



**ORIGINAL RESEARCH PAPER**

**Orthopaedics**

**A STUDY ON COMPARING LIVER FUNCTION TEST AND C-REACTIVE PROTEIN IN CHILDREN WITH HAND FOOT MOUTH DISEASE**

**KEY WORDS:**

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**ABSTRACT**

**Introduction:** Hand-foot-mouth disease (HFMD) is a common paediatric disease responsible for the development of erythematous papulovesicular rashes on the hand, foot, and mouth. Severe complications of HFMD include myocarditis, pulmonary oedema, aseptic meningoencephalitis, and even death. Therefore, early diagnosis of HFMD is of particular importance.

**Objectives of this study:** To compare the values of liver function test and CRP in mild and severe cases of HFMD.

**Materials and methods:** Retrospective hospital based study of 100 patients between August 2016 to July 2018 who were classified into mild and severe HFMD cases. Lab investigations included ALT,AST, CRP. Clinical and laboratory parameters in the two group of HFMD were compared in the study .

**Results:** Study group included 100 cases of HFMD of which was 58% Severe cases and 42% Mild cases of HFMD. Commonest presenting symptom was erythematous papulo vesicular rashes on the hand, foot, and mouth. Severe HFMD is characterized by rapid disease progression, continuous hyperpyrexia, significant increase in the peripheral white blood cell level and poor peripheral circulation. Lab parameters: Patients in the severe HFMD group showed significantly higher levels of ALT, AST and CRP compared to those in the mild HFMD group .

**Conclusion:** CRP and liver function play a major role in the diagnosis of severity of HFMD at an earlier stage.

**INTRODUCTION**

Hand-foot-mouth disease (HFMD) is a common paediatric infectious disease that chiefly transmitted through the respiratory and digestive tracts, and via intimate contact .HFMD +chiefly affects children aged below 3 years. Coxsackievirus A16 (CoxA16) and Enterovirus 71 (EV71) and Echo virus are chiefly responsible for HFMD<sup>2</sup>. The virus proliferates in the intestinal tract post-infection; subsequently, it enters the blood stream, and drifts away and colonizes in the hand and foot, inducing local pathological changes such as fever and erythematous papulo vesicular rashes in the hand, foot with or without oral ulcerations. While a majority of the infected children show mild symptoms and a relatively good prognosis; the disease develops rapidly in the others, leading to severe complications, such as meningitis, myocarditis, liver damage, acute flaccid paralysis, and even death<sup>1</sup>. Numerous Member States in the Western Pacific Region have since experienced large HFMD epidemics associated with EV71 (enterovirus) infection. Several countries have also reported substantial numbers of death. India has apparently not had any epidemic caused by EV-71 infection. Recently Coxsackievirus A 6 and A 10 are also causing HFMD<sup>3</sup>.

C-reactive protein (CRP), an acute-phase protein synthesized in the liver, combines with polysaccharides, lecithin, and nucleic acids from various microorganisms (such as bacteria, fungi, and protozoa) to activate the complement system, in order to induce an inflammatory response to the immunomodulatory and phagocytic invasion of host cells. However, CRP expression is up regulated under severe pathological conditions, such as acute myocardial infarction and traumatic inflammation; therefore, CRP expression is a non-specific diagnostic index and must be supplemented by other indices for early diagnosis of severity of paediatric HFMD<sup>1</sup>.

In this study, we compared CRP expression and liver function between patients with mild and severe HFMD in the early diagnosis of probable severity and improved prognosis of HFMD.

**OBJECTIVES**

- 1.To compare the liver function test values in children with mild and severe cases of HFMD.
- 2.To compare the CRP values in children with mild and severe cases of HFMD.

**MATERIAL AND METHODS**

**Study design:** A Retrospective study.

**Setting:** Hospital based study.

**Inclusion criteria:**

Children between 6months to 5 year of age with fever, erythematous papulo vesicular rashes on hand foot and mouth ; who attended OP and those who were admitted in the paediatric ward between August 2016 and July 2018 in a teaching hospital; and Liver function tests and CRP were done.

