



**Spatial association of the incidence of Hand Foot Mouth disease and its related factors in
Guizhou province, China 2019 – 2021**

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ABSTRACT

Background: Hand, Foot, and Mouth disease is a common infectious disease, mainly involve Enterovirus 71 and Coxsackievirus A-16 serotypes. In China especially Guizhou province, research and literature related to spatial pattern and its spatial association with the factors were very limited. Therefore, we analyzed the data of population, highway mileage, forest coverage, GDP, air quality, temperature and humidity, medical institutions, and primary schools in 82 counties of Guizhou Province to understand the spatial correlation of incidence rate and its related factors.

Objectives: This study aimed to determine the spatial association of incidence of hand-foot-mouth disease and its related factors in Guizhou province, China from 2019 to 2021.

Methods: This study used the global Moran's I and local Moran I or LISA to analyze the incidence of hand foot mouth disease and the spatial correlation of multiple factors reported in Guizhou province.

Results: This study clearly concluded that the incidence rate of HFMD in children under 6 years old in Guizhou province of China was negatively correlated with forest coverage with Moran's I of -0.131, -0.117, -0.111 and positively correlated with GDP with 0.091, 0.118, in 2019 and 2020 respectively. However, the correlation between the incidence rate of HFMD and temperature, humidity, the number of primary schools and other factors were not spatially significant.

Conclusion: There was a significant spatial correlation between the incidence rate of HFMD and socio-economic and environmental meteorological factors in Guizhou province. It is suggested to take policy intervention to prevent the large-scale spread of HFMD and reduce the incidence rate and transmission rate of HFMD.

Keywords: Spatial association, Incidence, Socio-economic, Hand Foot Mouth Diseases

1. Introduction

Hand, foot, and mouth disease (HFMD) is a common infectious disease caused by enteroviruses pathogens that mainly involve Enterovirus 71 and Coxsackievirus A-16 serotypes. The susceptibility and severity of HFMD are closely associated with age, and children under 5 years are identified as the most susceptible targets, especially in densely populated urban areas [1,2]. Major outbreaks of HFMD have been reported in China since 2008, posing a great threat to the health of children. Although, many studies have examined the effect of meteorological variables on the incidence of HFMD, the results have been inconsistent [3]. HFMD has been associated with a growing number of outbreaks resulting in fatal complications since the late 1990s. The outbreaks may result from a combination of rapid population growth, climate change, socioeconomic changes, and other lifestyle changes [4]. Therefore, HFMD is epidemic in a wide range, and has significant seasonality and regional differences. It is necessary to investigate HFMD incidence in time and space. Most studies use the following methods to do spatial and temporal analysis, and the results of these reports may be used to prevent and control HFMD [5].

HFMD has the highest mortality rate among class 'C' infectious diseases that was implemented in mainland China. As a common infectious disease, children younger than 5 years are especially prone to HFMD. Although in most patients it is a self-limiting illness, in some serious cases neurological and systemic complications can occur that can be fatal [6].

From 2019 to 2021, Guizhou Province reported 88,578 cases of HFMD through the network direct reporting system. In the past 3 years, although the number of cases of HFMD has shown a downward trend year by year, the number of cases of HFMD is still very high, which is a serious threat to life and the health and safety of patients [7].

Therefore, we have collected data of the population, administrative area, highway mileage, forest cover, GDP, air quality, temperature and humidity, medical institutions, primary schools and other data of 88 Counties in 9 cities of Guizhou province and were analyzed to understand the spatial association of the incidence of HFMD and its related factors in Guizhou province of the last three consecutive years. As result, this research had observed the spatial distribution pattern of HFMD among regions, analyzed and judge the epidemic characteristics and transmission pattern of HFMD in Guizhou

Province. So, the result of our present study is reliable and effective suggestions for health administrative departments to continuously strengthen the prevention and control measures and disposal of hand, foot and mouth disease.

2. Methods

2.1 Study area

This study has been carried out in Guizhou province, China. It is located at $24^{\circ} 37' - 29^{\circ} 13' N$ and $103^{\circ} 36' - 109^{\circ} 35' E$, and adjacent to Sichuan, Chongqing, Hunan, Guangxi and Yunnan province. Guizhou Province governs 9 cities, 82 administrative Counties and 1509 townships [8].

2.2 Study design and population

This study used the cases of number of HFMD in Guizhou province which was collected as an independent variable from 2019 to 2021, the data mainly from the network direct reporting information system of 82 county-level CDC.

2.3 Dependent and independent variables

The dependent variable in this study was incidence of HFMD in Guizhou province from 2019 to 2021. Similarly, the independent variables including Demographic variables, Socio-economic

variables, Environmental and Meteorological variables that were the Population density per 1000 Children, Temperature, Humidity, GDP, Road Density per sq.km, Air Quality Index, Percentage of Forest Coverage, No. of Medical and Health institutions per 1000 Children, No. of Primary Schools per 1000 sq.km.

