# Risk Factors for Severe Hand-Foot-Mouth Disease in China: A Systematic Review and Meta-Analysis

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**Background:** This study aimed to identify potential risk factors for severe hand-foot-mouth disease (HFMD).

**Methods:** The PubMed, Embase, the Cochrane Library, Sinomed, WanFang, CNKI, and VIP databases were searched (up to August 2021).

**Results:** Twenty-nine studies (9,241 and 927,355 patients with severe HFMD and controls, respectively; all from China) were included. EV71 was associated with higher odds of severe HFMD compared with other agents (OR = 4.44, 95%CI: 3.12–6.33, $p < 0.001$). Being home-raised (OR = 1.99, 95%CI: 1.59–2.50, $p < 0.001$), higher number of children in the family (OR = 2.09, 95%CI: 1.93–2.27, $p < 0.001$), poor hand hygiene (OR = 2.74, 95%CI: 1.78–4.23, $p < 0.001$), and no breastfeeding (OR = 2.01, 95%CI: 1.45–2.79, $p < 0.001$) were risk factors for severe HFMD. First consulting to a district-level or above hospital (OR = 0.34, 95%CI: 0.25–0.45, $p < 0.001$) and diagnosis of HFMD at baseline (OR = 0.17, 95%CI: 0.13–0.24, $p < 0.001$) were protective factors against severe HFMD. Fever, long fever duration, vomiting, lethargy, leukocytosis, tic, and convulsions were each associated with severe HFMD (all $p < 0.05$), while rash was not.

**Conclusions:** EV71, lifestyle habits, frequent hospital visits, and symptoms are risk factors for severe HFMD in children in China, while early diagnosis and admission to higher-level hospitals are protective factors.

Keywords: hand-foot-mouth disease, infection, meta-analysis, risk factors, disease severity

## INTRODUCTION

Hand-foot-mouth disease (HFMD) is widespread among children and is generally characterized by fever, oral ulcers, and rash on the hands, feet, and buttocks [1–3]. The main causative pathogens include human enterovirus 71 (EV 71), Coxsackievirus A16 (CA 16), and other enteroviruses [1–3]. The common route of transmission of HFMD is through the fecal-oral route, respiratory droplets, contact with blister fluid, or close contact with infected children [1, 2]. Although most cases are mild and self-limited, HFMD is a serious

public health concern in children throughout Asia (4). Indeed, the majority of outbreaks are reported in Malaysia, Vietnam, China, Cambodia, and India (2), with an incidence of 115–197 cases per 100,000 person-years (5, 6). Severe or fatal HFMD cases have been reported in epidemiological studies as being frequent in Malaysia, Japan, Vietnam, and China and have received extensive attention from the global public health sector (4, 7–10). Studies from China have reported 27,908 children with HFMD and 905 children with fatal HFMD in 2010 (11, 12).

The most common manifestations of fatal HFMD are encephalitis and subsequent pulmonary edema, but myocarditis, neurologic complications, and paroxysmal tachycardia have been reported (1–3, 8, 13–15). Moreover, brainstem and thalamus symptoms occur at an early stage and are associated with a poor prognosis of HFMD (16).

Therefore, it is important to examine the biological and behavioral characteristics of children to identify the risk factors associated with progression to severe HFMD due to the additional fatality risk in severe cases. Several factors were shown to be associated with an increased risk of severe HFMD in China (17). Various risk factors for severe HFMD were reported in the literature (18–20), but there is a lack of consensus because of different factors being analyzed in the first place, different outcomes, and different study populations.

Hence, these results were not consistent, so continued investigations are needed to confirm known and identify additional potential risk factors. The current meta-analysis was conducted to explore the potential factors associated with the progression to severe HFMD.

## METHODS

### Data Sources, Search Strategy, and Selection Criteria

This study was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement (21, 22). Any study (irrespective of the language) that investigated the risk factors for severe HFMD was eligible for inclusion in this study. The electronic databases of PubMed, Embase, the Cochrane Library, Sinomed, WanFang, CNKI, and VIP were systematically searched from their inception up to August 2021. The core search terms included "hand foot mouth disease" OR "coxsackievirus a16" OR "enterovirus 71" AND "risk factors." The reference lists from the retrieved studies were also reviewed to identify any potentially eligible studies.

Two authors independently conducted the literature search and study selection following a standardized form, and any disagreement was settled by a third author. The inclusion criteria were (1) study design: prospective or retrospective observational study, (2) participants: individuals with HFMD, (3) exposure: the study reported the effect estimates of potential risk factors for severe HFMD, (4) outcomes: severe HFMD [i.e., the development of nervous system involvement, physical signs of meningeal irritation, or weakened or missing tendon reflexes (23)]; and (5) sample size >30. Severe HFMD was diagnosed according to the

Chinese guidelines that were current when the included studies were conducted; the most recent version is 2018 (24).

### Data Collection and Quality Assessment

The data abstraction and quality assessment were conducted by two authors, and any inconsistency was resolved by a third author after referring to the original article. The following variables were collected: first author's surname, publication year, study design, country, sample size, number of boys and girls, mean age, the definition of severe cases, and reported factors. The study quality was assessed using the Newcastle-Ottawa score (NOS) scale, which is based on selection (four items), comparability (one item), and outcome (three items), and the star system ranges from 0 to 9 (25).

