

Determinants of a Case Series of Hand Foot Mouth Disease (HFMD) in Children Under the Age of 5 Years

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ABSTRACT

Background: Hand Foot Mouth Disease (HFMD) is an acute infectious disease. The epidemic of HFMD has been reported in some countries in the Pacific region, every three years in America, and almost every year in China. This study is conducted to determine risk factors that correlate with HFMD in children under five years old in Dusun Sengkrakan, Lawang. This study is a cross-sectional study with an analytical observational approach.

Method: The sample size was determined by total sampling, including 54 mothers with children under five years old in Dusun Sengkrakan, Lawang. The result was then analyzed with a statistical package for the social science (SPSS).

Results: This study shows that there is a significant correlation between children's age ($p = 0.012$) and HFMD occurrence, meanwhile, sex, birth weight, gestational age, exclusive breastfeeding, number of siblings in the house, and mother's age have no significant correlation with HFMD occurrence. Children's age is the most dominant factor among other independent variables [$p = 0.017$; OR 2.849 (95% CI: 1.203 – 6.750)]. The result of this study is expected to raise public awareness of promotive and preventive measures against HFMD for the public purpose of preventing HFMD outbreaks in Indonesia

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INTRODUCTION

Hand Foot Mouth Disease (HFMD) or "Singaporean flu" is an acute infectious disease that has similar symptoms to the flu and causes many deaths in Singapore. The cause of this disease is an infection of Enterovirus, specifically Coxsackievirus A16 (CA 16) and Enterovirus 71 (EV 71), that is transmitted via fecal-oral, respiratory, or through direct contact with respiratory droplets from the nasopharynx, saliva, and also vesicular fluid or fecal matter.¹ The incubation period usually lasts 3-5 days to 2 weeks. Enterovirus 71 can last up to 4 weeks in the throat and persist for 6-12 weeks in the feces.²

The epidemic of HFMD has been reported in some countries in the Pacific region, every three years in America, and almost every year in China.² Since the late 1990s, HFMD has become a common health problem in Southeast Asian countries. In Indonesia, in 2017, the Eijkman Institute for Molecular Biology identified positive Enterovirus 71 genotype B5 in a set of specimens from an outbreak of an HFMD-like disease in Banjarmasin, South Kalimantan.³

Diagnosis of HFMD can be established through clinical symptoms. Additional examinations are rarely required, but culture/PCR may be performed if an endemic occurs. PERDOSKI (2017) states that the criteria include a fever of 38-39° C for 1-2 days, malaise, abdominal pain, and symptoms of acute respiratory infection.⁴ Multiple lesions on the tongue, buccal mucosa, hard palate, or also in the oropharynx can be the most common abnormality accompanied by pain, after oral lesions appear, skin lesions will appear, especially on the palms and sides of the hands and feet.⁵ Most cases of HFMD are mild and self-limiting, but there have been reports of severe complications of HFMD, including encephalitis, meningitis, acute flaccid paralysis, myocarditis, and pulmonary edema. Encephalitis is the most common complication of HFMD.⁶

Several risk factors increase the transmission of the causative pathogen. HFMD patients are mainly in the age group under five years.^{2,7} Males were found to be more affected by HFMD than females in several studies.^{2,7,8} Social contact is a very crucial factor in the

transmission of HFMD. The number of siblings, such as brothers and sisters, living in the same house increases the risk of infection due to a closer density level, especially if siblings have HFMD. Children's playgrounds and the number of playmates are also important risk factors due to research showing classrooms or daycare centers with more than 21 children increase the risk of spreading HFMD.²

Protective factors against HFMD include breastfeeding and good hand-washing habits. Breastfeeding is thought to protect infants against various infectious diseases, including HFMD, through passive immunity obtained from maternal antibodies that enter through breast milk and better maturation of the immune system in breastfed infants.⁹ The habit of washing hands is one of the factors that can prevent various infectious diseases. HFMD is a virus that is mainly spread through the fecal-oral route, so good hygiene habits can be a protective factor, but one study showed that hand washing did not have a significant relationship with the incidence of HFMD. This is because the incidence of HFMD is still increasing even though the habit of washing hands properly has been emphasized.²

Multiple international studies have showcased HFMD as one of the most common viral exanthem in children, regardless of the self-limiting profile of viral exanthems. However, HFMD cases in Indonesia are rarely reported in national epidemiological data, research studies, or even being commonly discussed amongst the public in general. Most of the studies in HFMD were conducted in developed countries where public health policy and sanitation are much more regulated and stricter with higher levels of education among the population. Risk factors of HFMD could be more different and pronounced in countries with lower socioeconomic status and higher population density, such as Indonesia. In consideration of this, we aim to determine the determinants of HFMD occurrence in children under five years old in one of the regions in Indonesia, in particular Dusun Sengkrakan, Desa Bedali, Kecamatan Lawang, Malang Regency.