2.4 Statistical analysis

This study used the GIS program to describe the spatial distribution patterns of incidence of HFMD in all 82 counties of Guizhou province in 2019 to 2021. The obtained output is the statistics of Moran's I at each location I, which specifies the correlation between the value of X in area I and the weighted average of its neighbors. With the mathematical fundamental of the statistical correlation test, the outcome of this test can identify positive and negative associations numerically ranging between -1 and $+1$.

Distribution patterns of the HFMD was determined based on the localized detection of prevalent spatial patterns. To describe the spatial distribution patterns of HFMD incidence rate, QGIS version 3.20.3 (Odense) [9], Geo Da version 1.18.0.16 [10] were used to determine the measure of spatial autocorrelation analysis for an exploratory

spatial data analysis. QGIS was applied to integrate all data before being transferred to Geo Da for LISA.

After process with Quantum GIS on provincial map considering 82 Counties or polygon of Guizhou Province, data were imported into Geo da Program. In GeoDa Program, all spatial analyses require spatial weights. GeoDa program has been used to analyze spatial auto-correlation by specifying 4 k-Nearest neighbor province that connecting as a criterion to identify grouping which using the weight matrix to analyze spatial correlation. Therefore, Counties were considered as neighbors when they share at least a point or vertex in common, obtaining a squared matrix of dimension 31 (31 x 31 matrix) with all entries equal to zero or one, the latter value indicating that three provinces are neighbors. From these neighbors, weights were calculated by integrating a matrix in a row-standardized form, i.e., equal weights for each neighbor and summing one for each row. Moran's I statistic was obtained as an indicator of global spatial auto-correlation, and its significance was assessed through a random permutation inference technique based on randomly permuting the observed values over the spatial units.

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of prevalent spatial patterns. To describe the spatial distribution patterns of HFMD incidence rate, QGIS version 3.20.3 (Odense), Geo Da version 1.18.0.16 will be used to determine the measure of spatial autocorrelation analysis for an exploratory spatial data analysis. QGIS will be applied to integrate all data before being transferred to GeoDa for LISA analysis.

For data analysis of this study, Firstly, the cases of HFMD in 2019, 2020 and 2021 were collected and prepared for analysis. Second, the number of children under the age of 6 in each county in 2020 will be counted separately. Next, 82 Counties of Guizhou province of map are also arranged.

In the study, the dark red has illustrated an indication of spatial clusters when having a high frequency of geographic factor with a high frequency of HFMD incidence rate in the identified Counties with 4 neighboring Counties (high surrounded by high or Hot-spot or High-High). The dark blue locations were indicating spatial clusters when a low frequency of geographic factor with a low frequency of HFMD in the identified district with 4 neighboring districts (low surrounded by low or Cold-spot or Low- Low). In contrast, the light red and light blue was the indications of spatial outliers (respectively, high surrounded by low or High-Low, and

low surrounded by high or Low-High). The statistical significance level was 0.05. The simulation has been used 999 permutations to evaluate the sensitivity of the results.

2.5 Ethical Clearance

Ethical permission for the study was obtained from the Ethics Committee in Human Research of Khon Kaen University, Khon Kaen, Thailand (HE-652211).

3. Results

3.1 Population Density of U-6 Children per sq.km in 2019, 2020 and 2021.

In this study, we calculated the data of children under 6 years old in 2020, and calculated the prevalence of HFMD of children under 6 years old from 2019 to 2021 based on this data as well as. Among children under 6 old years, there are 55 counties with a population of less than 50,000; 18 counties with a population of 50,000d to 100,000; 9 counties with a population of more than

100,000. The least is Shibing county and the most is Guiyang county.

3.2 Spatial distribution characteristics of the incidence of HFMD in Guizhou province in China, 2019 to 2021.

In 2019, the highest incidence of HFMD was observed in Zunyi Shi County, where the incidence was 18.47 per 1000 children under 6 old years. Whereas the lowest incidence was observed in Tianzhu County with 1.18 per 1000 children under 6 old years. In 2020, the highest incidence of HFMD was observed in Duyun County. Where the incidence was 21.23 per 1000 children under 6 old years. whereas the lowest incidence was observed in Luodian County with 0.34 per 1000 children under 6 old years. In 2021, the highest incidence of HFMD was observed in Zhenyuan County, the incidence was 14.93 per 1000 children under 6 old years, the lowest incidence was observed in Wangmo County with 0.71 per 1000 children. (Figure 1)