### Statistical Analysis

The odds ratios (ORs) and their 95% confidence intervals (CIs) were extracted from the multivariable logistic regressions presented in the original papers. The summary ORs were calculated using the random-effects model to account for heterogeneity in study design and populations among studies (26, 27). Heterogeneity across included studies was assessed by $I^2$- and $Q$-statistics, and $p$-value $< 0.10$ was regarded as significant heterogeneity (28, 29). Sensitivity analyses were conducted for risk factors reported in more than four studies to assess the impact of a single study on the overall analysis (30), as well as for EV 71. Publication biases were evaluated using the funnel plot, Egger test (31), Begg test (32), and trim and fill analysis (33). Two-sided $p < 0.05$ was considered statistically significant. All statistical analyses were conducted using STATA 10.0 (Stata Corporation, College Station, TX, USA).

## RESULTS

### Literature Search

**Figure 1** presents the study selection process. The initial search yielded 993 entries, and 664 were screened after removing the duplicates. From these, 608 were excluded, and 56 full-text papers were screened. Then, 27 studies were excluded (sample size, $n = 2$; unclear diagnostic criteria, $n = 12$; data could be extracted, $n = 8$; outcome, $n = 5$). Finally, 29 studies were included.

### Characteristics of the Studies

**Table 1** presents the characteristics of the studies. There were 19 case-control studies, seven matched case-control studies, and two nested case-control studies. There were 9,241 patients with severe HFMD (31–3,738/study) and 927,355 controls (37–920,011/study). Regarding the NOS, nine studies scored five stars, seven scored six stars, eleven scored seven stars, and two scored eight stars out of a possible total of nine stars.

### Association of EV 71 With Severe HFMD

Nineteen studies presented data regarding the association of EV 71 with severe HFMD. The overall meta-analysis showed that EV 71 is associated with higher odds of severe HFMD compared with other etiologic agents (OR = 4.44, 95%CI: 3.12–6.33, $p$ < 0.001, $I^2$ = 92.9%, $p_{\text{heterogeneity}}$ < 0.001) (**Figure 2**). This

**FIGURE 1 |** PRISMA 2009 flow diagram of the study selection process.
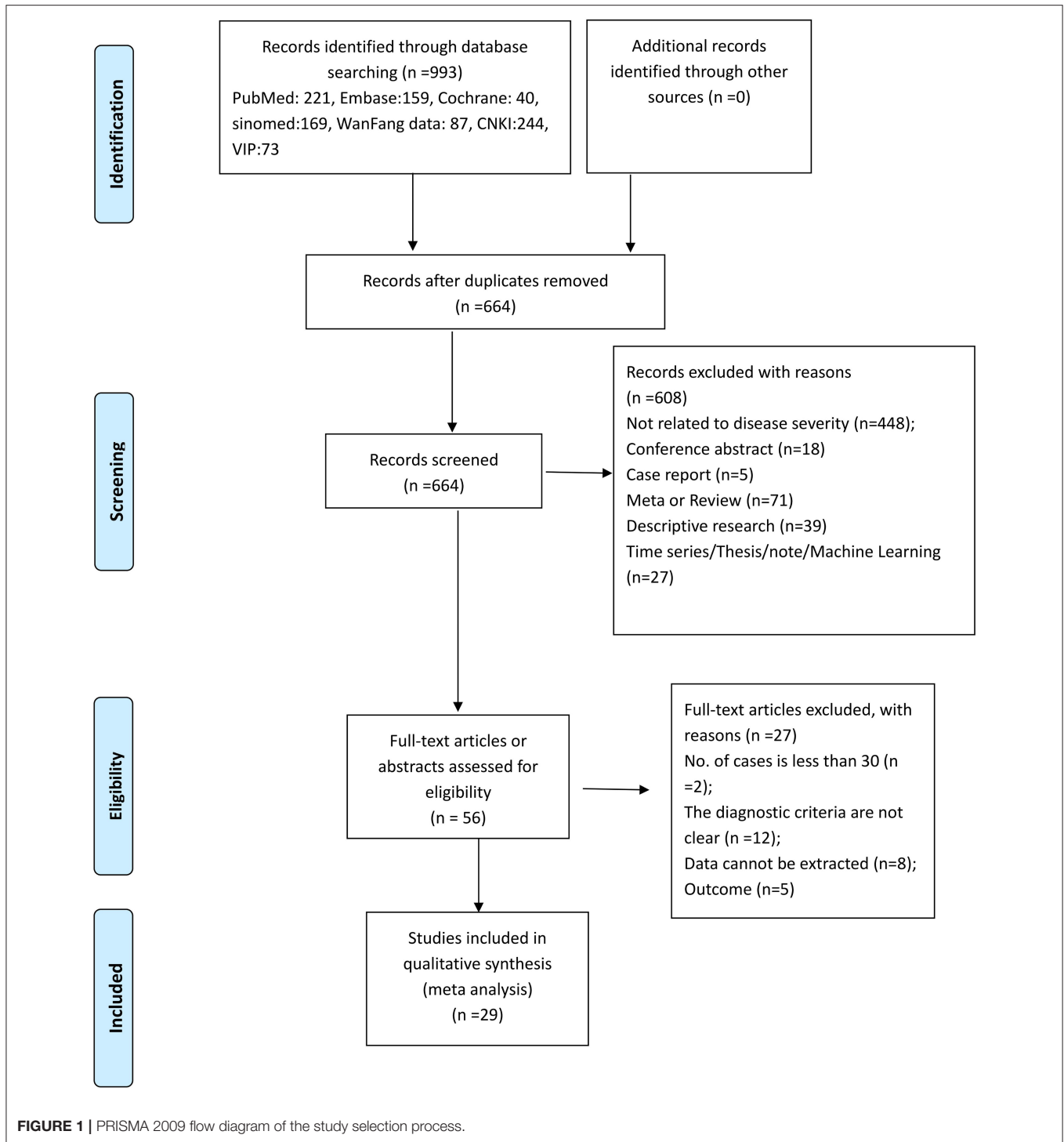
association was observed irrespective of the type of study: case-control (OR = 4.41, 95%CI: 2.86–6.79, $p < 0.001$, $I^2 = 94.8\%$, $p_{\text{heterogeneity}} < 0.001$), matched case-control (OR = 5.07, 95%CI: 2.29–11.24, $p < 0.001$, $I^2 = 74.1\%$, $p_{\text{heterogeneity}} = 0.004$), and nested case-control (OR = 3.91, 95%CI: 1.32–11.55, $p = 0.014$).