METHOD

The type of research used is a quantitative approach with a cross-sectional study. This study emphasizes the observation time of independent and dependent variable data only once at a time. In this type, the independent and dependent variables are assessed simultaneously at one time, so there is no follow-up. The population in this study were all toddlers (aged 6-59 months) in Dusun Sengkrakan, Bedali Village, Lawang District, Malang Regency. The sampling method used is a total sampling technique with a sample of 66 respondents, but when in the field, it becomes 54 subjects because 12

subjects are exclusion criteria. The inclusion criteria of this study were toddlers (aged 6-59 months) who were found in Dusun Sengkrakan, Bedali Village, Lawang District, Malang Regency, and toddlers (aged 6-59 months) with mothers who were willing to participate in this study, while for exclusion criteria included toddlers (aged 6-59 months) with mothers who had limited communication skills and toddlers (aged 6-59 months) with mothers who were not at the study site at the time of sampling.

The dependent variable in this study was the incidence of Hand Foot Mouth Disease (HFMD) in toddlers, and the independent variables were sex, age of toddlers, birth weight, gestational age, exclusive breastfeeding, number of siblings living in the same house, frequency of children playing with other children, mother's age, mother's last education, and mother's occupation of toddlers (aged 6-59 months) with HFMD. The instrument used in this study was a questionnaire. The questionnaire used for HFMD uses the diagnostic criteria from the Clinical Practice Guide for Dermatologists and Venereologists in Indonesia and risk factors using a questionnaire from Kua JA and Pang J. The questionnaire is divided into three parts: demographics, diagnosis of HFMD, risk factors for HFMD, and exclusive breastfeeding. This research was conducted from May 22-27, 2022. The data that has been collected from interviews will be processed in the following stages, namely editing, coding (making code sheets), data entry, and data cleaning. Data analysis used univariate analysis using frequency distribution. Then, for bivariate analysis, use Chi-Square and Fisher Exact's test. Multivariate test using logistic regression. The selection of the test is based on the nominal scale on the dependent variable and the nominal or ordinal scale on the independent variable. This study was approved by the Health Research Ethics Committee, Universitas Airlangga School of Medicine, Indonesia (No. 145/EC/KEPK/FKUA/2022).

RESULTS AND DISCUSSION

From Table 1, the characteristics of respondents in this study obtained that women are more than men with the most age distribution being 6-18 months. Maternal characteristics in this study, namely the majority of mothers are in the early adult group (26-35 years old) with the education level of junior high school with a job as a housewife. In this study, the characteristics of the variables studied found that the sample with normal birth weight was more than toddlers with low birth weight. The majority of the samples were aterm gestational age, exclusively breastfed, had one sibling in the household, and played every day. In this study, the highest incidence of HFMD was non-HFMD.

Table 1. The distribution of respondents' demographic characteristics

Variables	f	%
Sex		
Male	26	48.1
Female	28	51.9
Children's age		
6-18 months	19	35.1
19-31 months	17	31.5
32-44 months	9	16.7
45-59 months	9	16.7
Mother's age		
Late teens (17-25 years old)	16	29.6
Early adult (26-35 years old)	28	51.9
Late adult (36-45 years old)	7	12.9
Early elderly (46-55 years old)	2	3.7
Late elderly (56-65 years old)	1	1.9
Mother's educational level		
Elementary school	28	51.8
Junior high school	13	24.1
Senior high school	13	24.1
Mother's occupation		
Housewife	43	79.5
Female worker	2	3.7
Teacher	1	1.9
Private employee	5	9.3
Laborer	3	5.6
Birth weight		
Low birth weight	9	16,7
Normal birth weight	45	83,3
Gestational age		
Aterm	41	75,9
Preterm	13	24,1
Exclusive breastfeeding		
Exclusive breastfeeding	29	53,7
Non-exclusive breastfeeding	25	46,3
Number of siblings		
0	15	27,8
1	27	50,0
2	9	16,7
3	3	5,5
Playtime frequency		
Never	5	9,2
One time every 2-3 weeks	4	7,4
One time every week	2	3,7
More than once per week	7	13,0
Every day	36	66,7
HFMD incident		
Yes	13	24,1
No	41	75,9
Total	54	100