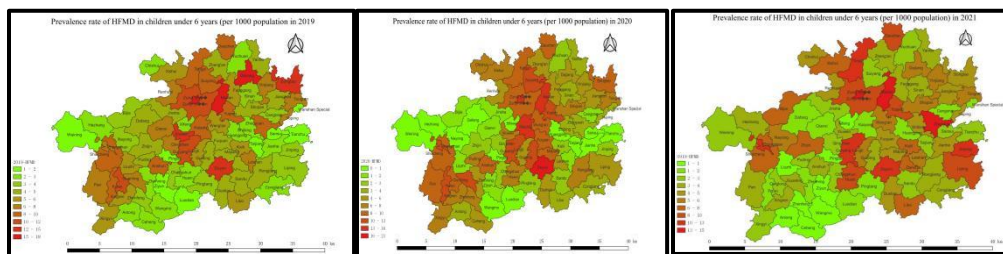
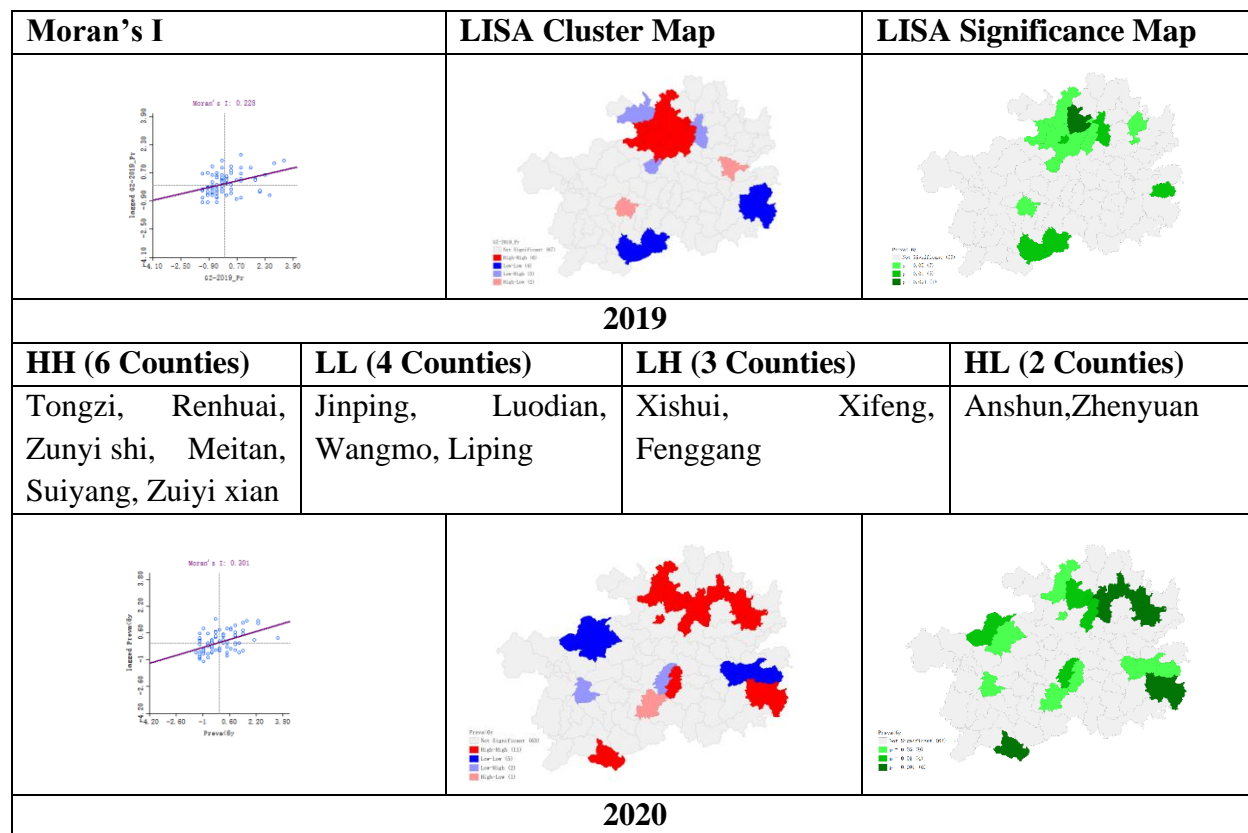


Figure 1: The incidence of HFMD in children under 6 years in the year 2019,2020,2021

3.3 The cluster of the incidence of HFMD under 6 years in children from 2019 to 2021.

The incidence of HFMD has local spatial clustering and autocorrelation, Moran's I value is 0.228, 0.301 and 0.116 respectively. In 2019, with positive spatial autocorrelation with the Moran's I value 0.228 with High-High clusters in Tongzi, Renhuai, Zunyi shi, Meitan, Suiyang, Zuiyi xian counties, Low-Low clusters in Jinping, Luodian, Wangmo, Liping counties; Low-High clusters in Xishui, Xifeng, Fenggang and High-Low clusters in Anshun, Zhenyuan counties respectively. In 2020, with positive spatial autocorrelation with the

