)	.0072
Length of stay, d	4.00 [4.00–5.00]	5.00 [4.00–6.00]	4.00 [4.00–5.00]	4.00 [4.00–5.00]	<.0001

Data are presented as No. (%) or median [interquartile range].

Abbreviations: CNS, central nervous system; HFMD, hand, foot, and mouth disease; IVIG, intravenous human immunoglobulin.

[a]The diagnosis categories were mutually exclusive.

[b]The comparison excluded unknown.

Table 2. Crude Association Between the Clinical Severity of HFMD Inpatients and Revised FAS Categories and Hospitalization Cost Distribution of HFMD Inpatients by Clinical Severity

Clinical Severity	Severe	Mild	*P* Value[a]	Crude OR (95% CI)	*P* Value[b]
CNS complications	171 (13.9)	1058 (86.1)			
High	17 (9.9)	161 (15.2)	<.0001	Reference	…
Intermediate	83 (48.6)	625 (59.1)		1.26 (0.74–2.25)	.404
Low	71 (41.5)	272 (25.7)		2.48 (1.44–4.47)	.0008
Hospitalization cost, yuan	8743.75 [3726.97–15 607.58]	2916.75 [2528.90–3399.99]	<.0001		
Receiving special treatments	215 (17.5)	1014 (82.5)			
High	22 (10.2)	156 (15.4)	.0044	Reference	…
Intermediate	118 (54.9)	590 (58.2)		1.42 (0.89–2.36)	.149
Low	75 (34.9)	268 (26.4)		1.98 (1.20–3.39)	.0066
Hospitalization cost, yuan	6201.24 [3634.86–12 907.10]	2887.14 [2502.92–3336.41]	<.0001		
ICU admission	49 (4.0)	1180 (96.0)			
High	1 (2.0)	177 (15.0)	<.0001	Reference	…
Intermediate	23 (46.9)	685 (58.1)		5.94 (1.24–106.64)	.0211
Low	25 (51.1)	318 (26.9)		13.92 (2.91–249.48)	.0001
Hospitalization cost, yuan	18 919.72 [15 751.26–26 730.58]	2978.92 [2557.43–3566.37]	<.0001		
LOS >5 d	237 (19.3)	992 (80.7)			
High	15 (6.3)	163 (16.4)	<.0001	Reference	…
Intermediate	127 (53.6)	581 (58.6)		2.38 (1.39–4.33)	.0010
Low	95 (40.1)	248 (25.0)		4.16 (2.40–7.70)	<.0001
Hospitalization cost, yuan	5230.63 [3817.30–11 648.80]	2861.18 [2496.86–3281.87]	<.0001		

Data were No. (%) or median [interquartile range].

Abbreviations: CNS, central nervous system; OR, odds ratio HFMD, hand, foot, and mouth disease; ICU, intensive care unit; LOS, length of stay.

[a] *P* value from Wilcoxon rank-sum test or Kruskal-Wallis test.

[b] *P* value from log-likelihood ratio test.

significantly associated with a lower material deprivation score and the lower categories of the revised FAS, and these associations increased as the revised FAS category descended (Tables 2 and 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 for 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 4 severity criteria. Given the associations of passive health-seeking behavior with the revised FAS and severe HFMD (Supplementary Tables 6 and 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; $P = .0509$). 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 categories, 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 4 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 2A). 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 2D).

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 re-analyzed. 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, 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 to investigate its association with clinical severity. In both the 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 >5000 yuan (US$740).

Table 3. Associations Between the Clinical Severity of HFMD Inpatients and Family Affluence–Based SES (Material Deprivation Score) by Clinical Severity

Model	Overall (n = 1229)		
	Adjusted OR (95% CI)	*P* Value[a]	*P* Value for Interaction Between EV-A71 and SES[a]
Univariate			
CNS complications	3.43 (1.99–5.98)	<.0001	-
Receiving special treatments	2.18 (1.35–3.53)	.0013	-
ICU admission	10.34 (3.51–33.00)	<.0001	-
LOS >5 d	3.86 (2.43–6.21)	<.0001	-
Model 1[b]			
CNS complications	2.81 (1.46–5.48)	.0019	.392
Receiving special treatments	1.86 (1.04–3.34)	.0374	.370
ICU admission	7.14 (2.17–25.39)	.0010	.570
LOS >5 d	4.09 (2.35–7.20)	<.0001	.968
Model 2[c]			
CNS complications	-	-	-
Receiving special treatments	1.89 (1.05–3.41)	.0326	.370
ICU admission	7.27 (2.21–25.78)	.0009	.597
LOS >5 d	4.25 (2.43–7.50)	<.0001	.968
Model 3[d]			
CNS complications	2.72 (1.41–5.31)	.0029	.358
Receiving special treatments	1.80 (0.99–3.26)	.0509	.330
ICU admission	7.30 (2.21–25.97)	.0009	.598
LOS >5 d	4.28 (2.44–7.58)	<.0001	.970
Sensitivity analysis (multiple imputation)			
Model 3[d]			
CNS complications	1.85 (1.02–3.34)	.0438	.334
Receiving special treatments	1.45 (0.86–2.46)	.166	.468
ICU admission	4.01 (1.23–13.09)	.0223	.483
LOS >5 d	3.19 (1.84–5.54)	.0001	.612