The sensitivity analysis (**Supplementary Figure 1A**) showed that Du 2018 (41) influenced the results of the association

of EV 71 with severe HFMD. It can be seen that the $I^2$ decreased to 78.1% after Du 2018 (41) was removed (**Supplementary Figure 1B**).

## Demographic Factors

**Figure 3** and **Supplementary Figure 2** shows that age (seven studies, OR = 0.98, 95%CI: 0.95–1.02, $p = 0.35$, $I^2 = 77.6\%$,

TABLE 1 | Characteristics of the included studies.

| | Country and province | Study design | Sample size (cases/controls) | Mean age (cases/controls, month) | Sex [cases/controls, males (%)] | Guidelines version for the diagnosis and treatment | Total quality score (NOS) |
|---|---|---|---|---|---|---|---|
| Li and Xu (34) | China, Shenyang | Case-control | 112/224 | NA | 57.1/60.3 | 2018 | 7 |
| Liu and Qi (35) | China, Shenzhen | Case-control | 131/174 | 20.6/20.5 | 64.1/55.8 | 2018 | 7 |
| Wang et al. (23) | China, Zhengzhou | Case-control | 1,750/582 | 28.0/24.3 | 64.8/64.9 | 2010 | 5 |
| Zhou and Li (36) | China, Kaifeng | Case-control, matched | 162/245 | 20.4/20.3 | 63.0/67.0 | 2010 | 7 |
| Zhai et al. (37) | China, Danzhou | Case-control, matched | 582/582 | 30.3/38.4 | 64.9/61.0 | 2010 | 5 |
| Xiong et al. (38) | China, Shenzhen | Case-control, matched | 36/38 | 29.4/37.2 | 75.0/60.5 | 2010 | 7 |
| Xiong et al. (39) | China, Shenzhen | Case-Control, matched | 101/101 | 22.1/21.1 | 62.4/62.4 | 2010 | 7 |
| Bai and Wu (40) | China, Nanyang | Case-control | 94/337 | 37.2/45.6 | 56.4/51.0 | 2010 | 5 |
| Du et al. (41) | China, Guangdong | Case-control | 3,738/920,011 | NA | 64.4/66.6 | 2008 or 2010 | 6 |
| Liu et al. (42) | China, Shantou | Case-control, matched | 225/492 | 28.6/30.8 | 67.6/61.6 | 2010 | 6 |
| Fu et al. (43) | China, Hainan | Case-control | 663/624 | 29.8/38.0 | 66.5/62.7 | 2010 | 5 |
| Zhang et al. (44) | China, Chongqing | Case-control | 90/90 | NA | 67.8/62.2 | 2010 | 5 |
| Xuan et al. (45) | China, Jilin | Case-control | 50/50 | 24/24 | NA | 2010 | 7 |
| Luo et al. (46) | China, Qiandongnan Miao and Dong Autonomous Prefecture | Case-control, matched | 43/43 | NA | 62.8/NA | 2009 | 8 |
| Li and Gu (47) | China, Wuxi | Case-control | 177/240 | NA | 63.8/NA | 2009 or 2010 | 5 |
| Ying et al. (48) | China, Lianyungang | Case-control | 151/1,535 | NA | / | 2010 | 6 |
| Lv et al. (49) | China, Shaoxing | Case-control | 175/183 | NA | 70.9/66.1 | 2010 | 5 |
| Du et al. (50) | China, Zhaoqing | Case-control | 182/265 | 21/21.6 | 65.9/69.8 | 2009 or 2010 | 7 |
| Wang et al. (12) | China, Liuzhou | Case-control | 57/114 | 21.4/22.8 | NA/68.4 | 2009 | 7 |
| Mou et al. (51) | China, Shenzhen | Nested case-control | 286/286 | 24.1/29.8 | 62.9/65.7 | 2009 or 2010 | 7 |
| Duan et al. (52) | China, Zhengzhou | Nested case-control | 65/37 | 23.5/22.6 | 60.0/62.2 | 2010 | 7 |
| Xie et al. (53) | China, Huaihua | Case-control | 80/262 | 26.1/24.5 | 50.0/49.6 | 2010 | 5 |
| Zhibing (54) | China, Beijing | Case-control | 56/56 | 56.7/51.6 | 57.1/62.5 | 2010 | 5 |
| Li et al. (55) | China, Xi'an | Case-control | 116/202 | NA | 71.6/63.4 | 2010 | 7 |
| Yang et al. (56) | China, Wuhan | Case-control | 50/100 | NA | 68.0/53.0 | 2009 | 6 |
| Ruan et al. (57) | China, Xiamen | Case-control | 31/69 | 28.8/37.2 | NA | 2010 | 6 |
| Pan et al. (58) | China, Shanghai | Case-control | 105/210 | 25.8/32.9 | 69.5/55.2 | 2010 | 6 |
| Wu et al. (59) | China, Shanghai | Case-control, matched | 73/146 | 23/25.4 | 63.0/64.4 | 2010 | 8 |
| Cao et al. (60) | China, Anhui | Case-control | 85/57 | NA | NA | 2008 | 6 |

$p_{\text{heterogeneity}} < 0.001$) and male sex (five studies, OR = 1.20, 95%CI: 0.90–1.61, $p = 0.22$, $I^2 = 51.7\%$, $p_{\text{heterogeneity}} = 0.082$) were not associated with severe HFMD.

