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# Geospatial analysis of the hospitalisation rate of patients with rheumatoid arthritis in Hunan: a cross-sectional Chinese study

Yan Ge ,[1,2] Shiwen Wang,[3] Qianshan Shi,[4] Jingcheng Shi ,[3] Jing Tian[1,2]

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YG and SW contributed equally. JS and JT contributed equally.

YG and SW are joint first authors.

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For numbered affiliations see end of article.

**Correspondence to**
Dr Jingcheng Shi;
shijch@csu.edu.cn and
Dr Jing Tian;
tianjing001@csu.edu.cn

## ABSTRACT

**Objective** Little is known about spatial variability of hospitalisation rate (HR) of patients with rheumatoid arthritis (RA) worldwide, especially in China.

**Methods** A cross-sectional study was conducted among patients with RA admitted to hospitals in Hunan Province. Global Moran's *I* and local indicators of spatial association were used to explore the geospatial pattern of the HR of patients with RA. Generalised estimating equation analysis and geographically weighted regression were used to identify the potential influencing factors of the HR of patients with RA.

**Results** There were a total of 11 599 admissions, and the average HR was 1.57 per 10 000 population in Hunan. We detected different cluster patterns of the HR among patients with RA by local indicators of spatial association. Age, ethnicity, average temperature, average temperature range, average rainfall, regions, gross domestic product per capita, and doctors and hospitals per 10 000 people were risk factors for the HR. However, only average temperature, gross domestic product per capita and hospitals per 10 000 people showed different regression coefficients on the HR in different counties. The increase in hospitals increased the probability of HR from east to west in Hunan with a positive coefficient, while temperature decreases increased the risk of HR from south to north negatively. Similarly, the growth of gross domestic product per capita decreased the probability of HR from southwest to northeast.

**Conclusion** A non-random spatial distribution of the HR of patients with RA was demonstrated in Hunan, and average temperature, gross domestic product per capita and hospitals per 10 000 people showed different regression coefficients on the HR in different counties. Our study indicated that spatial and geostatistics may be useful approaches for further study among patients with RA.

### STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is the first spatial analysis of geographical variation in the hospitalisation rate of patients with rheumatoid arthritis (RA) at the district and county levels in Hunan, China.
- ⇒ The data came from secondary and tertiary hospitals from provincial administrative databases, which increased accuracy.
- ⇒ Geospatial analysis, a promising in-depth approach in the study of RA, was used.
- ⇒ Many risk factors, such as air pollutants, were not fully investigated due to a lack of data.

## INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease characterised by abnormal synovial hyperplasia and progressive destruction of cartilage and bone, affecting approximately 0.5%–1% of the adult population worldwide.[1 2] Although the aetiology and pathogenesis of RA remain unclear, it is generally believed that multifactorial factors are involved, combining genetic predispositions[3 4] and a variety of environmental factors, such as smoking, infection, microbiota, air pollution and climate factors.[5–9]

There are differences in the incidence of RA. Alamanos *et al*[10] showed that RA varies geographically, with southern European countries having lower median incidence rates than northern European countries and North America. Geographical variation in incident RA has also been observed at the regional level in the USA.[11 12] The findings suggest women living at higher latitudes may be at greater risk for RA. Furthermore, the risk of RA may be greater for locations that occur earlier in residential histories. Similar geographical clusters were observed for other autoimmune diseases, such as systemic lupus erythematosus, dermatomyositis, polymyositis and vasculitis.[13–15] Recently, Liu *et al* found a notable rural–urban variation in RA prevalence in Alberta, Canada. However, little is known about what is behind these geographical differences. Geostatistics are emerging tools that combine statistical, geographical and epidemiological methodologies in describing the spatial characteristics of both infectious and non-infectious diseases, which may be a promising in-depth approach in the study of RA, providing more information on genetic, socioeconomic and environmental information while simultaneously taking into account their spatial diversity. Most of the previous work on the pathogenesis and prevalence of RA explores potential risk factors using classical statistical techniques.

The hospitalisation rate (HR) is an important index which can reflect the local medical and health service capacity and, to some extent, may indicate the prevalence and onset of disease.[16] In addition, hospitalisation of patients consumes the majority of medical resources. To date, the application of geospatial analyses in the HR of patients with RA and its risk factors, especially in China, is lacking in the literature. Therefore, we conducted a geospatial study to explore the spatial distribution of the HR of patients with RA in Hunan province from a global to local scale and to investigate the potential geographical, socioeconomic, environmental and healthcare risk factors while simultaneously considering their spatial diversity.

## MATERIAL AND METHODS

### Study location

Hunan Province is located in the southern-central China (24°38′N-30°08′N, 108°47′E-114°15′E), with a total area of 211800 $km^2$ (http://www.gov.cn/guoqing/2005-09/13/content_5043917.htm). The terrain is a horseshoe-shaped landform surrounded by mountains on three sides and facing the north, and it has a subtropical monsoon climate. Hunan Province has jurisdiction over 14 prefecture-level administrative regions, including 13 prefecture-level cities and 1 autonomous prefecture. There are 36 municipal districts, 19 county-level cities, 60 counties and 7 autonomous counties, totalling 122 county/district-level divisions. In 2019, Hunan Province had a total population of 73.1953 million people and a gross domestic product (GDP) of 3975.21 billion yuan (http://tjj.hunan.gov.cn/). The Dongting Lake region is an area around Dongting Lake, which is located south of the middle reaches of the Yangze River and north of Hunan Province. In terms of administrative regions, the Dongting Lake region includes 21 counties and districts belonging to Yueyang, Yiyang and Changde in Hunan Province, with a land area of approximately 31 700 $km^2$, accounting for 15% of the province's total area. The Dongting Lake region is a famous 'land of fish and rice', rich in natural resources, with a large population and relatively high economic level. In this study, Hunan Province was chosen as the representative region of southern-central China, which has four distinct seasons with a varied climate throughout the year and contains many geographical elements, such as mountains and lakes. These geographical advantages are helpful for studying the effects of the HR of patients with RA on population health and extrapolating the results.

### Data collection

This study enrolled patients aged 16 or older who were admitted to secondary or tertiary hospitals with main diagnosis of RA from 1 January 2019 to 31 December 2019 using the statistical information Direct Reporting System of the Hunan Health Commission. RA-related records were identified as those with the International Classification of Diseases, 10th Revision codes of M05.X or M06.X. The admission times of patients were collected as well as their individual demographic data, including age, sex, permanent address, place of origin, residential postcode and vital status. In this study, we used the permanent address to define the patient's location rather than his or her place of origin. The names, ID numbers and telephone numbers of patients were deidentified in the data collection phase. Data confidentiality principles were followed throughout this study. Patients and the public were not involved in the design, conduct, reporting or dissemination plans of our research.