Abbreviations: CNS, central nervous system; HFMD, hand, foot, and mouth disease; ICU, intensive care unit; LOS, length of stay; OR, odds ratio; SES, socioeconomic status.

[a] *P* value of log-likelihood ratio test.

[b] Model 1 was adjusted by age, sex, rural residence, and EV-A71 infection.

[c] Model 2 was further adjusted by time of first medical consultation, based on model 1.

[d] Model 3 was further adjusted by 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.

The quantitative SES measurement used in this study was derived from the FAS II, which has characteristics of insensitivity, simplicity, and high response rate [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 Data) showed that the revised FAS was an acceptable measurement with a moderate response rate (Supplementary Figure 3, Supplementary Table 8), internal reliability (Supplementary Tables 9 and 10), and adequate external (Supplementary Table 11) and structural validity (Supplementary Figure 4). 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 [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 [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 to be significantly associated with severe HFMD (Supplementary Table 6), which was consistent with previous risk factor studies of severe HFMD [3, 11, 13, 15].

The present study demonstrates 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 traditional SES indicators were categorical or semiquantitative measurements that lacked unified definitions

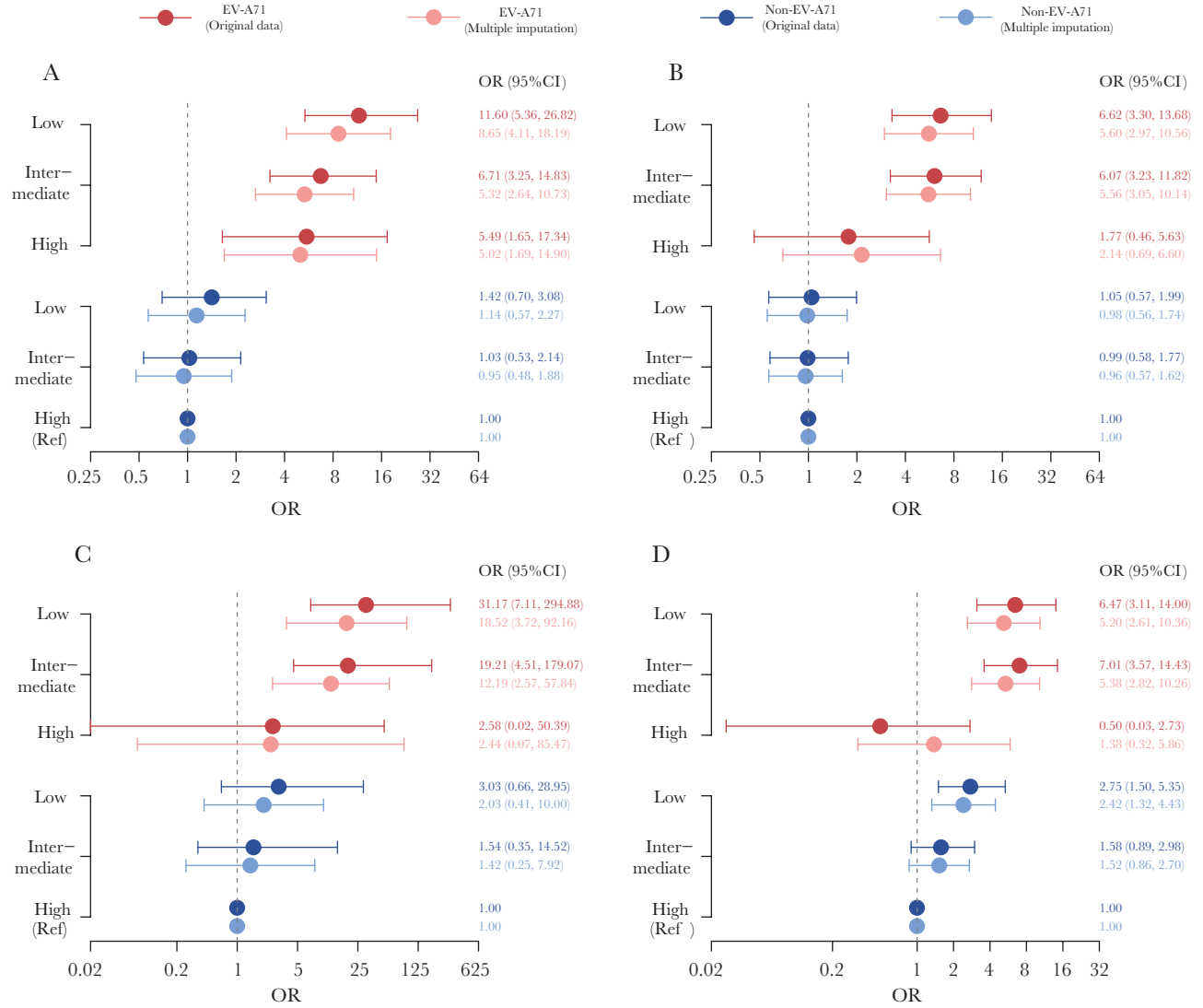

Figure 2. Adjusted associations of the clinical severity of HFMD inpatients with EV-A71 infection and revised FAS categories. A, CNS complications. B, Receiving special treatments. C, ICU admission. D, LOS >5 days. ORs were adjusted by age, sex, rural residence, and health-seeking behavior. Specifically, 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. Abbreviations: CNS, central nervous system; FAS, Family Affluence Scale; HFMD, hand, foot, and mouth disease; ICU, intensive care unit; LOS, length of stay; OR, odds ratio.

and consistent classifications. For example, Zeng et al. [12] and Pan et al. [15] used different definitions of floating population in their studies, and they reached inconsistent results on the association between floating population and severe HFMD. Similarly, Huang et al. [13] and Cao et al. [14] used inconsistent income classifications in their studies, and their results about the effect of household income on HFMD clinical severity were conflicting. Additionally, ecological indicators like rural residents and floating populations may lead to misclassification of SES [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 supports 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 that the association between caregiver education level and severe HFMD decreased as education level increased [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 EV-A71 is the neurotrophic virus that has accounted for most of the severe HFMD for many years [1–6]. It is 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 discharge out of concerns about incompetent parental monitoring of lower-SES families and their limited medical resource