**Exclusion criteria:**

Children with other disease causing raised Liver function tests and CRP values.

**Variables:**

Quantitative variables: Age, Liver function test values (ALT, AST) and CRP

Qualitative variables: Fever, erythematous papulo vesicular rashes over hand foot and with or without oral ulceration, rapid disease progression, continuous hyperpyrexia, and poor peripheral circulation.

**Data source:**

For data entry, all the symptoms and lab Investigations were entered and checked by Senior Consultants.

**Bias:** none

**Study size:** 100 patients.

After obtaining case records, the patients were classified as mild and severe cases of HFMD based on symptoms specified. Lab investigations included total count, Liver function tests (ALT,AST) and CRP was monitored .

Cut-off values for laboratory tests are defined as followings: elevated serum aminotransferase AST >34U/L , ALT >34 U/L and elevated C-reactive protein (CRP) (>8.0 mg/L). Clinical and laboratory parameters in mild and severe cases of HFMD were compared in the study.

HFMD was diagnosed according to the diagnostic criteria of A Guide to clinical management and public health response for hand foot and mouth disease (HFMD) formulated by World Health Organisation(WHO 2011). The severe HFMD group was composed of 23 male and 19female patients aged 6 months to 5year .The mild HFMD group was composed of 37male and 21 female patients aged 6 months to 5 years.

**Diagnostic criteria**

The patients were classified into the mild and severe HFMD groups according to disease severity. Mild HFMD manifests as acute-onset fever, erythematous papulo vesicular rash on the hand, foot, and hip, inflammatory flush around the rash, liquid-filled blisters, and poor feeding. Some cases of mild HFMD only manifest as herpangina or rashes. Severe HFMD is characterized by rapid disease progression, continuous hyperpyrexia, significant increase in the peripheral white blood cell level, clinical features of myocarditis, encephalitis and poor peripheral circulation. Some patients also develop complications associated with the nervous, respiratory, and circulatory systems such as encephalomyelitis, meningitis, encephalitis, emesis, limb tremor, pulmonary oedema, and circulatory disturbance<sup>3</sup>.

**Data analysis**

The ALT, AST, and CRP levels were compared between patients included in the mild and severe HFMD groups. Lab reports of these patients are obtained from MRD with permission.

**Statistical analysis**

The obtained data were analysed using the R software (Version 1.32) platform. The measured data are reported as means ± standard deviations (M±SD).

**RESULTS**

Study group included 100 cases of which 35 belong to 24-35 months of age.

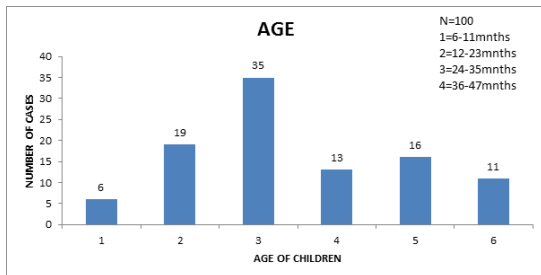


FIGURE-1

In our study; maximum number of cases were reported in the time period September-December 2017.

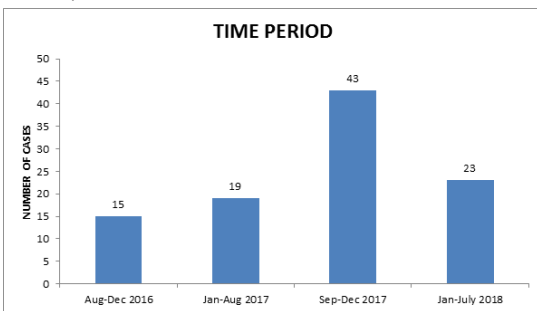


FIGURE-2

In our study; maximum number of cases reported in both mild and severe cases were males (Mild cases-37 males;21 females Severe cases-23 males; 19 females)