Table 2. The relationship between the independent variable and HFMD incidence

Variables	Hypertension occurrence		f (%)	p-value
	No f (%)	Yes f (%)		
Sex				
Male	22 (84.6)	4 (15.4)	26 (100)	0.15
Female	19 (67.9)	9 (32.1)	28 (100)	
Children's age				
6-18 months	14 (73.7)	5 (26.3)	19 (100)	0.01
19-31 months	9 (52.9)	8 (47.1)	17 (100)	
32-44 months	9 (100)	0 (0)	9 (100)	
45-59 months	9 (100)	0 (0)	9 (100)	
Birth weight				
Low birth weight	8 (88.9)	1 (11.1)	9 (100)	0.32
Normal birth weight	33 (73.3)	12 (26.7)	45 (100)	
Gestational age				
Aterm	30 (73.2)	11 (26.8)	41 (100)	0.40
Preterm	11 (84.6)	2 (15.4)	13 (100)	
Exclusive breastfeeding				
Exclusive breastfeeding	21 (72.4)	8 (27.6)	29 (100)	0.51
Non-exclusive breastfeeding	20 (80.0)	5 (20.0)	25 (100)	
Number of siblings				
0	11 (73.3)	4 (26.7)	15 (100)	0.34
1	22 (81.5)	5 (18.5)	27 (100)	
2	7 (77.8)	2 (22.2)	9 (100)	
3	1 (33.3)	2 (66.7)	3 (100)	
Playtime frequency				
Never	4 (80.0)	1 (20.0)	5 (100)	0.50
One time every 2-3 weeks	3 (75.0)	1 (25.0)	4 (100)	
One time every week	2 (10.0)	0 (0)	2 (100)	
More than once per week	7 (100)	0 (0)	7 (100)	
Every day	25 (69.4)	11 (30.6)	36 (100)	
Mother's age				
Late teens (17-25 years old)	13 (81.3)	3 (18.8)	16 (100)	0.77
Early adult (26-35 years old)	21 (75.0)	7 (25.0)	28 (100)	
Late adult (36-45 years old)	5 (71.4)	2 (28.6)	7 (100)	
Early elderly (46-55 years old)	1 (50.0)	1 (50.0)	2 (100)	
Late elderly (56-65 years old)	1 (100)	0 (0)	1 (100)	
Mother's educational level				
Elementary school	18 (64.3)	10 (35.7)	28 (100)	0.14
Junior high school	11 (84.6)	2 (15.4)	13 (100)	
Senior high school	12 (92.3)	1 (7.7)	13 (100)	
Mother's occupation				
Housewife	30 (69.8)	13 (30.2)	43 (100)	0.57
Female worker	2 (100)	0 (0)	2 (100)	
Teacher	1 (100)	0 (0)	1 (100)	
Private employee	5 (100)	0 (0)	5 (100)	
Laborer	3 (100)	0 (0)	3 (100)	

In this study, the most influential factor in the incidence of HFMD was the age of the children (see Table 2). The age of under-five is the most dominant factor among other independent variables ($p=0.017$; OR: 2.849). Multivariate analysis was performed using logistic regression by including variables that had a p -value <0.25 (Table 3). Variables that have p -value < 0.25 include the

age of the child ($p = 0.01$), sex of the child ($p = 0.15$), and maternal last education ($p = 0.14$). From this analysis, there is a significant relationship between the age of the child ($p<0,05$) with the incidence of HFMD. However, the sex of the child and maternal last education did not have a significant relationship with the incidence of HFMD.