The independent variables were selected based on the literature review and a priori expert knowledge about the variables that were known to be associated with the time as well as on their availability in the dataset.[9 17–19] Meteorological data (temperature, air pressure and rainfall) were collected from the China Meteorological Data Network (https://data.cma.cn/). Map information came from the standard map service system (http://bzdt.ch.mnr.gov.cn/). Spatiotemporal kriging interpolation analysis was used to complement the daily meteorological data for each district/county of Hunan Province in 2019, then the average annual value was calculated as the total daily value divided by 365 days. The population, economy (GDP; GDP per capita, PGDP) and health resource (number of doctors, number of beds, number of hospitals) data for each district/county were collected from Hunan Statistical Yearbook 2019 (http://tjj.hunan.gov.cn/). The HR of patients with RA in Hunan and in each district/county were calculated per 10000 population (the total RA admissions divided by the number of permanent residents), as well as GDP, PGDP, numbers of doctors, numbers of beds and numbers of hospitals. ArcGIS V.10.8 was used to make a spatial distribution map of the HR and other variables in Hunan Province at the district/county level. The same colour with different shades indicates the variables, the darker the colour, the greater the values of the variables in this area.

Data checking and data screening were also carried out: (1) logical verification was performed by removing cases with obvious logical errors and duplication, such as individuals with 0 hospitalisation costs. Patients with multiple admissions on the same day were counted as a single admission; (2) missing data, such as cases with missing vital information (such as present residence, household registration address or discharge diagnosis information) were deleted; (3) for outliers, graphical representation and Q-test were used to discriminate univariate outliers, and multivariate outliers were determined by Mahalanobis distance. The discovered outlier data were verified for deletion or conversion.

### Statistical methods

In this study, quantitative data were presented as the medians and the 25th–75th percentile IQRs. Data, such as demographic data, meteorological conditions, socioeconomic factors and medical resources, were described as frequency (percentage) percentiles. The $\chi^2$ method was used for intergroup comparisons of categorical variables, and the statistical significance level was corrected by Bonferroni correction. Global spatial autocorrelation analysis and local spatial autocorrelation analysis were used to determine whether the HR of patients with RA was clustered in the province and to analyse the index of local spatial autocorrelation. The included variables were divided into county and individual levels. To analyse the influencing factors more scientifically, a generalised estimating equation (GEE) in two levels was used (district/county level and individual level) to identify the influencing factors of the HR of patients with RA. ORs and 95% CIs) were calculated, and variables with a $p<0.05$ were considered candidates for the geographically weighted regression (GWR) model, which was used to reveal the spatially varying relationships between the RA admission rates and the influencing factors and a set of location-specific parameter estimates. We also conducted Ordinary least square (OLS) and collinearity tests on variables that can be included in GWR to ensure that variables were not omitted. Data were analysed by using SPSS statistical software (V.26.0, IBM) and ArcMap (V.10.8, ESRI, Redlands, California, USA). Districts and counties served as the basic units for spatial analysis (n=122).

### Global spatial autocorrelation analysis

The global spatial autocorrelation analysis started from the macrolevel of the whole province and compared the mean value of the attribute in the general area and the attribute value for each spatial unit to obtain the average degree of association between the HRs of RA in various districts/counties across the province. That is, we conducted an analysis on whether the HR of patients with RA was clustered within the province. Global Moran's $I$ is a commonly used global correlation index ranging from −1 to 1.[20] $I>0$ indicates a positive spatial correlation at the given significance level. The larger the value is, the more pronounced the spatial correlation; a high HR of RA accumulates in space with a high HR of RA and a low HR of RA accumulates spatially. $I<0$ indicates a negative spatial correlation. The smaller the value is, the more significant the spatial difference, and the greater the tendency of a high HR of RA to cluster with low HR of RA. If $I=0$, the observations are randomly distributed in space.[21] This method describes whether there is a clustering phenomenon but cannot confirm where the clustering area is.

### Local spatial autocorrelation analysis

The local indicator of spatial association (LISA) is the analysis index of local spatial autocorrelation analysis.[22] In this study, LISA was used to measure the degree of spatial dependence between the RA admission rates of a district/county and the RA admission rates of its neighbouring districts/counties and identify its spatial cluster pattern in a local space. There are four spatial correlation patterns: high-high (H-H) cluster, low-low (L-L) cluster, high-low cluster and low-high cluster. The H-H cluster and L-L clusters indicated that the HR of RA had a strong positive spatial correlation. The two patterns indicated that the high-HR RA areas were adjacent to the high-HR RA areas, and the low-HR RA areas were adjacent to the low-HR RA areas. The high-low cluster and low-high cluster signified that the HR of RA had a strong negative spatial correlation. The two patterns mean that high-HR RA areas are adjacent to low-HR RA areas.

### Two-level GEE

The GEE is used to estimate the parameters of the generalised linear model, which was first proposed by Zeger *et al* in 1986.[23] It is a regression model for analysing correlation data by using the quasi-likelihood estimation method to estimate parameters in the generalised linear model and repeated measurement data. In addition to the normal distribution, the GEE uses the connection function to fit the stress variables of binomial distribution, Poisson distribution, gamma distribution and other distributions into corresponding statistical models, which solves the problem of non-independence of repeated measurement data and can obtain robust parameters.

In this study, we used the GEE at two levels (district/county level and individual level) to study the influencing factors of HR of patients with RA. The dependent variable was the HR of the patients with RA, and according to the literatures review, independent variables at the district/county level included (1) environmental factors, such as the average temperature, average temperature range, average air pressure, average rainfall, whether the location was the Dongting Lake region and seasons; (2) socioeconomic indicators, including PGDP, GDP and population and (3) healthcare resources, including the number of doctors, number of beds and hospitals per 10000 people. Independent variables at the individual level included sex, age and ethnic group. The correlation among the variables were tested. A pair of variables with a correlation coefficient greater than 0.7 were considered to be strongly correlated, and we also took VIF>5 as the basis for collinearity.[24] A better variable was selected to be included in the model according to the clinical significance and the goodness of fit of the model. Finally, sex, ethnicity, age, average temperature, average temperature range, average rainfall, Dongting Lake area, PGDP, number of hospitals and number of doctors were chosen for the final regression model, as our preliminary analyses found that there was a high correlation between average temperature and average air pressure ($r_s=-0.8674$), number of beds and number of doctors ($r_s=0.940$), and GDP and PGDP ($r_s=0.787$).