Moran's I value 0.301 with High-High clusters in Tongzi, Zunyi shi, Meitan, Suiyang, Fenggang, Dejiang, Yinjiang, Jiangkou, Guiding, Ceheng, Liping counties; Low-Low clusters in Bijie, Dafang, Jianhe, Jinping, Taijiang counties; Low-High clusters in Longli, Liuzhi and High-Low clusters in Huaxi counties. In 2021, with positive spatial autocorrelation with the Moran's I value 0.116 with High-High clusters in Xishui and Shiqian counties; Low-Low clusters in Wangmo, Ceheng, Anlong, Xingren, Guanning, Ziyun, Anshun, Qinglong and Low-High clusters in Renhuai, Suiyang, Fenggang, Jianhe, Majiang counties respectively. (Figure 2)



HH (11 Counties)	LL (5 Counties)	LH (2 Counties)	HL (1 Counties)
Tongzi, Zunyi shi, Meitan, Suiyang, Fenggang, Dejiang, Yinjiang, Jiangkou, Guiding, Ceheng, Liping	Bijie, Dafang, Jianhe, Jinping, Taijiang	Longli, Liuzhi	Huaxi
2021			
HH (2 Counties)	LL (8 Counties)	LH (5 Counties)	
Xishui, Shiqian	Wangmo, Ceheng, Anlong, Xingren, Guanning, Ziyun, Anshun, Qinglong	Renhuai, Suiyang, Fenggang, Jianhe, Majiang	

Figure 2: The cluster of the incidence of HFMD under 6 years in children from 2019 to 2021.

3.4 Bivariate analysis of Temperature with incidence of HFMD /1000 U-6 Children in 2019, 2020 and 2021.

The Bivariate Moran’s I value is -0.142, -0.069, -0.029 with p-value<0.05 in 2019, p-value>0.05 in 2020 and 2021 respectively. In 2019, with negative spatial autocorrelation with the Moran’s I value is -0.142 with Low-low clusters in Weining, Hezhang, Bijie, Dafang, Xifeng counties; Low-High clusters in Anlong, Ceheng, Wangmo, Luodian, Dushan, Sandu, Congjiang, Liping counties and High-Low clusters in Zhongshan, Qianxi, Qingzhen, Xiuwen, Kaiyang counties. In 2020, with negative spatial autocorrelation with the Moran’s I value is -0.069 with High-High

clusters in Dejiang, Fenggang, Yinjiang, Jiangkou, Liping, Ceheng counties; Low-Low clusters in Weining, Hezhang, Nayong, Bijie, Dafang, Qianxi counties; Low-High clusters in Anlong, Wangmo, Luodian, Congjiang counties and High-Low clusters in Zhongshan, Shuicheng counties. In 2021, with negative spatial autocorrelation with the Moran’s I value is -0.029 with High-High clusters in Liping counties; Low-low cluster in Weining, Hezhang, Pan, Dafang, Qianxi counties; Low-High clusters in Wangmo, Luodian, Dushan, Congjiang, Rongjiang, Jiangkou counties and High-Low clusters in Zhongshan, Shuicheng, Nayong, Bijie counties respectively. (Figure 3)