## Socio-Economic Status and Lifestyle

**Figure 4** and **Supplementary Figure 2** shows that rural residency (OR = 1.99, 95%CI: 0.97–4.08, $p < 0.059$, $I^2 = 84.2\%$, $p_{\text{heterogeneity}} < 0.001$) was not a risk factor for severe HFMD, while being home-raised (i.e., not frequenting kindergarten) (OR = 1.99, 95%CI: 1.59–2.50, $p < 0.001$, $I^2 = 81.8\%$, $p_{\text{heterogeneity}} < 0.001$), higher number of children in the family (OR = 2.09, 95%CI: 1.93–2.27, $p < 0.001$, $I^2 = 0.0\%$, $p_{\text{heterogeneity}} = 0.790$), poor hand hygiene (OR = 2.74, 95%CI: 1.78–4.23, $p < 0.001$, $I^2 = 57.8\%$, $p_{\text{heterogeneity}} = 0.093$), and no breastfeeding (OR = 2.01, 95%CI: 1.45–2.79, $p < 0.001$, $I^2 = 0.0\%$, $p_{\text{heterogeneity}} = 0.558$) were risk factors for severe HFMD.
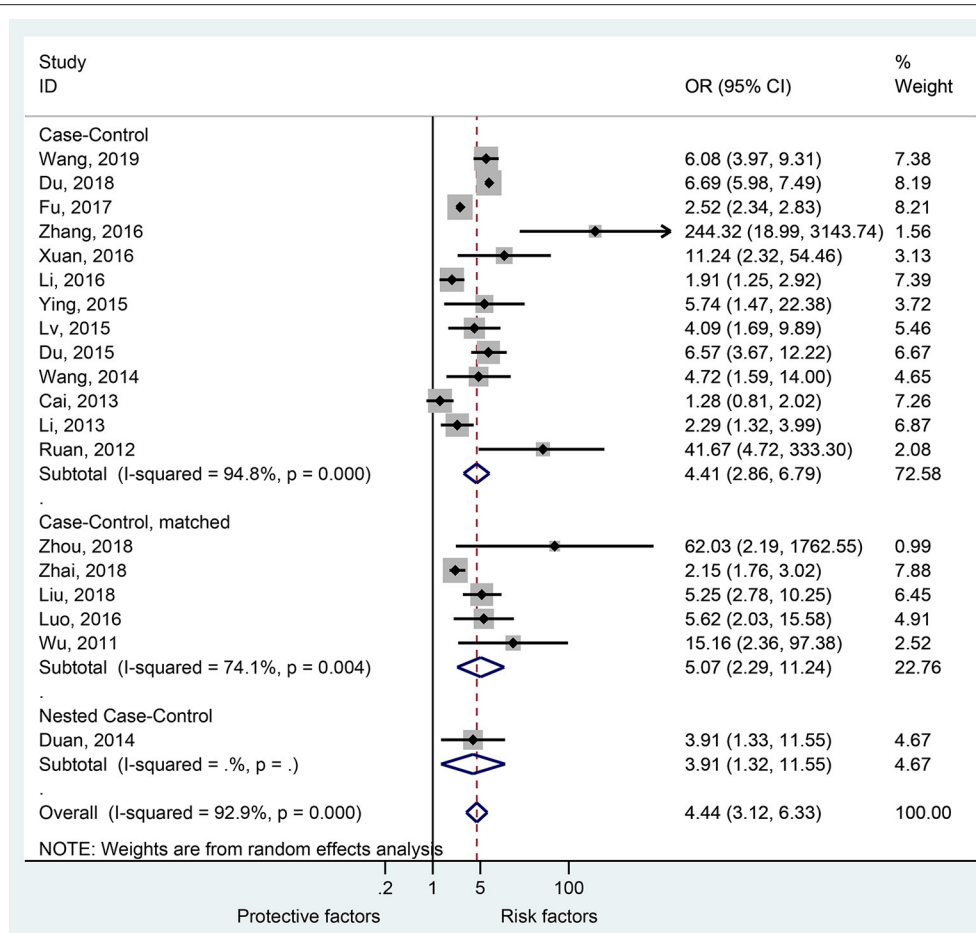
**FIGURE 2 |** Forest plot for the association of enterovirus 71 with severe hand foot mouth disease.