### Geographically weighted regression

GWR considers spatial dependency by performing several separated regressions, identifying significant geographical clusters within the studied area.[22] Additionally, GWR produced an estimate for the association between the HR of patients with RA and its predictor variables from analysis of the local spatial variability for each district and county.

**Table 1** Characteristics of hospitalisations of patients with rheumatoid arthritis in Hunan in 2019

| | Hospitalisations (n, %) | Hospitalisation rate (per 10 000 people) | P value |
|---|---|---|---|
| Total | 11 599 (100) | 1.57 | |
| Gender | | | <0.001 |
| Male | 3376 (29.1) | 0.91 | |
| Female | 8223 (70.9) | 2.32 | |
| Age groups in years | | | <0.001 |
| 16–18 | 28 (0.2) | 0.024*† | |
| 19–59 | 4694 (40.5) | 0.86 | |
| ≥60 | 6877 (59.3) | 10.71* | |
| Ethnic group | | | <0.001 |
| Han | 11 211 (96.7) | 1.88 | |
| Ethnic minorities | 388 (3.3) | 0.58 | |
| Region | | | <0.001 |
| Dongting Lake | 2491 (21.48) | 2.06 | |
| Non-Dongtin Lake | 9108 (78.52) | 1.61 | |
| Seasons | | | <0.001 |
| Spring (March–May) | 3195 (27.6) | 0.44 | |
| Summer (June–August) | 3139 (27.1) | 0.43‡ | |
| Autumn (September–November) | 2848 (24.6) | 0.39‡ | |
| Winter (December–February) | 2417 (20.8) | 0.33‡ | |

*Compared with the 19–59 years group, p<0.01.
†Compared with 60 years and above group, p<0.01.
‡Compared with the spring (March–May), p<0.01.

It is assumed that the regression coefficient is a function of regional geographical location and changes in geographical location. In this study, meaningful independent variables from the GEE results were selected for the GWR model. The Akaike information criterion (AIC) and $R^2$ were adopted to build the best fit model for analysis; the smaller the AIC and larger the $R^2$ were, the better model was. Based on Raza O *et al*,[25] the GWR model with one independent variable can be expressed as follows:

$$y_i = \beta_0\left(u_i, v_i\right) + \beta_1\left(u_i, v_i\right) x_i + \varepsilon_i$$

where $u_i$ and $v_i$ are the coordinates of the ith location, and $\beta_0$ $(u_i, v_i)$ is the local intercept for ith location, $\beta_1$ $(u_i, v_i)$ is the estimated local regression coefficient for the ith location and $\varepsilon_i$ is the random error at the ith location.

### Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

## RESULTS

### Characteristics of hospitalisations of patients with RA in Hunan

Basic and admission information of patients with RA is shown in table 1. In 2019, the total number of hospitalisations of patients with RA in Hunan Province was 11 599, including 8223 (70.9%) females and 3376 (29.1%) males (2.441:1). The median age of the admitted patients with RA was 63($P_{25}$=54, $P_{75}$=70) years. Patients aged 60 and above accounted for 59.3% (6877), those aged 19–59 accounted for 33.9% (4694) and those aged 16–18 accounted for 0.2% (28). The total HR was 1.57 per 10 000 people, and significant differences were found in terms of sex, age groups, ethnic groups, regions (whether the patients were located in the Dongting Lake region) and seasons ($p<0.001$). The HR of patients with RA was much higher among female, elderly people (≥60 years), those of Han ethnicity and in the region around Dongting Lake ($p<0.01$). Regarding admission time, there was a higher HR of patients with RA in spring than in summer, autumn and winter ($p<0.01$).

### Distribution of the HRs of patients with RA and demographic data, meteorological conditions, socioeconomic factors and medical resources among 122 counties and districts in Hunan

Online supplemental table 1 lists the basic information of demographic data, meteorological conditions, socioeconomic factors, medical resources and HRs for patients with RA at the district/county level (n=122). Higher HRs of patients with RA were observed in the central area, the northeast region and the Dongting Lake basin in Hunan Province (figure 1). In contrast, the lowest HRs were observed in regions mainly located in the mountainous areas. There was only one patient with RA admitted in Wu lingyuan District, Zhang jiajie, with a low HR of 0.01 per 10 000 people, while in Xiangxiang, a city near the provincial capital of Changsha, the HR was 26.57 per 10 000 people. A significant variation