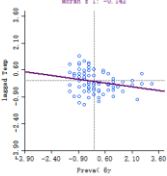
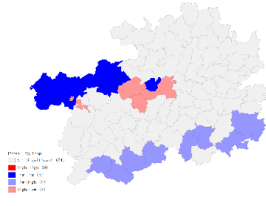
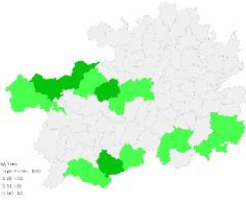
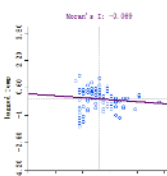
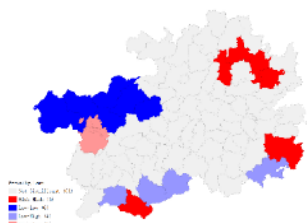
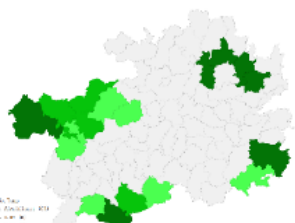
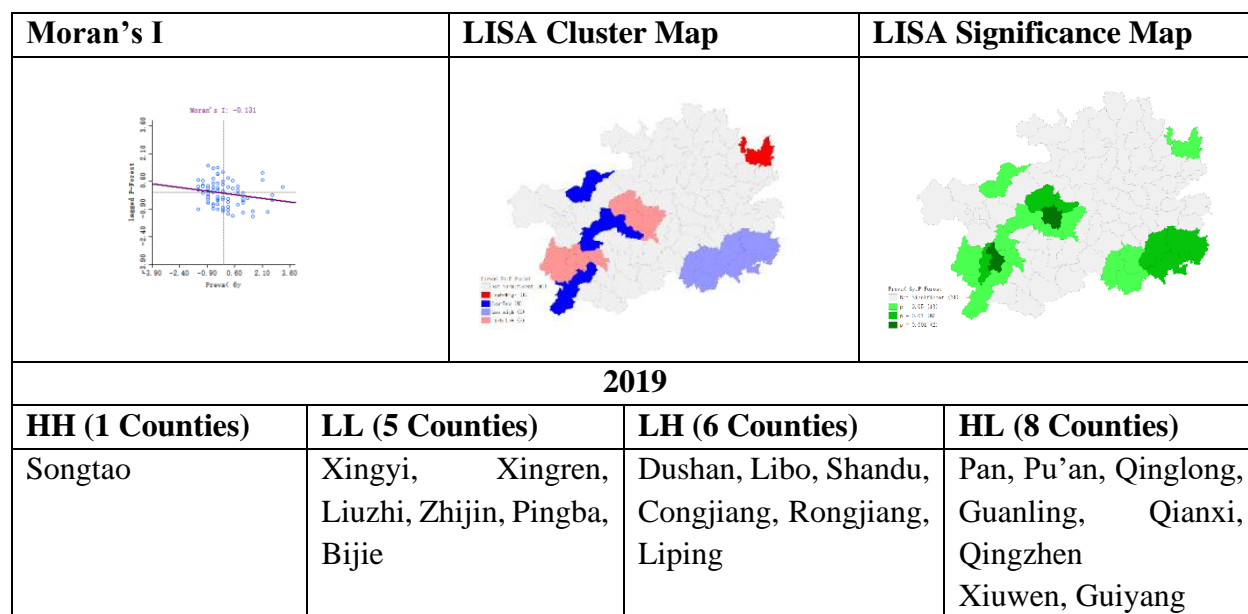
Moran's I	LISA Cluster Map	LISA Significance Map	
2019			
LL (5 Counties)	LH (8 Counties)	HL (5 Counties)	
Weining, Hezhang, Bijie, Dafang, Xifeng	Anlong, Ceheng, Wangmo, Luodian, Dushan, Sandu, Congjiang, Liping	Zhongshan, Qianxi, Qingzhen, Xiuwen, Kaiyang	
			
2020			
HH (6 Counties)	LL (6 Counties)	LH (4 Counties)	HL (2 Counties)
Dejiang, Fenggang, Yinjiang, Jiangkou, Liping, Ceheng	Weining, Hezhang, Nayong, Bijie, Dafang, Qianxi	Anlong, Wangmo, Luodian, Congjiang	Zhongshan, Shuicheng
			
2021			
HH (3 Counties)	LL (7 Counties)	LH (6 Counties)	HL (5 Counties)
Liping	Weining, Hezhang, Pan Dafang, Qianxi	Wangmo, Luodian, Dushan, Congjiang, Rongjiang, Jiangkou	Zhongshan, Shuicheng, Nayong, Bijie

Figure 3: The bivariate analysis of Temperature (F°) with incidence of HFMD

3.5 Bivariate analysis of Percentage of Forest Coverage with incidence of HFMD/1000 U-6 Children in 2019, 2020, 2021.

The Bivariate Moran's I value is -0.131, -0.117, -0.111 (p-value<0.05). In 2019, with negative spatial autocorrelation with the Moran's I value is -0.131 with High-High clusters in Songtao county; Low-Low clusters in Xingyi, Xingren, Liuzhi, Zhijin, Pingba, Bijie counties; Low-High clusters in JDushan, Libo, Shandu, Congjiang, Rongjiang, Liping counties; High-low clusters in Pan, Pu'an, Qinglong, Guanling, Qianxi, Qingzhen, Xiuwen, Guiyang counties. In 2020, with negative spatial autocorrelation with the Moran's I value is -0.117 with High-High clusters in Ceheng, Dejiang, Fenggang,

Yinjiang, Songtao, Jiangkou, Liping, Rongjiang counties; Low-low clusters in Zhijin, Liuzhi, Qingzhen, Pingba counties; Low-High clusters in Dushan, Libo, Sandu, Congjiang counties; High-Low clusters in Xiuwen, Guiyang, Anshun, Guanling, Qinglong, Pu'an, Pan, Xingren, Xingyi counties. In 2021, with negative spatial autocorrelation with the Moran's I value is -0.111 with High-High clusters in Libo, Liping counties; Low-low clusters in Xingyi, Pan, Pu'an, Qinglong, Xingren, Liuzhi, Qianxi, Xiuwen, Qingzhen, Pingba, Anshun, Changshun counties; Low-High clusters in Dushan, Sandu, Rongjiang, Congjiang, Yuping, Songtao counties; High-Low clusters in Zhijin, Guiyang counties. (Figure 4)



