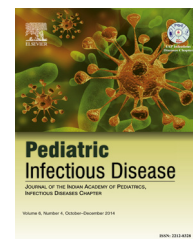


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## Review Article

# The relevance of the serum levels of C-reactive protein and creatine kinase-MB to the severity of hand-foot-and-mouth disease patients in China: A meta-analysis

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## ABSTRACT

**Objective:** The goal of this meta-analysis was to determine whether the serum levels of C-reactive protein (CRP) and creatine kinase-MB (CK-MB) are correlated with the severity of hand-foot-and-mouth disease (HFMD).

**Methods:** We conducted a systematic search and meta-analysis of the MEDLINE, PubMed, EMBASE, Cochrane Library, China National Knowledge Infrastructure, VIP information, and Wanfang Chinese Periodical databases. The analysis included all published case-control, cohort, and cross-sectional studies of serum CRP and/or CK-MB levels in children with HFMD up to December 4, 2014. Pooled estimates were calculated using a random-effects model or a fixed-effects model.

**Results:** Thirty-eight articles are included in this meta-analysis. The summary estimates revealed that the average serum CRP levels, prevalence of high CRP, average serum CK-MB levels, and prevalence of high CK-MB increased with the severity of HFMD. There were no significant differences in the average levels of serum CK-MB (pooled MD = 22.29 U/L; 95% CI: -0.82–45.39 U/L,  $P = 0.06$ ) between patients who were critically ill and those with severe HFMD. Therefore, we compared the average levels of serum CRP (pooled MD = 1.17 mg/L; 95% CI: -0.88–3.21 mg/L,  $P = 0.26$ ) between patients infected with enterovirus 71 and those infected with coxsackievirus A16.

**Conclusions:** The result of these analyses indicated that the CRP and CK-MB levels are correlated with HFMD severity. Thus, these frequently used and accessible measures may aid clinicians in effectively diagnosing, treating, and predicting the prognosis of children with HFMD.

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## 1. Introduction

Hand-foot-and-mouth disease (HFMD) is an acute infectious viral disease that is frequently caused by coxsackievirus A16 (CA16) and enterovirus 71 (EV71) of the *Enterovirus* genus, which belong to the *Picornavirus* family of small viruses with single-stranded, positive-sense genomic RNA.<sup>1,2</sup> The typical clinical manifestations are a brief febrile illness and cutaneous lesions, including a blistering rash on the hands, feet, and buttocks, with or without oral ulcers. HFMD is most frequently observed in infants and children  $\leq 3$  years old.<sup>3</sup> In most instances, the disease is mild, self-limited, and uncomplicated, with a duration of 3–5 days. In contrast, patients with severe HFMD present with rapid progression of the disease accompanied by severe complications, such as lethargy, drowsiness, irritability, delirium, headache, vomiting, limb shaking, myoclonus, ocular fluttering, ataxia, asthenia, meningeal irritation, diminished/disappeared tendon reflexes, seizures, coma, cerebral hernia, respiratory distress, cyanosis, bloody frothy sputum, lung rales, poor peripheral perfusion, shock, or even death.<sup>4–6</sup>

The last decade saw the development of a global epidemic of HFMD, with increasing rates of severe HFMD and associated mortality. This poses a rising threat to infants and young children and is a persistent and severe public health problem, particularly in China. Previous studies have reported that patients with HFMD have present variations in biochemical laboratory measurements,<sup>7</sup> including the serum levels of CRP and CK-MB. C-reactive protein (CRP or hs-CRP), an acute phase protein that is produced by the liver and involved in many biological activities, is well known for its role in infectious diseases caused by bacteria.<sup>8</sup> Creatine kinase-MB (CK-MB), an isoenzyme of CK that is mostly found in myocardial cells, is a well-known and sensitive indicator of myocardial injury. Interestingly, several studies<sup>9–12</sup> have demonstrated that CRP and/or CK-MB exhibit changes in relation to the severity of HFMD. To gain a comprehensive understanding of the clinical meaning of the CRP and CK-MB levels and to help clinicians monitor the severity and prognosis of patients with HFMD, we pooled the relevant data and performed a meta-analysis of the levels of serum CRP and CK-MB in patients with HFMD in China.