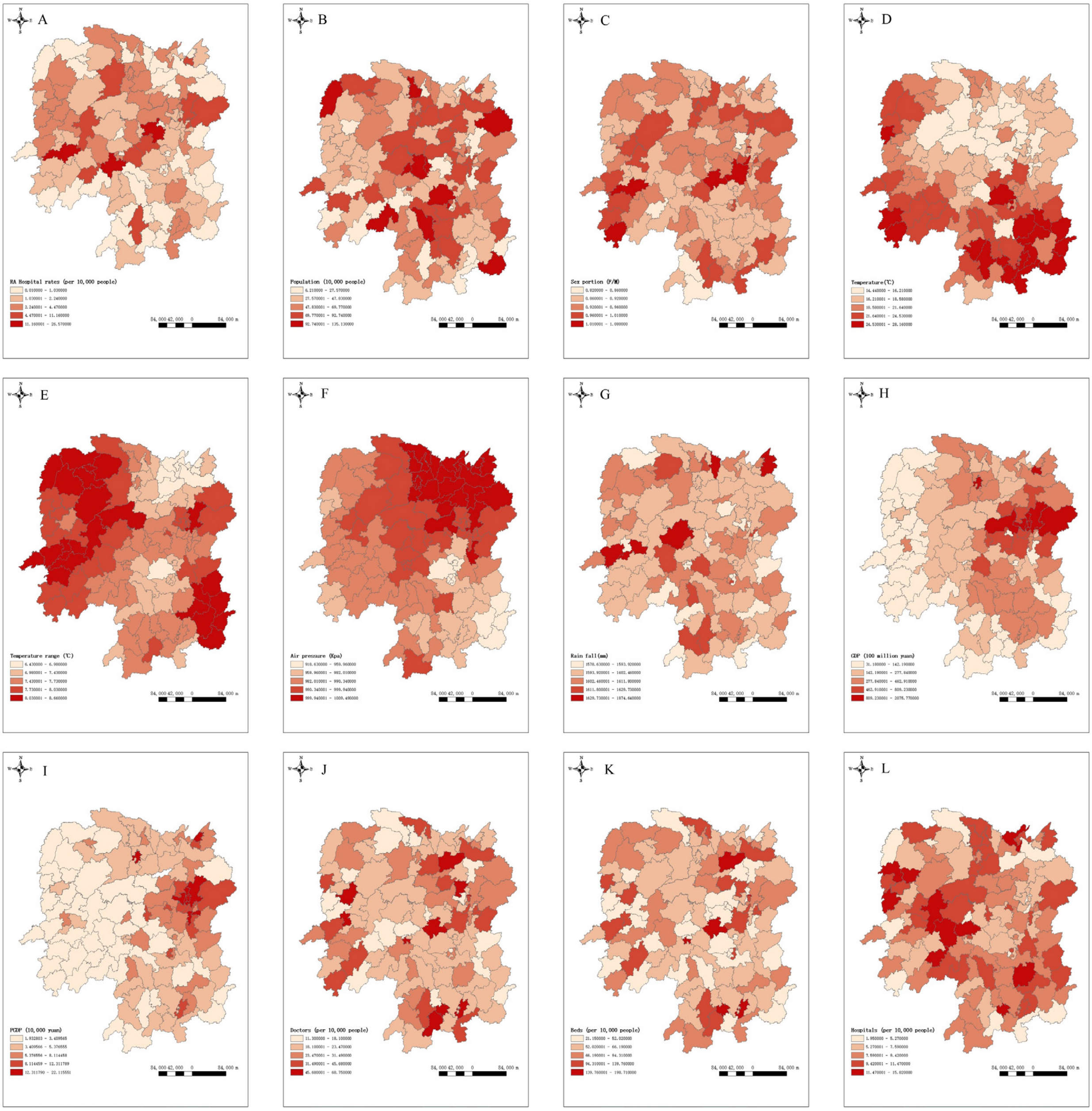

**Figure 1** Distribution of the HR and average demographic data, meteorological conditions, socioeconomic factors and medical resources among 122 districts and counties in Hunan in 2019. A non-random distribution of HR for patients with RA was demonstrated in 122 districts and counties in Hunan (A), and distribution of demographic data (population per10 000 people, sex portion (F/M); B–C), meteorological conditions (temperature, air pressure, temperature range, rainfall; D–G), socioeconomic factors (GDP, PGDP; H–I) and medical resources (doctors, beds, hospitals per 10 000 people; J–L) were different in Hunan. GDP, gross domestic product; HR, hospitalisation rate; PGDP, per capita gross domestic product; RA, rheumatoid arthritis.

in the distribution of HRs among patients with RA was noted in different districts and counties as well as the distribution of other climatic factors, socioeconomic indicators and medical resources (figure 1).

## Global and local spatial autocorrelation of the HRs of patients with RA among 122 districts and counties in Hunan, China

Global spatial autocorrelation analysis showed a globally spatiality of the HR of patients with RA in Hunan Province (Moran's $I$=0.2585, Z=4.0318, $p$<0.000). LISA analysis detected two HH pattern clusters (Ningxiang county and Shuangfeng county) in the central regions of Hunan, in which high RA admission rates close to neighbours were also associated with high RA admission rates. Eleven LL pattern clusters were also observed in the northwestern and southern mountainous areas in Hunan, indicating districts and counties with low RA admission rates with neighbours with low RA admission rates (figure 2, online supplemental table 2). Notably, six L-L clusters (four districts and two counties) were found in Hengyang city. We also found one high-low pattern cluster and