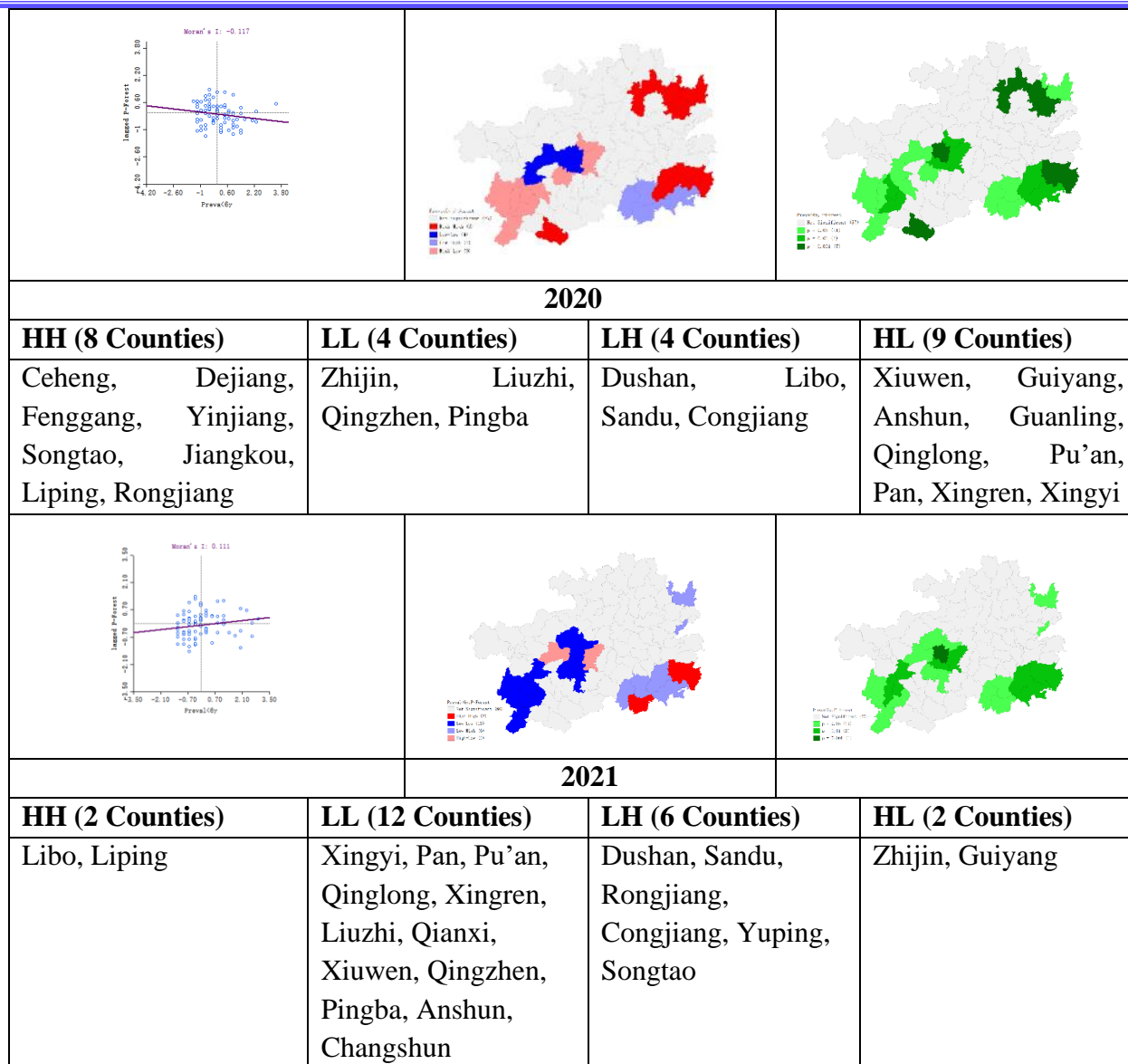


Fig 4: The bivariate analysis of Percentage of Forest Coverage with incidence of HFMD /1000 U-6 Children

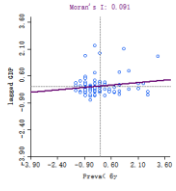
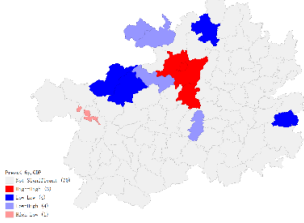
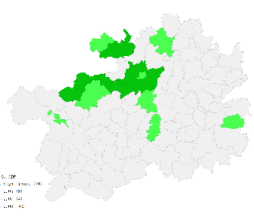
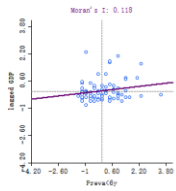
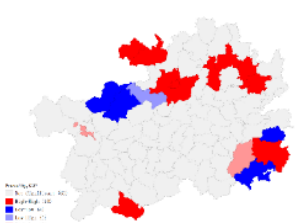
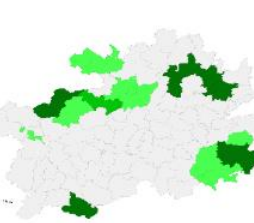
3.6 Bivariate analysis of Gross Domestic Product percent capita with incidence of HFMD/1000 U-6 Children in 2019, 2020, 2021.