Table 3. Logistics regression results

Variables	B	P value	OR	CI for OR	
				Lower	Upper
Age of child	1.047	0.017	2.849	1.203	6.750
Sex of child	0.777	0.302	2.174	0.498	9.493
Mother's educational level	-1.445	0.018	0.236	0.071	0.782

Sex and HFMD

Previous studies showed that sex is a risk factor for HFMD occurrences. In these studies, the male sex has a higher risk than females because the tendency to play outside is higher in males.^{3,9-12} However, we found no statistically significant sex-specific differences in HFMD in this study. This finding is aligned with another study by Kua and Pang (2020) and Ang et al. (2011), which also found no statistically significant differences between male and female sexes with HFMD occurrences. This is possibly due to no differences in playing activity between sexes in this village, similar to a study by Reimers et al. (2018), thus reducing the possibility of exposure to enterovirus.^{2,13,14}

Children's age and HFMD

Association between age and HFMD occurrences is found in previous studies.^{2,15,16} Most of the studies found that age below 6 years old is the most vulnerable age group to be infected with HFMD.^{2,17-19} In this study, we also found an association between age and HFMD occurrences. This study found age 1 years 7 months old to 2 years 7 months old is the most common age group to be infected with HFMD. Antibody is the most responsible immune response in eliminating enterovirus.²⁰ However, this does not eliminate the role of innate immunity, as the results of viral infections depend on the initial response of innate immunity. In children, antibody response is not as good as in adults. This is because the nature of the adaptive immunity that produces antibodies is still immunologically naïve.²¹ Therefore, innate immunity is the main key to preventing HFMD infection. However, this is also complicated by the evasion mechanisms of Enteroviruses, especially the blockade of interferon 1 activation cascade.²²

The condition of naive adaptive immunity in children may lower antibody seroconversion to pathogens that cause HFMD at a young age. This can be seen in the study of Rabenau et al. (2010), who found much lower antibody seroconversion to CA16 and EV71 in the 1 - 4 years age group and increased more steadily at the age of 5 - 9 years and 10 - 14 years. As antibody production increases with age, the incidence of HFMD may become less common in people over the age of 5 years old.²³

Birth Weight and HFMD

In previous studies, birth weight is a risk factor for HFMD occurrence. Children with low birth weight (<2500 grams) have a higher risk of HFMD occurrences.²⁴⁻²⁶ These findings contradict this study, which found no statistically significant differences between birthweight and HFMD occurrences. A study by Kua and Pang (2020) also found no association between birthweight and HFMD infections. In infants with low birth weight (<2500 grams)², there is an immune function defects (lower concentrations of CD3 T Cells and IL-7) which may affect susceptibility to infectious diseases²⁷, however, this immune defect was not found to be persistent over time with age.²⁸

Gestational Age and HFMD

A study by Zhu et al. (2012) found that gestational age is a risk factor for HFMD occurrences. Children with younger gestational age have lower physical condition and innate immune response.²⁹ In this study, we found no association between gestational age and HFMD. Similar results were also reported by Kua and Pang (2020), who did not find an association between gestational age and the incidence of HFMD. In their study, Kua and Pang hypothesized that the protective effect of maternal antibodies in infants born at 37-42 weeks' gestation may not be higher than that of infants born less than 37 weeks' gestation in cases of HFMD infection.²

Exclusive Breastfeeding and HFMD

In a previous study, Chen et al. (2015) found that non-exclusive breastfeeding is a risk factor for HFMD occurrences³⁰. Other studies found that exclusive breastfeeding can alleviate immunity by producing proinflammatory cytokines and increasing calorie intake.²⁹⁻³¹ This is contrary to this study, which found no association between breastfeeding and HFMD. Kua and Pang state in their study that exclusive breastfeeding protective factors last for 6 to 28 months. It is also affected by factors such as volume, duration, and composition of exclusive breastfeeding.² Low socioeconomic and education levels in our study may affect these factors thus, exclusive breastfeeding is not protective.

Number of siblings in household and HFMD

The association between the number of siblings in a household and HFMD infection was not statistically significant in this study. HFMD infections were mostly found in children with only 1 sibling in the house. This is contrary to previous studies, which showed the number of siblings in the household as a risk factor associated with HFMD^{2,32}. Household with more children was significantly associated with HFMD due to the highly infectious nature of CA16 and EV71. Infectious diseases tend to spread faster in more crowded areas such as daycare and family members, especially in HFMD infection.^{32,33} Some explanations that could address the different results of this study are factors related to duration and proximity of contact between siblings and age-related differences in immune responses to HFMD infection. Many studies have already highlighted age-related differences in immune responses to other infectious diseases, as the immune system is still developing in younger children.^{34,35}