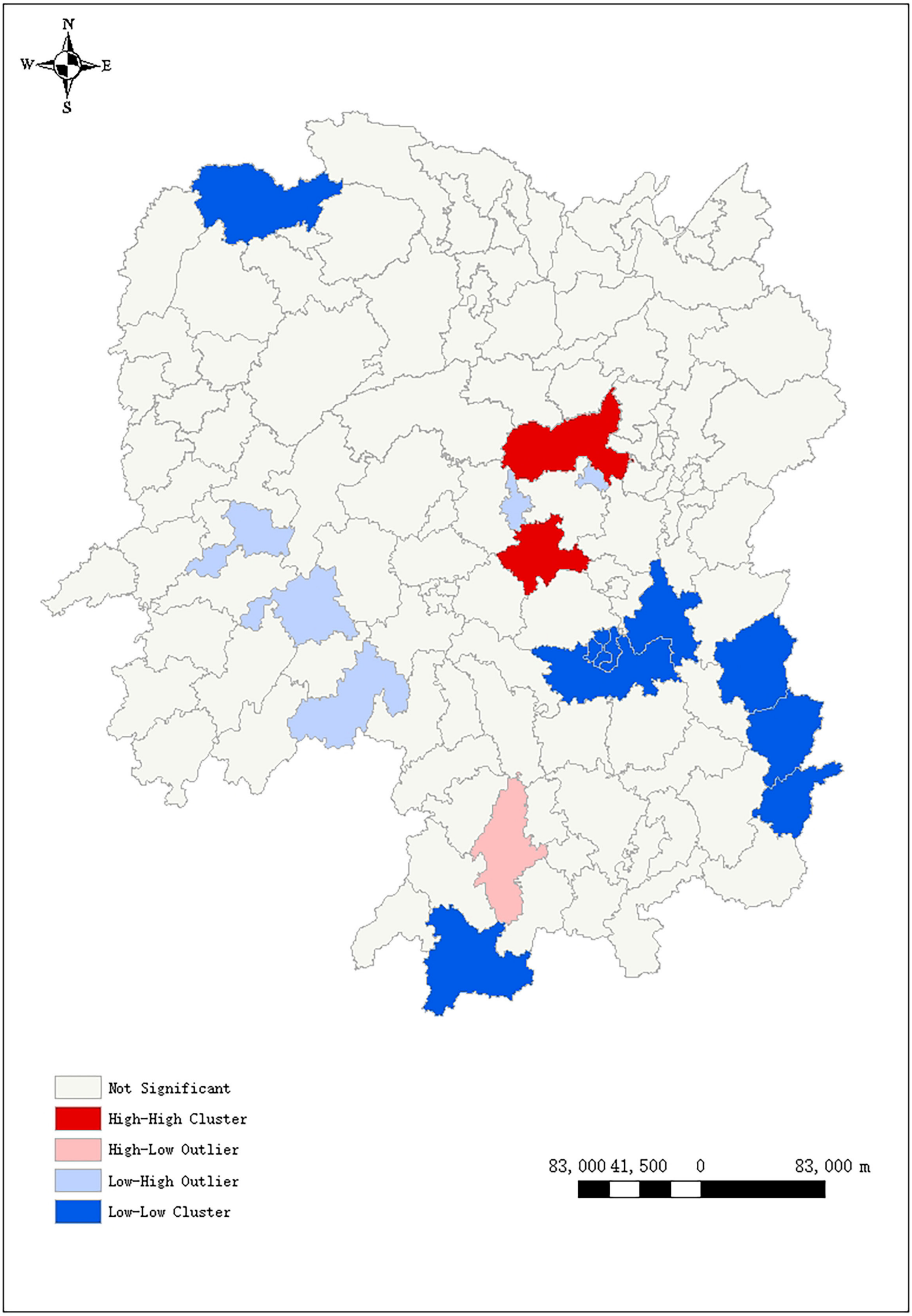

**Figure 2** Spatial distribution clusters of the HR of patients with RA among 122 districts and counties in Hunan in 2019 by local indicators of spatial association (LISA) analysis. LISA analysis indicates clusters according to high and low HR distribution patterns. HR, hospitalisation rate; RA, rheumatoid arthritis.

**Table 2** The two-level GEE analysis for risk factor of the HR of patients with RA in Hunan in 2019

| | | | | 95% CI | |
|---|---|---|---|---|---|
| **Variables** | | **OR** | **P value** | **Lower** | **Upper** |
| (Intercept) | 216.868 | – | <0.001 | 150.845 | 311.788 |
| Gender | | | | | |
| Female | | 1.036 | 0.213 | 0.848 | 1.151 |
| Male | | 1 | | | |
| Age | | | | | |
| 16–18 | | 0.089 | <0.001 | 0.024 | 0.139 |
| 19–59 | | 0.837 | <0.001 | 0.742 | 0.913 |
| ≥60 | | 1 | | | . |
| Ethnic group | | | | | |
| Han | | 4.482 | <0.001 | 3.341 | 5.868 |
| Ethnic minorities | | 1 | | | |
| Temperature | | 0.876 | <0.001 | 0.785 | 0.983 |
| Temperature range (°C) | | 1.459 | <0.001 | 1.246 | 1.641 |
| Rainfall (mm) | | 0.997 | <0.001 | 0.996 | 0.999 |
| Region | | | | | |
| Non-Dongting | | 1 | | | |
| Dongting Lake | | 1.340 | <0.001 | 1.145 | 1.511 |
| PGDP | | 0.953 | <0.001 | 0.936 | 0.983 |
| Doctors (per 10 000 people) | | 0.965 | <0.001 | 0.948 | 0.971 |
| Hospitals (per 10 000 people) | | 1.167 | <0.001 | 1.157 | 1.181 |

Estimated ORs were compared with the reference (OR=1) in each group.
GEE, generalised estimating equation; HR, hospitalisation rate; PGDP, per capita gross domestic product; RA, rheumatoid arthritis.

five low-high pattern clusters in Hunan. The global and local spatial autocorrelation coefficients were considered significant at $p<0.05$.

### Factors including demographic indicators, meteorological conditions, socioeconomic conditions and medical resources were associated with the HR of patients with RA in Hunan in two-level GEE analysis

In the two-level GEE analysis, age, ethnicity, average temperature, average temperature range, average rainfall, regions (whether the patients were located in the Dongting Lake region area or not), PGDP and the number of doctors and hospitals per 10 000 people were risk factors for hospitalisation among patients with RA, sex was not a risk factor ($p=0.213$, table 2). Among the factors, the average temperature range and number of hospitals per 10 000 had a slightly positive effect on the HR of patients with RA (OR 1.459; 95% CI 1.246 to 1.641; $p<0.001$; OR 1.167; 95% CI 1.157 to 1.181; $p<0.001$). In contrast, the risk of hospitalisation was negatively correlated with temperature, rainfall, PDGP, number of doctors per 10 000 people (OR 0.876; 95% CI 0.785 to 0.983; $p<0.001$; OR 0.997; 95% CI 0.996 to 0.999; $p<0.001$; OR 0.953; 95% CI 0.936 to 0.983; $p<0.001$; OR 0.965; 95% CI 0.948 to 0.971; $p<0.001$). The subgroup analysis demonstrated the risk of hospitalisation in the Han group, the elderly group (≥60 years), and the Dongting Lake region group was much higher than that in the minority group, the younger group (<60 years) and the non-Dongting Lake region group ($p<0.001$).

### The impact of average temperature, PGDP and number of hospitals on the HR of patients with RA among 122 districts and counties in Hunan by GWR analysis

To further identify risk factors that had the greatest geospatial impact on the spatial distribution of HRs among patients with RA, we performed a multivariate spatial regression analysis using GWR based on the above GEE analysis.

The GWR model showed that average temperature, PGDP, hospitals per 10 000 people were independent influencing factors for the HR of patients with RA with spatial trend ($R^2$ 0.521; adjust $R^2$ 0.493; AIC 124.543). The distinctive spatial impact of each significant variable on the HR of patients with RA is indicated in figure 3. The effect of average temperature and PGDP on the HR of patients with RA in Hunan Province was negative. The great reduction in temperature, the lower of the PGDP and the higher the HR of patients with RA. Overall, the influence of temperature on the HR decreased from the south of Hunan to the northern regions (regression coefficient −0.0548 to −0.0546)and the HR of patients with RA in the south was more likely to be affected by average temperature. Similarly, the influence of PGDP decreased