The bivariate Moran's I value is 0.091, 0.118, 0.015 with p-value<0.05 in 2019 and 2020, p-value>0.05 in 2021 respectively. In 2019, with positive spatial autocorrelation with the

Moran's I value is 0.091 with High-High clusters in Zhunyiishi, Zhunyixian, Kaiyang counties; Low-low clusters in Bijie, Dafang, Jinping, Zheng'an counties; Low-High clusters in Chishui, Xishui, Jinsha, Guiding counties. In 2020, with positive spatial autocorrelation with the Moran's I value is 0.118 with High-High

clusters in Ceheng, Chishui, Xishui, Zunyishi, Zunyixian, Dejiang, Fenggang, Yinjiang, Jiangkou, Liping counties; Low-low clusters in Bijie, Dafang, Jinping Congjiang counties; Low-High clusters in Jinsha and High-Low clusters in Zhongshan, Rongjiang counties. In 2021, with positive spatial autocorrelation with the Moran's I value is 0.015 with High-High

clusters in Xishui, Zunyishi, Zunyixian counties; Low-low clusters in Dafang, Congjiang, Taijiang counties; Low-High clusters in Jinsha and High-Low value in Bijie, Zhongshan, Liping, Jinping counties respectively. (Figure 5)

Moran's I	LISA Cluster Map	LISA Significance Map	
2019			
			
HH (3 Counties)	LL (4 Counties)	LH (4 Counties)	
Zhunyishi, Zhunyixian, Kaiyang	Bijie, Dafang, Jinping, Zheng'an	Chishui, Xishui, Jinsha, Guiding	
			
2020			
HH (10 Counties)	LL (4 Counties)	LH (1 Counties)	HL (2 Counties)
Ceheng, Chishui, Xishui, Zunyishi, Zunyixian, Dejiang, Fenggang, Yinjiang, Jiangkou, Liping	Bijie, Dafang, Jinping, Congjiang	Jinsha	Zhongshan, Rongjiang

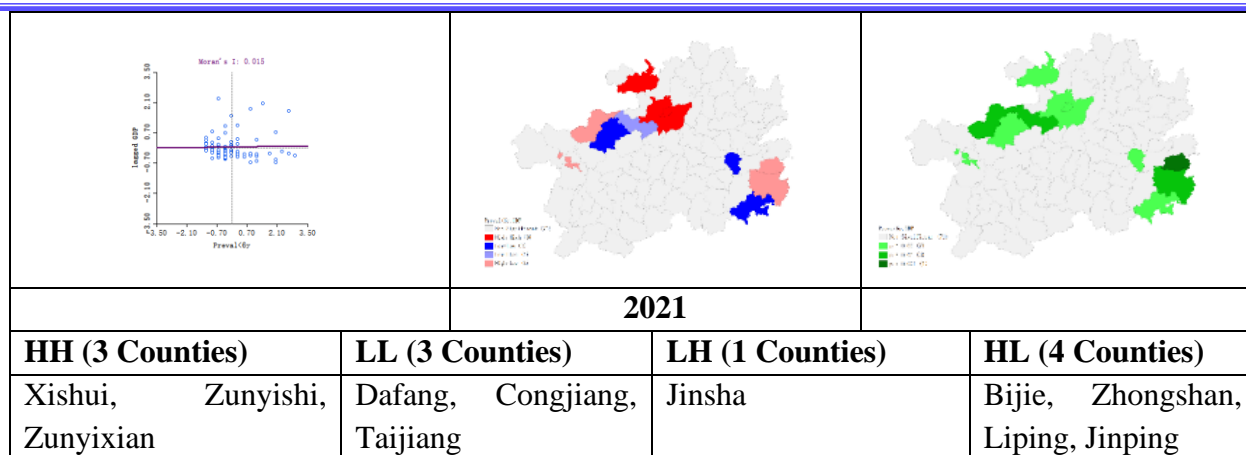


Fig 5: The bivariate analysis of GDP per capita with incidence of HFMD /1000 U-6 Children

4. Discussion

This current study mainly aimed to explore the clusters of HFMD in all (82) Counties of Guizhou province in China and associated factors based on socio-economic status using the spatial analysis. We have gathered the data of HFMD associated factors as well in 2019, 2020, 2021, the data include population, regional area, temperature, humidity, GDP, AQI, forest coverage, road mileage, medical and health institutions, primary schools. We also collected the number of populations in children under 6 years old and the number of children under 6 years old suffering from hand foot mouth disease. The incidence of HFMD has obvious seasonal variations. Spatio-temporal analysis was able to explore risk factors in different regions of China, and the incidence of HFMD was affected by meteorological factors. Spatio-temporal analysis has been increasingly used in epidemiological research to explore possible

clusters based on data from different sources [5]. Meteorological factors are important effects of regional climate, and they impact the incidence and development of infectious diseases[11].