## Clinical Pathway

Among the clinical pathway factors that could influence the outcomes of HFMD, first consulting to a district-level or above hospital (OR = 0.34, 95%CI: 0.25–0.45, $p < 0.001$, $I^2 = 0.0\%$, $p_{heterogeneity} = 0.649$) and diagnosis of HFMD at baseline (OR = 0.17, 95%CI: 0.13–0.24, $p < 0.001$, $I^2 = 42.9\%$, $p_{heterogeneity} = 0.081$) were protective factor against severe HFMD (**Figure 5**; **Supplementary Figure 2**), while >3 visits at the clinic in the past 6 months was a risk factor for severe HFMD (OR = 1.80, 95%CI: 1.03–3.14, $p = 0.037$, $I^2 = 97.8\%$, $p_{heterogeneity} < 0.001$). The time from onset to the first visit at the hospital was not associated with severe HFMD (OR = 1.60, 95%CI: 0.45–5.70, $p = 0.467$, $I^2 = 87.0\%$, $p_{heterogeneity} < 0.001$).

## Symptoms

**Supplementary Table 1** and **Supplementary Figure 2** show that fever (OR = 3.23, 95%CI: 2.31–4.70, $p < 0.001$, $I^2 = 66.2\%$, $p_{heterogeneity} < 0.001$), long fever duration (OR = 5.36, 95%CI: 2.33–12.35, $p = 0.001$, $I^2 = 91.3\%$, $p_{heterogeneity} < 0.001$), vomiting (OR = 64.30, 95%CI: 5.53–747.80, $p < 0.001$, $I^2 = 48.1\%$, $p_{heterogeneity} = 0.103$), lethargy (OR = 8.89,

95%CI: 2.55–30.93, $p = 0.001$, $I^2 = 84.1\%$, $p_{heterogeneity} < 0.001$), leukocytosis (OR = 2.26, 95%CI: 1.42–3.61, $p < 0.001$, $I^2 = 87.5\%$, $p_{heterogeneity} = 0.720$), tremors/myoclonic jerks (OR = 5.20, 95%CI: 3.14–8.64, $p < 0.001$, $I^2 = 5.9\%$, $p_{heterogeneity} < 0.001$), and convulsions (OR = 12.64, 95%CI: 1.15–139.00, $p = 0.038$, $I^2 = 53.0\%$, $p_{heterogeneity} = 0.145$) were each associated with severe HFMD, while rash was not (OR = 1.40, 95%CI: 0.25–7.87, $p = 0.704$, $I^2 = 87.3\%$, $p_{heterogeneity} < 0.001$).

## Publication Bias

The Egger test ($p < 0.001$) and the Begg test ($p = 0.021$) showed that there is publication bias (**Figures 6, 7**). Five studies would be needed to balance de publication bias (**Figure 7**).

## DISCUSSION

Various risk factors for severe HFMD were reported in the literature (18–20, 61), but there is a lack of consensus. This study aimed to identify potential risk factors for severe HFMD. The results indicate that EV 71, lifestyle habits (rural, being home-raised, a higher number of children in the family, poor
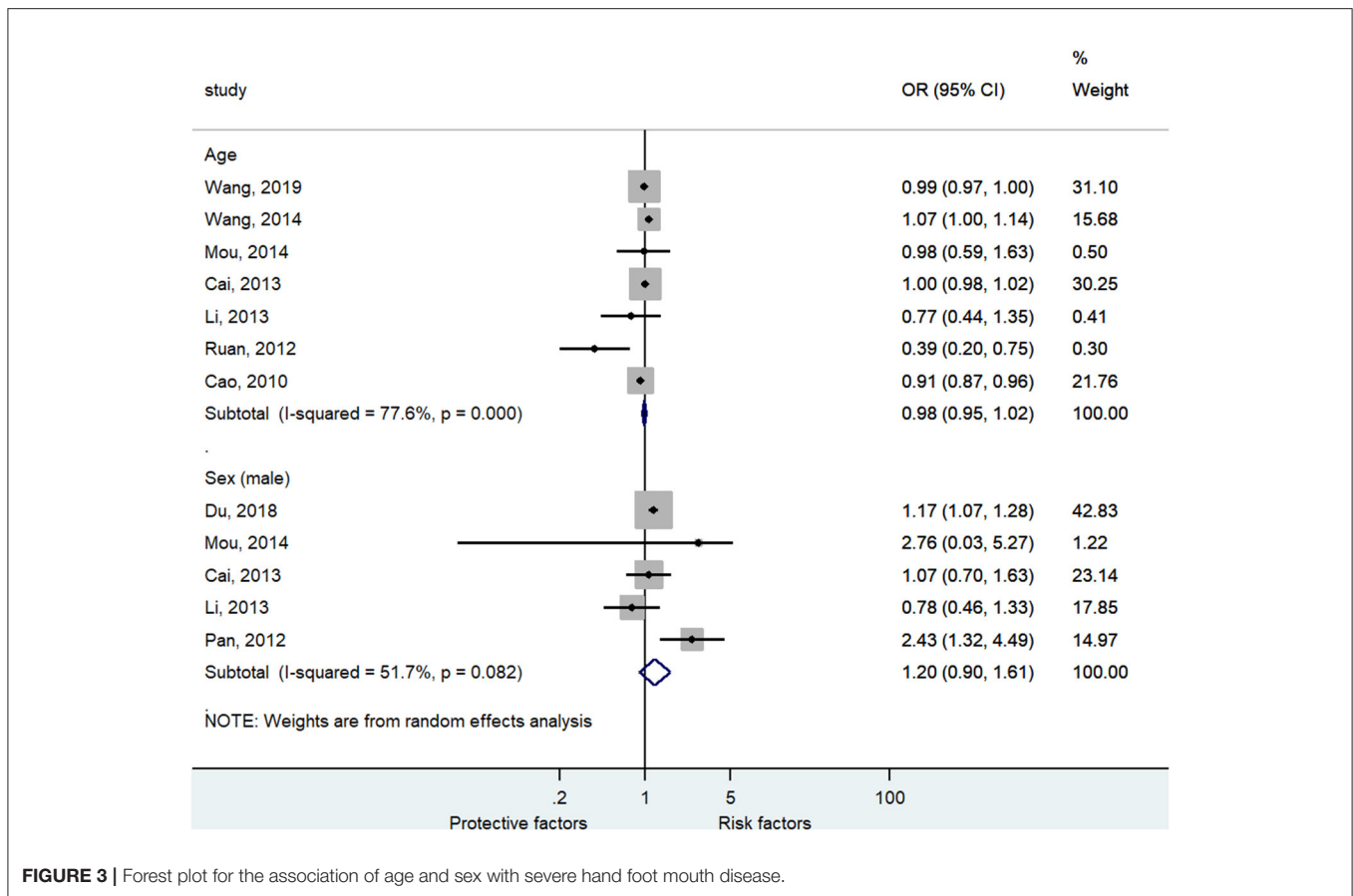
**FIGURE 3** | Forest plot for the association of age and sex with severe hand foot mouth disease.