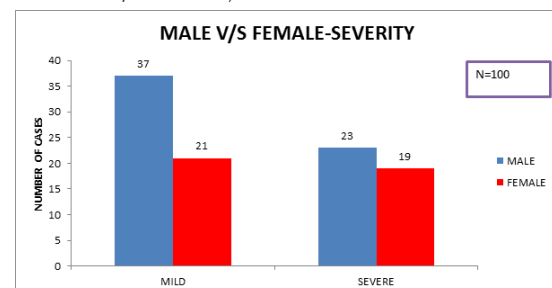


FIGURE-3

TABLE-1

Variables	Values (U/L)	Mild (no:of cases)	Severe (no:of cases)
ALT	17.1-19.9	13	0
	20.0-24.9	15	1
	25.0-29.9	17	0
	30-34.9	13	0
	35-44.9	0	1
	45-54.9	0	4
	55-64.9	0	26
	65-74.9	0	9
75-84.9	0	1	
Variables	Values (U/L)	Mild	Severe
AST	13.0-19.9	46	1
	20.0-24.9	10	0
	25-27.1	2	0
	43.9-45.9	0	8
	46-49.9	0	12
	50-54.9	0	15
	55-59.9	0	5
60-64.9	0	1	
Variables	Values (U/L)	Mild	Severe
CRP	1-3.9	35	1
	4-6.9	16	0
	7-8	7	1
	14.2-24.9	0	29
	25-34.9	0	10
	35-44.9	0	1

TABLE-2

VARIABLES	VALUES	MILD	SEVERE
ALT	MEAN	25.04	59.98
	SD	5.13	9.51
AST	MEAN	16.85	49.8
	SD	3.27	7.0
CRP	MEAN	3.86	21.13
	SD	1.9	5.98

**Liver function and CRP levels in the HFMD groups**

Patients in the severe HFMD group showed significantly higher levels of ALT and AST compared to those in the mild HFMD group.

Patients in the severe HFMD group showed significantly higher levels of CRP compared to those in the mild HFMD group.

**DISCUSSION**

Hand Foot Mouth Disease (HFMD) was identified as a clinical entity in 1957 in Toronto, Canada during the outbreak of a mild febrile illness characterised by papulovesicular lesions on the skin and in the mouth, but the name HFMD was first used only in 1960 during a similar outbreak in Birmingham, England. The causative agents were identified as enterovirus principally Coxsachie virus A16 and also Cox.A 4-7,9,10; B 1-3 and 5 serotypes.

In the 1970s when a new pathogen Enterovirus 71(EV 71) appeared giving rise to large epidemics with much fatality among children. Japan, Taiwan, Singapore, Malaysia, Indonesia and other countries in Asia pacific region reported extensive epidemics involving thousands of patients. The mortality and complication rates were much more in later epidemics than in those preceding. Because of this transformation of a mild self limited condition to a killer disease, increasing attention is now being paid to the study of HFMD<sup>4</sup>.

Hand-foot-mouth disease (HFMD) is chiefly transmitted through the respiratory and digestive tracts, and via intimate contact. EV71 replicates in the intestinal tract and is typically shed for between two and four weeks, and sometimes for as long as 12 weeks post-infection. Replication also occurs in the upper respiratory tract and the virus has been recovered from throat swabs for up to two weeks post-infection. Thus transmission can include faecal-oral and respiratory secretions through direct person-to-person

contact, droplets or fomites. Incubation period averages 3-6 days. Factors that affect the transmission include level of hygiene, water quality, and the extent of Crowding. Patient education includes good hygiene and avoidance of rupturing blisters<sup>7</sup>.

In our study of 100 cases; 35 belong to 24-35 months of age; as shown in figure 1. In our study; maximum number of cases reported in both mild and severe cases were males; as shown in figure 3.