accessibility, irrespective of EV serotypes [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 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 [8, 27]. Many clinical signs and symptoms have been identified as predictors of severe HFMD [1, 2, 16], and an unawareness of these predictors may lead to missed opportunities to prevent disease progression at an early stage [1, 2]. In addition, specific antiviral drugs are still unavailable, and mainstream strategies for clinical management are limited to supportive therapies [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 [7–9, 28].

Notably, we found that severe HFMD inpatients incurred high hospitalization costs, which accounted for a non-negligible proportion of the per capita annual disposable income of Henan province in 2017 (20 170 yuan/US$2987), ranging from 25.9% for prolonged hospitalization to 93.8% for ICU admission [29]. In contrast, the 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, as socioeconomically disadvantaged populations themselves are vulnerable to heavy economic burden. Therefore, our findings add to the evidence in support of offering sufficient monetary support to severe HFMD inpatients via medical subsidy and reimbursement policies. This intervention could help alleviate the HFMD-related economic burden of low-SES populations and reduce potential SES inequality.

There are some limitations associated with this study. First, 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 be representative of the overall population of HFMD inpatients, and extrapolation should be conducted with caution. In the future, multicenter studies or HFMD surveillance systems that include SES information are needed to verify our findings. Second, socioeconomic information was self-reported without external validation in this study, and reporting bias inevitably existed. However, the items of the revised FAS have been deemed simple and insensitive [19, 20]; therefore, this bias should not be a major concern. Finally, the nonresponse 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 HMFD inpatients was significantly associated with family affluence–based SES, and severe HFMD inpatients were more likely to have lower SES than nonsevere 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.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases online*. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Author contributions. H.J.Y. and Y.L. designed the study. H.J.Y. supervised the study. F.W., Y.L., L.L., P.C., S.J.H., Y.B.C., C.G., M.Y.Z., L.L., and T.C.Z. collected data and specimens. Y.H.Z. and Q.Q. performed virologic testing. Y.L., L.L., P.C., Y.H.Z., Q.Q., C.G., M.Z.Y., L.L., and T.C.Z. cleaned the data. K.W. analyzed the data and wrote the drafts of the manuscript. H.J.Y., K.W., and Y.L. interpreted the findings. F.W., S.J.H., and Y.B.C. commented on and revised drafts of the manuscript. All authors have verified the underlying data. All authors read and approved the final report.

Patient consent. The Institutional Review Boards of Henan Children's Hospital (IRB#YZ-17-006), the 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.

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