hand hygiene, and no breastfeeding), clinical pathway (frequent hospital visits), and symptoms are risk factors for severe HFMD in children, while early diagnosis and admission to higher-level hospitals are protective factors.

Previous meta-analyses examined HFMD (18, 19, 61). Indeed, Sun et al. (18) examined the risk factors for severe HFMD. Peng et al. (19) examined the risk factors for neurogenic pulmonary edema in children with severe HFMD. Fang et al. (62) examined the risk factors for severe HFMD. Ni et al. (61) investigated the association between risk factors and death from HFMD. Therefore, in an innovative view, the present study focused on the risk factors and the changes in disease severity (from mild to severe).

EV 71 is a well-known risk factor for severe HFMD (4, 63–65), and it was confirmed once again. This EV serotype is the cause of HFMD outbreaks in the Asia-Pacific region, although it has been reported to be the cause of outbreaks in Europe and North America in the 1970s (66). This meta-analysis also showed that rural inhabitants are at higher risk of severe HFMD, probably because of poorer hygiene, lower education, lower economic status, and closer proximity to farm animals (e.g., living on a farm) which are supported by previous studies (67–69). In addition, being home-raised, a higher number of children in the family, and poor hand hygiene are already known to be associated with higher risks

of transmission of various pediatric diseases, as previously observed (44, 70, 71). On the other hand, a study showed that children attending daycare centers were at higher risk of severe HFMD (72). No breastfeeding is associated with a lower immune status in some children and could lead to more severe HFMD. Some previous studies showed that exclusive breastfeeding protected against HFMD (18, 73), supporting this meta-analysis.

As for any disease, early diagnosis and management are associated with better outcomes, as observed for HFMD (67, 74, 75). Higher-level hospitals are more likely to have experienced physicians with more awareness for the fast and accurate diagnosis of HFMD, as well as for proper management (35). In this study, the diagnosis of HFMD as the first diagnosis and higher-level hospitals were protective factors against severe HFMD. Frequent visits to the hospital might lead to higher nosocomial exposure to hospitals' pathogens, frailer constitution, or decreased awareness from the healthcare professionals toward children and their parents consulting too often. This will have to be examined more closely in future studies.

Symptom severity has already been associated with severe HFMD in previous meta-analyses and reviews. Our previous study illustrated a causal relationship between EV 71 infection and severe HFMD risk, the symptoms of critical illness including autokinetic eyeball, eyeball ataxia, severe coma, respiratory
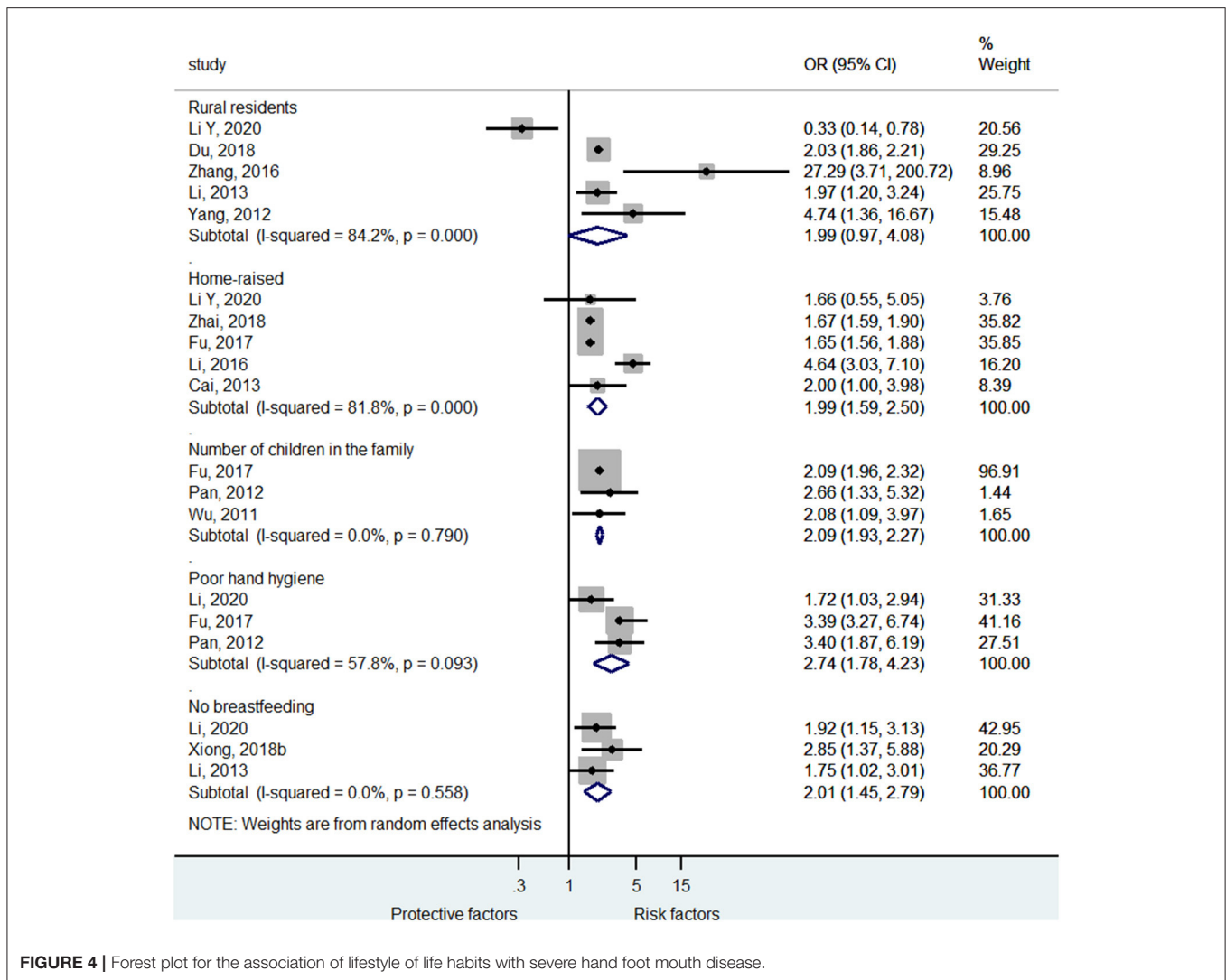
**FIGURE 4** | Forest plot for the association of lifestyle of life habits with severe hand foot mouth disease.