## 2. Materials and methods

### 2.1. Search strategy

Two independent reviewers (F.R. and Y.W.) identified pertinent case-control, cohort, and cross-sectional studies of the levels of serum CRP and/or CK-MB in children with HFMD from the following databases: MEDLINE, PubMed, EMBASE, Cochrane Library, China National Knowledge Infrastructure, VIP information, and the Wanfang Chinese Periodical Database. The limits were articles investigating children and humans published in English or Chinese during any year. The literature was searched through an iterative process that involved Medical Subject Headings (MeSH) and keywords with the following terms: “hand-foot-and-mouth disease,” “HFMD,” “mild cases,” “severe cases,” “death case,” “risk factors,” “C-reactive protein,” “CRP,” “high-sensitivity C-reactive protein,”

“hs-CRP,” “creatinase-MB,” “CK-MB,” and “myocardial enzymes.” We also attempted to include relevant bibliographies, personal studies, and the gray literature via scanning the reference lists of all of the included studies, performing manual searches, and reviewing e-mails for additional articles. The last search was conducted on December 20, 2014, and all of the citations were exported to EndNoteX6 (New York, NY).

### 2.2. Inclusion and exclusion criteria

After removing duplicates, the abstracts and titles of the articles were evaluated independently by two reviewers (F.R. and Y.W.). A full review was then conducted to determine each article's suitability for inclusion. Any discrepancies were reconciled through consensus or referred to a third reviewer as necessary. We included studies with any design that concerned the serum levels of CRP and/or CK-MB. In cases of duplicate study designs, we included the study with more cases. The levels of serum CRP, which is also defined as hs-CRP when detected using highly sensitive or ultrasensitive methods, range from 0 mg/L to 3.36 mg/L, and CK-MB levels range from 2 U/L to 28 U/L. Serum levels of CRP or CK-MB that exceed the medical reference range are defined as high CRP or high CK-MB levels. The diagnostic and grouping criteria for HFMD were determined based on typical clinical symptoms according to published “guidelines on the diagnosis and treatment of hand, foot, and mouth disease” published by the Ministry of Health of the People's Republic of China.

Mild cases of HFMD were defined as having clinical features including an acute onset, lesions on the buccal or labial mucosae, and erythematous vesicles with a red areola over the palms, soles, and buttocks. Patients may have complained of a cough, nasal discharge, or anorexia, among other symptoms. A portion of the patients presented with only cutaneous lesions or herpangina. Severe cases displayed the same clinical manifestations of children with mild HFMD but progressed rapidly to complications including encephalitis, aseptic meningitis, acute flaccid paralysis, myocarditis, pulmonary hemorrhage, severe sequelae, or even death.

In this meta-analysis, the exclusion criteria included the following: (1) publications in languages other than English and Chinese; (2) review articles; (3) studies that lacked an appropriate control; (4) studies that included patients with only mild or severe HFMD; (5) studies with serum levels of CRP (hs-CRP) and/or CK-MB that were not presented as the mean and standard deviation ( $\bar{x} \pm s$ ); (6) studies that reported levels of CRP (hs-CRP) in whole blood or plasma; and (7) case reports.

### 2.3. Data extraction and statistical analysis

Two reviewers (F.R. and Y.W.) assessed the characteristics of the studies and extracted the relevant data independently. The third reviewer (L.Q.Z.) checked the extracted data. Discrepancies were reconciled by consensus or were referred to a fourth reviewer (Z.Q.L.) as necessary. For all of the articles included, relevant information was extracted regarding the first author and year of publication, sample size and age of the participants, male to female ratio, diagnostic criteria for HFMD, assay method, and assay time for CRP and CK-MB, as well as ethnicity.

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