In general, the enteroviruses have a distinct seasonal pattern of circulation that varies by geographic area. In tropical and subtropical countries, circulation tends to be year round, with more outbreaks in the rainy season.

In our study, 100 cases of Hand Foot Mouth diseases were included from Aug 2016-Jul 2018. We found that maximum number of cases (43%) were in the period from Sep-Dec 2017; as shown in figure 2.

HFMD usually manifests in a mild manner in children, in the form of a fever, erythematous papulo vesicular rash, on the hand, foot, and mouth. However, some patients also develop encephalitis, acute flaccid paralysis, and myocarditis induced by impairment of central nervous system and respiratory system. Mild cases that rapidly develop these conditions have a short therapeutic time window and high fatality rate (Wang et al., 2007). The enteroviruses EV71, Coxsackie A, and Echo, are characterized by strong infectivity. Hence there is a high probability of unapparent infection with a complex (and rapid) transmission approach with high risk of outbreak of HFMD (Zhang et al., 2016). Early diagnosis of severe cases and timely intervention could lower the disability and fatality rates and improve the prognosis of patients with HFMD. Therefore, a highly efficient, accurate diagnostic method must be developed to accurately diagnose severe cases at an early stage.

The severity of HFMD is closely associated with the activation of an inflammatory cytokine cascade.

CRP is a typical inflammatory marker secreted by an acute phase protein that is closely correlated with the oxidative stress response (Wang et al., 2007)<sup>8</sup>. For example, the serum CRP level increases rapidly during the early stages of infection, the increase being positively correlated to the degree of infection (Shekhar et al., 2005). Chen et al. (2007) reported that hs-CRP played a major role in determining the severity of HFMD based on the observation that the level of CRP was much higher in the severe cases than that in the mild cases (which in turn was higher than that in normal children). In this study, patients with severe HFMD showed higher CRP levels compared to those with mild HFMD, which was consistent with the results of the previous study. This indicated that CRP has a considerable diagnostic value in determining the severity of HFMD in children.

According to recent studies ;virus invasion and continuous breeding in children with severe hand-foot-mouth disease lead to viremia and various viscera complications, and the liver function injury is the most common.

Recent studies (Huang et al., 2006; Zhao et al., 2011) have reported that liver function abnormality is a major complication of HFMD; in fact, studies have indicated that the liver cells of children with acute-phase HFMD are more likely to be injured, which might be correlated with the proliferative capacity and toxicity of viruses that invade the liver cells during the early stages of the disease. In this study, the AST, ALT, levels were significantly higher in severe HFMD cases compared to the mild cases. Therefore, mild HFMD was characterized by an absence of liver function impairment, whereas severe cases were likely to develop liver function injury. Currently, it is universally recognized that impaired liver presents an abnormal hepatic enzyme spectrum. ALT, AST are important indices that reflect impairments in the liver function; therefore, an increase in the hepatic enzyme spectrum is usually a predictor of HFMD aggravation (Hsueh et al., 2000; Wang et al., 2003). In our

study also; patients with severe HFMD showed significantly higher levels of ALT, AST compared to those with mild HFMD.

In our study ; liver enzymes were elevated in severe HFMD cases that indicated the severity of disease. The rise of ALT is more than AST (Mean AST in severe cases-49.8; Mean ALT in severe cases - 59.9). CRP values were also elevated in severe cases of HFMD compared to mild group (Mean CRP values in severe HFMD cases is 21.13 and that in mild HFMD cases is 3.86; as shown in table 2.

## CONCLUSION

In our study we conclude that CRP and liver function could be used to characterize the severity of HFMD; that severe cases of HFMD have elevated AST, ALT and CRP.

## PITFALLS OF STUDY

We have not conducted any virological study whether caused by coxsackie A 16, enterovirus 71 or Echo virus.

## Conflicts of interest

The authors declare no conflict of interest.

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