rhythm abnormality, ataxic respiration, absence of pharyngeal reflex, ultrahyperpyrexia (>40°C), excessive tachycardia (>220 bpm), pulmonary edema, and/or hemorrhage and refractory shock; and four indicators with time-correlation with half of the symptoms above, including CRT (capillary refill time) extension, tachycardia, hyperventilation, and nystagmus, which occurred before the above-mentioned critical illness symptoms and also indicated the risk of critical illness (76). Sun et al. (18) showed that fever >3 days and vomiting were associated with severe HFMD. Peng et al. (19) showed that limb tremors, vomiting, abnormal respiration, atypical rash, and drowsiness were associated with HFMD-associated pulmonary edema. The present study also showed that fever, long fever duration, vomiting, lethargy, leukocytosis, tremors/myoclonic jerks, and convulsions were risk factors for severe HFMD. Nevertheless, this study did not examine the risk factors of various complications of HFMD.

This study has limitations that must be considered when analyzing the results. First, although the eligibility criteria did not restrict the country and western databases (PubMed, Embase, and the Cochrane Library) were queried, all included studies were from China. It is probably because HFMD reaches epidemic proportions in some regions of China nearly every year and that EV 71 is particularly present and associated with severe forms of HFMD (4, 63–65). Western countries like the United States of America only have episodic HFMD epidemic events once every few years (3). Furthermore, heterogeneity was observed among the studies because of different study designs, different diagnostic criteria for severe HFMD, and different confounding factors included in the multivariable models. Of note, for