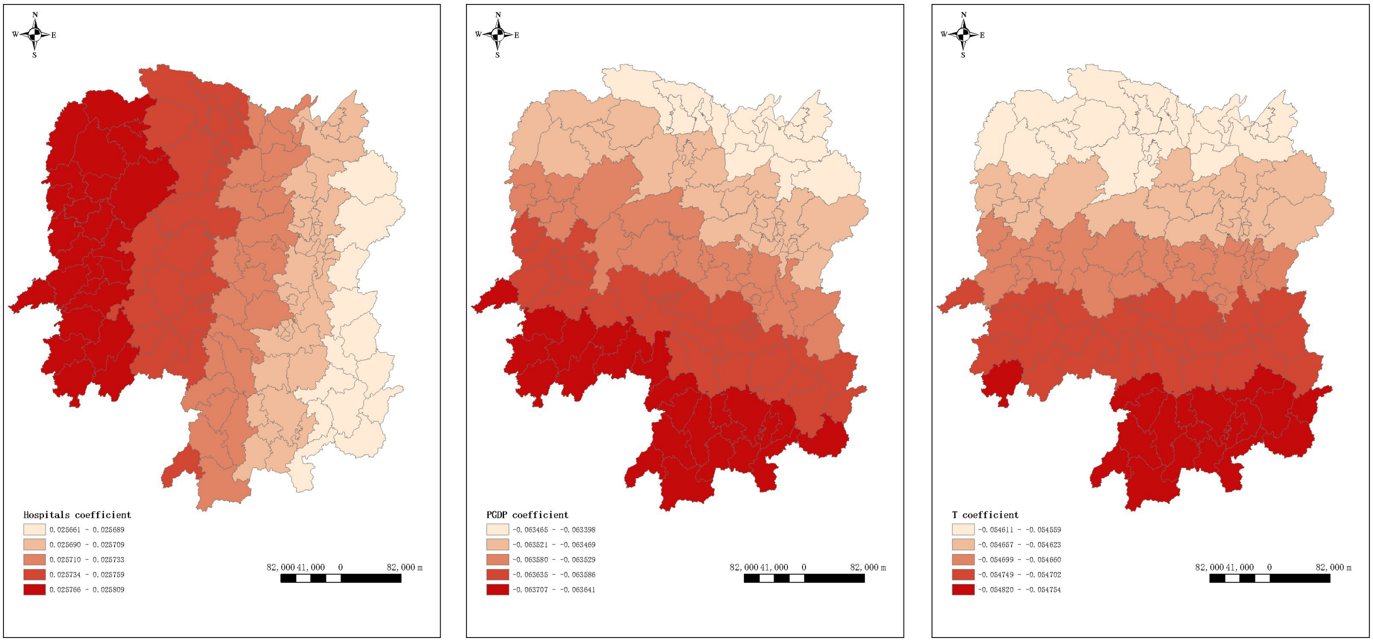

**Figure 3** The effect of average temperate, PGDP and hospitals per 10 000 on the hospitalisation rate (HR) of patients with rheumatoid arthritis (RA) among 122 districts and counties in Hunan by GWR analysis. Average temperate, PGDP and hospitals per 10 000 show distinctive spatial impact on HR of patients with RA. GWR, geographically weighted regression; PGDP, per capita gross domestic product.

from the southwest to the northeast regions in Hunan, which means that the HR of patients was more likely to be affected by PGDP in the southwest (regression coefficient −0.0637 to −0.0634). In contrast, the impact of the number of hospitals per 10 000 people on the HR of patients with RA was positive and increased from the eastern to the western regions; the greater the number of hospitals was, the higher the HR of people was, especially in western Hunan (regression coefficient 0.0257–0.0258). The GWR analysis suggested that the HR of patients with RA was indeed affected by local temperature, PGDP and the number of hospitals and varied by region.

## DISCUSSION

RA is a chronic autoimmune disease and a leading cause of working disability, and this situation will become more serious with the increase of ageing. Although the aetiology is not entirely clear, RA is a multifactorial disease involving genetics, immunology and environment. The ultimate therapeutic goal for RA is to achieve long-term disease remission or low disease activity. Thus, the management of RA requires collaboration not only between patients and health provider but also the formulation of corresponding medical policies, medical resource allocation and support from the government. There are large gaps in economic conditions, medical resource allocation and medical service efficiency among different regions in China and even different cities in the same province, and meteorological conditions differ by region. In this study, the spatial distribution of the HR of patients with RA by district/county was first evaluated, and its association with demographics, meteorological conditions, socioeconomic indicators and medical resources, taking spatial dependence into account, by GWR analysis and GEE analysis was investigated in Hunan, a southern-central province in China with a median national PGDP level. To the best of our knowledge, this is the first spatial analysis study on the HR for patients with RA in China.

In 2019, the annual HR for RA was 1.57 per 10 000 people in the whole province, but we found a notable variation from 0.01 case/10 000 population to 26.57 cases/10 000 population between geographical areas. The HR of patients with RA was significantly higher in the central and northeast areas and the Dongting Lake region in Hunan. We identified 2 H-H clusters located in the northeastern and central region and 11 L-L clusters located in mountain areas. Furthermore, we investigated the possible risk factors associated with disparities in the HR of patients with RA in Hunan. Notably, age, ethnicity, temperature, temperature range, rainfall, Dongting Lake area, PGDP and number of doctors and hospitals per 10 000 people were risk factors ($p<0.001$) in the GEE analysis. However, only temperature, PGDP and number of hospitals per 10 000 people were related to the risk of hospitalisation among patients with RA in GWR when considering spatial dependence. In total, patients in regions with lower temperature, lower PGDP or more hospitals per capita had a higher risk of hospitalisation. Notably, the influence of temperature, PGDP and number of hospitals on the HR of patients with RA in Hunan varied by region. These spatial variations and risk factors should be considered when designing evidence-based interventions and planning programmes to improve RA care in Hunan. Our findings highlight the need for regional approaches for the planning and delivery of RA care as well as the management of patients with RA. Further studies should investigate the underline pathogenesis of the difference in HRs among patients with RA in Hunan, especially the relationship with temperature, PDGP and numbers of hospitals per 10 000 people.

A total of 11 599 patients with RA were admitted to hospitals in Hunan in 2019, with a female predominate, and the mean age was 63 (54, 70) years old, which was similar to the results in other reports in China.[9] In our study, the HR of RA was 1.57 per 10 000 population, which was much lower than the prevalence of RA (approximately 0.5%–1% of the adult population). In recent years, a decrease in the number of RA hospitalisation in Western countries has been reported. The number of RA hospitalisation in Washington, USA, decreased from 202.6 per 100 000 population in 1995 to 87.3 per 100 000 population in 2002.[16] In New Zealand, the HR of RA decreased from 11.3 to 8 per 100 000 inhabitants between 1995 and 2002.[26] In Canada, the annual HR of RA was decreased from 15.4 to 12.4 per 100 000 population between 2000 and 2002.[27] Due to the lack of data on the HR of patients with RA in Hunan, even in China, it is difficult to know whether the HR will decrease or increase, but there has been dynamic change in recent years. On one hand, the HR may increase because of the overall improvement in the numbers of rheumatologists and departments in hospitals, access to information and health insurance system coverage in low-income areas for patients. On the other hand, as an increasing number of patients with RA are detected early and receive better management, a decline in the HR of patients with RA might occur.