Playtime frequency and HFMD

Conceptually, children's playtime may increase the risk of contracting HFMD due to additional contact with other children. However, the results of previous studies regarding this risk factor were varied. In this study, we found no significant association between playtime frequency and HFMD. Similar to the result of our study, Kua and Pang (2020) also reported no association between playtime frequency and HFMD, both in children who played at the playground and children who played with their neighbors.² Contrary to a previous study, Ruan et al. (2011) mentions that children who played with their neighbors are 11 times more likely to contract HFMD than children who played alone. In addition to Ruan et al. (2011), Xie et al. (2015) also reported outdoor activity has a higher association with HFMD infection.^{36,37} Factors that may affect the contradicting results between studies are UV exposure and disinfecting habits in the playground. EV71 is inactivated by exposure to UV light^{38,39}, but geographical conditions may also affect this factor.

Mother's age and HFMD

Mother's age is known to affect knowledge level and mental maturity in the development of disease prevention awareness and attitude.⁴⁰ However, there was no significant association found between the mother's age and HFMD in this study. Supporting this finding, Inta et al. (2017) and Rajamoorthy et al. (2022) also reported no statistically significant correlation regarding this risk factor.^{41,42} As parents grow older, their responsibility and commitment are also increasing, which may lead to a lack of prevention behavior toward HFMD.⁴² As opposed to

other studies, Kua and Pang (2020) showed a significant association between mother's age and HFMD in 41 to 50-year-old mothers, which may reduce the risk of HFMD infection compared to 21 to 30-year-old mothers.² This association might be due to the increasing mental maturity and experience that comes with the increase in age, which may support a more open-minded approach toward the prevention of HFMD. Even so, numerous factors may affect the development of awareness and attitude in certain mother's age groups. This might cause the differences between studies regarding the mother's age and HFMD.

Mother's educational level and HFMD

There was no statistically significant correlation between the mother's educational level and HFMD in this study. This finding is contrary to the result of Kua and Pang's (2020) study, which mentions a significant association between a mother's educational level and HFMD. Children with parents who have a high education level such as a university have a higher risk of HFMD infection than children with parents whose education level is not as high.² Parental education level is also found to be significantly associated with other infectious diseases and may reduce the under five years mortality rate as good education may help direct better decisions regarding children's health.^{43,44} Even so, Rajamoorthy et al (2022) report that parental education level was not significantly associated with knowledge and awareness regarding HFMD. Most mothers in this study have only an elementary school level of education. Access to information through the internet has bridged a lot of barriers and thus may affect the level of knowledge and awareness regarding HFMD even though education levels vary between mothers.⁴²

Mother's occupation and HFMD

No statistically significant association was found between the mother's occupation and HFMD. This result is aligned with a previous study that also mentioned that occupation does not correlate with awareness of HFMD but correlates with knowledge of HFMD.^{41,42} Most of the subjects in this study work as housewives and raise their children at home by themselves. A previous study found that children who were raised at home and rarely went to daycare were a risk factor for HFMD infection.⁴⁵ As one of the main caretakers of their children, stay-at-home mothers have much more power in enforcing certain prevention behaviors in their children, thus highlighting the importance of knowledge and awareness of infectious diseases.

CONCLUSION

There was a significant relationship between the age of toddlers and the incidence of HFMD. There was no significant relationship between the sex of children under five, birth weight, gestational age, exclusive breastfeeding, number of siblings living in the same house, frequency of children playing, mother's age, mother's last education, and mother's occupation with the incidence of HFMD. Children's age is the most dominant factor compared to other factors in the incidence of HFMD. This study was one of the first studies which mapped the determinants of HFMD infection in Indonesia. Due to its self-limiting nature, HFMD cases are often underreported in Indonesia, resulting in much anxiety among parents regarding the symptoms of this disease. Thus, our study could bridge more information about HFMD to the general public. We were also one of the first to use photographic screening of HFMD lesions using current National Dermatology Association guidelines. Nonetheless, this study has some limitations that could be further explored in future studies. Laboratory confirmation of the subject samples could be beneficial to confirm the viral infection and most likely beneficial for genotyping epidemiological purposes. The HFMD study could also benefit more from a multi-center collaboration in multiple regions of Indonesia, as this study only provides a glimpse of the magnitude of HFMD in the Indonesian population.

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Conflicts of Interest

The authors declare that there's no conflict of interest.

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