the analysis of the association between EV 71 and severe HFMD, excluding Du 2018 (41) decreased heterogeneity. The possible reason is that the sample size of that study is too large compared with the other studies. Finally, publication bias was observed and indicated that positive-findings studies were overrepresented compared with the negative-findings ones. According to **Figure 7**, five studies would be needed to balance de publication bias.
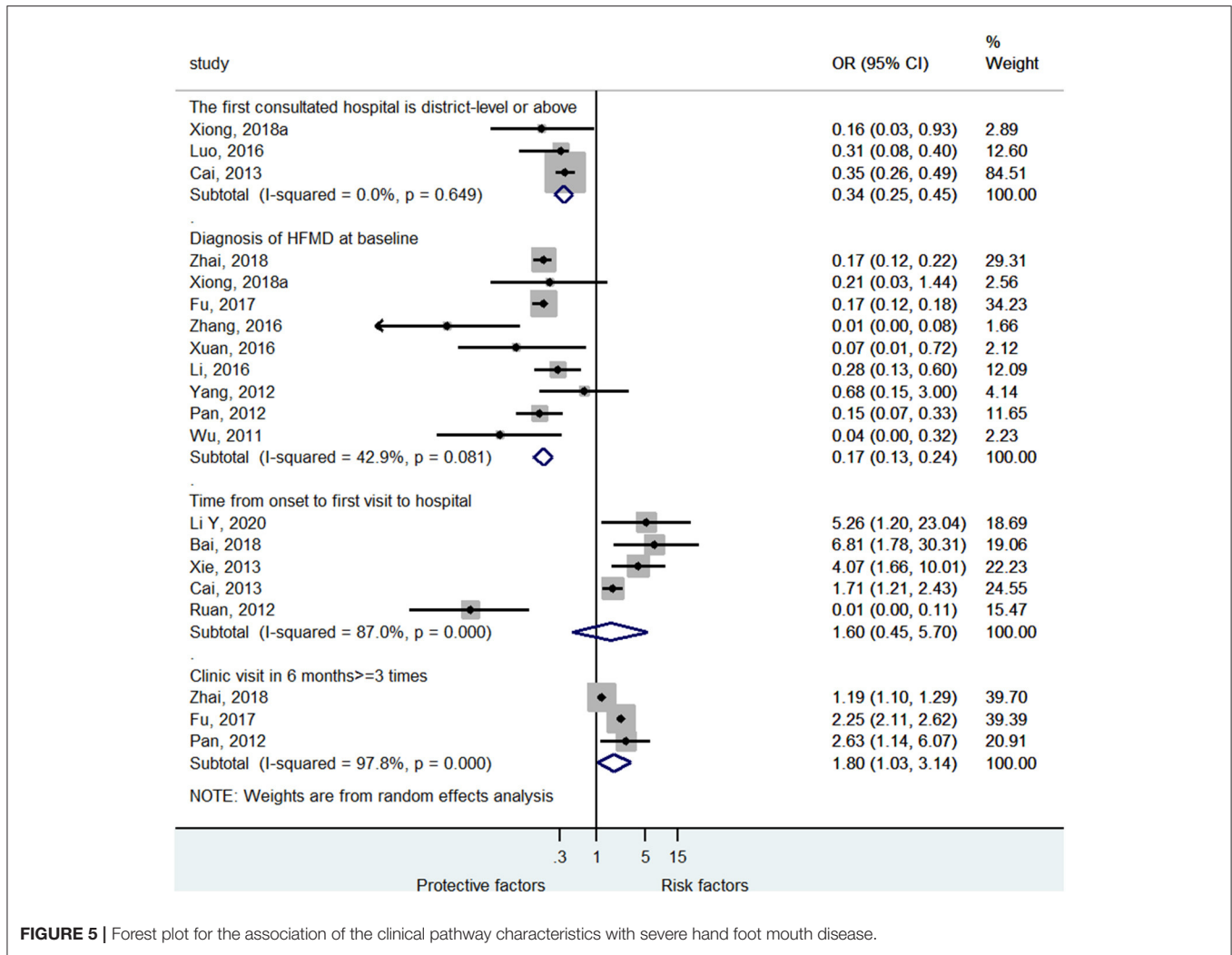
**FIGURE 5** | Forest plot for the association of the clinical pathway characteristics with severe hand foot mouth disease.
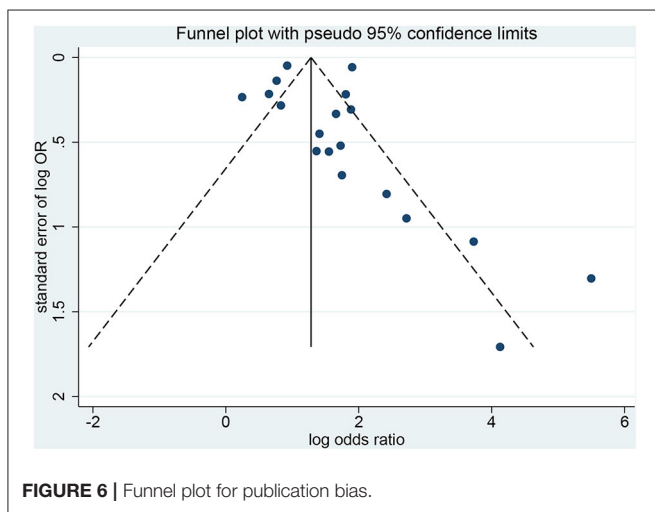


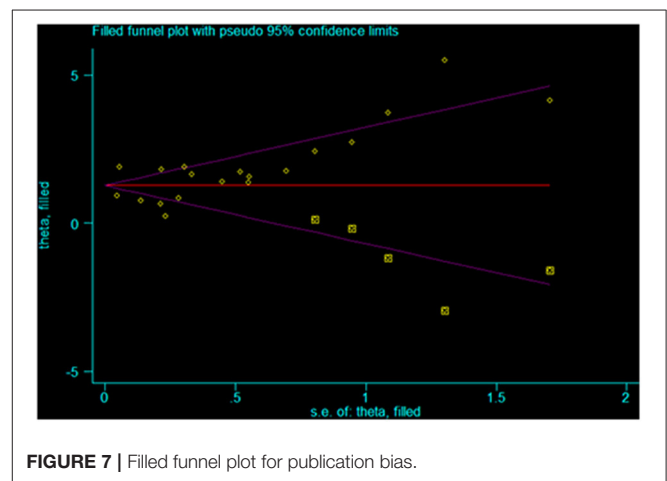**FIGURE 6** | Funnel plot for publication bias.



**FIGURE 7** | Filled funnel plot for publication bias.

In conclusion, this meta-analysis indicates that EV 71 infection, lifestyle habits (rural, being home-raised, a higher number of children in the family, poor hand hygiene, and no breastfeeding), clinical pathway (frequent hospital visits), and symptoms are risk factors for severe HFMD in children, while early diagnosis and admission

to higher-level hospitals are protective factors. Age, sex, and time from onset to admission are not associated with HFMD severity.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

## AUTHOR CONTRIBUTIONS

PL and YH conceived and coordinated the study, designed, performed and analyzed the experiments, and wrote the paper. DZ, DH, and SY carried out the data collection, data analysis, and revised the paper. All authors reviewed the results and approved the final version of the manuscript.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2021.716039/full#supplementary-material

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