The spatial distributions of infectious diseases have been extensively studied,[28–30] for the spread of the pathogenic microbial agent. However, non-communicable diseases in humans also show clustering in space. Such is the case for heart diseases, diabetes and autoimmune inflammatory rheumatic diseases.[15 31–33] Sapina *et al* found that incidences of childhood IgA vasculitis and IgA vasculitis-associated nephritis in Croatia were not randomly distributed but clustered in space.[34] An enormous variation in the HRs of patients with RA among 122 districts and counties in Hunan was found, ranging from 0.01 to 26.57 per 10 000 population. In addition, the existence of spatial autocorrelation was observed in the HR of RA in our study. H-H clusters of HR for patients with RA were found in Ningxiang county and Shuangfeng county in the northeastern and central areas, showing higher positive HR autocorrelations in those areas. Ningxiang county is located in the capital city of Changsha. Five L-L clusters were found dispersed partially in the northwestern, southeastern and southern mountainous areas, while other six L-L clusters, belonging to Hengyang city, were located in the south-central part of Hunan. Surprisingly, Shuangfeng county, an H-H cluster, was near the L-L clusters in Hengyang city. One of the possible reasons may be their geographical differences. The terrain of Shuangfeng is closer to the northern and central plains but separated from the latter by Mountain Hengshan. However, subsequent questions arise and should be discussed: why do these hotspots and cold spots occur, and how can they be explained?

Previous studies using GAMs and GLS have shown that incident RA varies geographically at the regional level in the USA as well as worldwide.[11 12] The findings suggested that women living at higher latitudes may be at greater risk for RA. Furthermore, the risk of RA may be greater for older locations with a longer residential history. Recently, a significant rural–urban variation in RA prevalence in Alberta, Canada, was reported in 2021.[15] The authors reported factors such as obesity, socioeconomic factors, genetic and environmental factors such as aboriginal and immigrant status, and local meteorological conditions may partially explain these variations.

Consistent with the HR, the demographic characteristics, meteorological conditions, socioeconomic indicators and healthcare resources also demonstrated geospatial discrepancies at the district and county levels in our study. In addition, we found that age, ethnicity, temperature, temperature range, rainfall, Dongting Lake region, PGDP and number of doctors and hospitals per 10 000 people were risk factors for hospitalisation among patients with RA in the GEE analysis.

However, if we consider the spatial variation, only temperature, PGDP and number of hospitals per 10 000 people affected the risk of hospitalisation among patients with RA with spatial dependence using the GWR model. There have been many studies on the effect of temperature on RA incidence, joint pain and medical seeking behaviours, such as clinic visits or admissions; however, the results are conflicting, which may be mainly explained by different statistical analysis methods and adjustment for climate covariates. Recently, Huang *et al*[2] reported the exposure to cold temperatures increased the risk of RA admissions in Anhui using spatiotemporal series analysis with a distributed lag non-linear model. Notably, we found that the influence of temperature on the HR was negative regardless of whether spatial dependence was considered. A significant trend was demonstrated in which the effect of temperature on the HR increased from north to south. When the temperature dropped, the risk of hospitalisation among patients with RA in the southern area increased slightly compared with that in the northern area. This result indicated that geospatial analysis may provide a new approach in future studies to address the conflicting influence of climate factors in RA and other autoimmune and inflammation diseases. Low temperatures were also associated with increased risks of all types of inflammation-related diseases in Yanchi County, Ningxia, China (RR 4.344, 95% CI 2.887 to 6.535).[35] Abundant evidence indicates that extreme high or low temperatures could increase risks of mortality and morbidity for cardiovascular and respiratory diseases.[36 37] Some researchers believe that the underlying reasons may be that inflammatory factors such as interlukin-6 and C reactive protein play an important role in triggering the adverse effects of low or extreme temperatures.[38 39]

It is well known that lower socioeconomic status increases the risk of RA prevalence, functional decline and overall mortality rate over time.[40 41] In this study, we also demonstrated that lower PGDP was associated with a higher risk of hospitalisation among patients with RA, and the effect of GDP showed spatial variation in different regions in Hunan. The HR of patients with RA seemed more likely to be affected by the PGDP in the southwest, while it was much lower in the northeast region. Greater attention should be given to the economic situation of patients with RA in the southwest region, and more should be done to improve their poverty. In addition, the inequalities in healthcare, low accessibility to healthcare centres and limited health coverage offered to the patients may also be responsible for the HR of RA. In this study, the number of hospitals per 10 000 people had a positive effect on the HR of patients with RA. In addition, the impact of the number of hospitals per 10 000 people on the HR of patients with RA was positive, increasing from the eastern to the western regions in Hunan. The greater the number of hospitals was, the higher the HR, especially in western Hunan. This was consistent with the lack of healthcare centres in the western region of Hunan. Thus, increasing access to healthcare centres and the disrupting barriers to healthcare delivery would greatly benefit patients with RA in western Hunan in the future. Large-scale studies based on epidemiological and physiological data are necessary to further determine whether there are differences in the HR of RA and the related mechanisms behind the influence of temperature, economic level and medical resources on the HR of patients with RA. The GWR analysis suggested that inequalities in healthcare and major disparities in individual income and local temperature may be responsible for the HR of patients with RA in Hunan. However, there are also other factors that affect the HR of RA.

This study has strengths and limitations. First, we applied spatial analysis to explore the geographical variation in the HR of patients with RA at the district and county levels, which may fill the gap in the knowledge of the HR of patients with RA at local levels in Hunan, providing important information for healthcare planning. Second, our study indicated that geospatial analysis may be a promising in-depth approach in the study of RA, providing more genetic, socioeconomic and environmental information. However, several limitations must be taken into consideration when interpreting the results. First, this was a cross-section study from Hunan Province that used provincial administrative databases from secondary or tertiary hospitals as the source. All of these factors may have led to biases. Previous studies suggest that the RA case definition using health administrative databases has excellent sensitivity when multiple physician claims are included.[15] Due to the lack of rheumatologists in primary hospitals in Hunan, we believe that these estimates may largely represent the true number of hospitalisations for patients with RA in Hunan Province. However, these data have inherent limitations and should be interpreted with caution. Second, we used the annual average data of climate factors for analysis, ignoring their short-term influence on the patients, which needs to be further studied in subsequent studies. Third, there are numerous determinants of the HR of patients with RA; nevertheless, a number of risk factors, such as air pollutants, were not investigated in the present study due to the lack of data, which may be considered as a limitation of the present study. Fourth, GWR can analyse the HR of RA from multiple spatial factors but ignores the different spatiotemporal scales of various factors. Thus, for a more reasonable analysis, we first took a two-level GEE to identify significant variables. Finally, it is not possible to accurately ascertain individual exposures, which may have led to certain measurement biases.