The Chinese CDC showed that the incidence of HFMD in China held different seasonal variation in the south and north. Previous studies suggested that climate (including temperature, humidity, precipitation, air pressure, etc.) was related to the yearly seasonality of HFMD incidence [12]. To our knowledge there are very limited studies on HFMD of children under 6 old years using the spatial analysis in Guizhou province in China. Therefore, we have fully considered the situation of Guizhou Province and included population, regional area, temperature, humidity, GDP, AQI, forest coverage, highway mileage, medical and health institutions, primary schools, etc. into the spatial correlation factors affecting the incidence of HFMD. Li

Ding et al findings spatial-temporal analysis and its tools proved to be effective research method for analyzing the outbreak of HFMD, especially for local governments [13].

Our current study revealed a total of 6 Counties including Tongzi, Renhuai, Zunyishi, Meitan, Suiyang, Zuiyixian with higher incidence of HFMD in 2019. A total of 11 Counties including Tongzi, Zunyi shi, Meitan, Suiyang, Fenggang, Dejiang, Yinjiang, Jiangkou, Guiding, Ceheng, Liping with higher incidence of HFMD in 2020. There will be only 2 counties with high incidence of HFMD in 2021, it is respectively Xishui and Shiqian.

Our study shows that Socio-economic, Environmental and Meteorological factors affect the distribution and transmission of HFMD in Guizhou Province. As far as we know, this is the first time to use QGIS and GeoDa spatial data analysis software to study the spatial correlation between the incidence of HFMD and its related factors in Guizhou Province, China, from 2019 to 2021. In this study, QGIS and GeoDa spatial data analysis software were used to assess the incidence of HFMD and the impact of 9 Socio-economic, Environmental and Meteorological factors, including Density of population (under 6 years) per km², Temperature (F°), Humidity, GDP per capital, Air Quality Index, Percentage of Forest Coverage, No. of Medical and Health

institutions per 1000 Children, and No. of Primary Schools per 1000 sq.km. The results of the study may help researchers better understand the epidemic characteristics and transmission rules of HFMD in Guizhou Province, China, and provide reliable basis and effective suggestions for policymakers to continuously strengthen the prevention, control, and disposal of HFMD.

Shuman Sun et.al found there exist significant spatiotemporal non-stationarity between HFMD, meteorological and socioeconomic factors [14]. The socioeconomic factors have significant spatiotemporal non-stationary on HFMD disease.

According to SEM, Density of population (under 6 years' children) per km², Road Density per sq.km, No. of Primary Schools per 1000 sq.km are the spatially significant factors for HFMD in 2019. Density of population (under 6 years' children) per km² is the spatially significant factor for HFMD in 2020. Density of population (under 6 years' children) per km² and Percentage of Forest Coverage are the spatially significant factors for HFMD in 2021.

In conclusion, our study clearly shows for the first time that there is a spatially heterogeneous association between the Density of population under 6 years' children, Road density per sq.km, No. of Primary schools per 1000 sq.km

and the incidence rate of HFMD in Guizhou Province, China. The incidence rate of HFMD in northern Guizhou Province is very sensitive to population density. Other factors need to be further explored for other areas with low incidence.

5. Conclusion

Our study found that the areas with high incidence of HFMD were mainly Tongzi, Renhuai, Zunyi shi, Meitan, Suiyang, Zuiyi xian concentrated in 2019; with high incidence of HFMD were mainly Tongzi, Zunyi shi, Meitan, Suiyang, Fenggang, Dejiang, Yinjiang, Jiangkou, Guiding, Ceheng, Liping in 2020; with high incidence of HFMD were mainly Xishui, Shiqian in 2021. In a word,

the high incidence rate of HFMD is mainly in the north of Guizhou Province in the past three years. there is a significant spatial correlation between the incidence rate of HFMD and socio-economic and environmental meteorological factors in Guizhou Province. New policy recommendations should be adopted to solve the problem of intervention, so as to prevent the risk of large-scale transmission of HFMD, thereby significantly reducing the incidence rate and transmission rate of HFMD, and reducing the economic burden of the government on unpredictable infectious diseases.

6. Conflict of Interest

No conflict of Interest

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