## CONCLUSION

A non-random spatial distribution of the HR of patients with RA was demonstrated in Hunan. In addition, average temperature, PGDP and hospitals per 10 000 people showed different regression coefficients across the regions on the HR of patients with RA. Our study indicated that spatial and geostatistics may be useful approaches for the further study in RA to provide more information on genetic, socioeconomic and environmental risk factors while taking into account their spatial diversity.

**Author affiliations**
[1]Department of Rheumatology and Immunology, The Second Xiangya Hospital of Central South University, Changsha, Hunan, China
[2]Clinical Medical Research Center for Systemic Autoimmune Diseases in Hunan Province, Changsha, Hunan, China
[3]Department of Epidemiology and Medical Statistics, Xiangya School of Public Health, Central South University, Changsha, Hunan, China
[4]Information Statistics Center of Health Commission of Hunan Province, Changsha, Hunan, China

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**ORCID iDs**
Yan Ge http://orcid.org/0000-0003-4378-6990
Jingcheng Shi http://orcid.org/0000-0001-8071-5927

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**Table S1. Characteristics of average demographic data, meteorological conditions, socioeconomic factors, medical resources and the HR of RA patients among 122 districts and counties in Hunan in 2019**

| Variables | Percentile | | | | |
|---|---|---|---|---|---|
| | $X_{min}$ | $P_{25}$ | $P_{50}$ | $P_{75}$ | $X_{max}$ |
| **Population** (10,000 people) | 6.21 | 34.60 | 57.06 | 81.07 | 135.13 |
| **Sex portion** (F/M) | 0.82 | 0.92 | 0.94 | 0.96 | 1.08 |
| **Age**(years) | 40 | 45 | 52 | 60 | 63 |
| **Temperature** (℃) | 14.44 | 16.49 | 19.17 | 23.20 | 28.16 |
| **Air pressure** (Kpa) | 918.63 | 982.28 | 990.19 | 997.53 | 1009.49 |
| **Temperature range** (℃) | 6.43 | 7.40 | 7.67 | 7.94 | 8.66 |
| **Rain fall** (mm) | 1578.63 | 1596.27 | 1598.92 | 1606.81 | 1874.64 |
| **GDP** (100 million yuan) | 31.18 | 117.59 | 234.72 | 364.87 | 2075.77 |
| **PGDP** (10,000 yuan) | 1.93 | 2.90 | 4.42 | 6.72 | 22.11 |
| **Doctors** (per 10,000 people) | 11.30 | 19.31 | 22.47 | 29.36 | 68.75 |
| **Beds** (per 10,000 people) | 21.15 | 50.75 | 58.69 | 78.39 | 198.71 |
| **Hospitals** (per 10,000 people) | 1.95 | 6.70 | 8.53 | 10.09 | 15.82 |
| **HR of RA patients** (per 10,000 people) | .01 | .88 | 1.65 | 2.75 | 26.57 |

F: female; M: male; GDP: Gross Domestic Product; PGDP: GDP per capita; HR: Hospitalization rates

**Table S2. Different cluster patterns of the HR of RA patients in Hunan in 2019**

| District/county | Local Moran's *I* | *Z* Score | *P* | Patterns |
|---|---|---|---|---|
| Ningxiang county[a] | $4.46\times10^{-6}$ | 2.16 | 0.04 | HH |
| Shuangfeng county[b] | $1.51\times10^{-3}$ | 2.85 | 0.02 | HH |
| Chaling county[c] | $1.86\times10^{-5}$ | 0.88 | 0.04 | LL |
| Yanling county[c] | $1.99\times10^{-5}$ | 0.87 | 0.04 | LL |
| Zhuhui district[d] | $8.80\times10^{-5}$ | 0.99 | 0.03 | LL |
| Yanfeng district[d] | $5.59\times10^{-5}$ | 1.17 | 0.00 | LL |
| Shigu district[d] | $1.04\times10^{-4}$ | 1.10 | 0.02 | LL |
| Zhengxiang district[d] | $1.07\times10^{-4}$ | 1.00 | 0.02 | LL |
| Hengnan county[d] | $5.51\times10^{-5}$ | 0.98 | 0.03 | LL |
| Hengdong county[d] | $3.21\times10^{-5}$ | 1.19 | 0.02 | LL |
| Sangzhi county[e] | $1.52\times10^{-5}$ | 0.85 | 0.00 | LL |
| Guidong county[f] | $1.04\times10^{-5}$ | 0.87 | 0.05 | LL |
| Jianghua county (Yao Autonomous)[g] | $2.98\times10^{-6}$ | 0.69 | 0.03 | LL |
| Ningyuan county[g] | $-1.53\times10^{-4}$ | -1.15 | 0.04 | HL |
| Shaoshan city[h] | $-1.36\times10^{-4}$ | -3.01 | 0.01 | LH |
| Dongkou county[i] | $-3.22\times10^{-5}$ | -3.01 | 0.03 | LH |
| Louxing district[b] | $-6.75\times10^{-5}$ | -3.55 | 0.02 | LH |
| Xinning county[i] | $-2.50\times10^{-5}$ | -1.51 | 0.05 | LH |
| Zhongfang county[j] | $-3.36\times10^{-5}$ | -2.17 | 0.05 | LH |

HR: Hospitalization rates; HH: high-high pattern; LL: low-low pattern; HL: high-low pattern; LH: low-high pattern; a: belongs to Changsha city; b: belongs to Loudi city; c: belongs to Zhuzhou city; d: belongs to Hengyang city; e: belongs to Zhangjiajie city; f: belongs to Chenzhou city; g: belongs to Yongzhou city; h: belongs to Xiangtan city; i: belongs to Shaoyang city; j: belongs to Huaihua city.