Epidemiological Investigation of Hemophagocytic Lymphohistiocytosis in China

Shuyan Yao
Capital Medical University Affiliated Beijing Friendship Hospital
Yini Wang (wangyini@ccmu.edu.cn)
Capital Medical University Affiliated Beijing Friendship Hospital https://orcid.org/0000-0001-8545-2660
Yuan Sun
Beijing Jingdu Children's Hospital
Li Liu
Tangdu Hospital Fourth Military Medical University: Air Force Medical University Tangdu Hospital
Rui Zhang
Beijing Children's Hospital Capital Medical University
Jianpei Fang
Sun Yat-Sen University 2nd Affiliated Hospital: Sun Yat-Sen Memorial Hospital
Runming Jin
Huazhong University of Science and Technology Tongji Medical College First Clinical College: Wuhan Union Hospital
Jie Yu
Chongqing Medical University Affiliated Children's Hospital
Fei Li
First Affiliated Hospital of Nanchang University
Jie Bai
Tianjin Medical University Second Hospital
Yun Zeng
Kunming Medical University First Affilliated Hospital
Cheng Zhang
Third Military Medical University Second Affiliated Hospital: Xinqiao Hospital
Huo Tan
Guangzhou Medical College First Affiliated Hospital
Fan Zhou
General Hospital of Shenyang Military Region: General Hospital of Northern Theatre command
Yan Chen
Zunyi Medical College Affiliated Hospital: Affiliated Hospital of Zunyi Medical University
Qiaohua Zhang
Shanxi Bethune Hospital
Zhao Wang
Capital Medical University Affiliated Beijing Friendship Hospital

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Research Article

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Abstract

Background. At present, most research on HLH focus on etiology and therapy, leaving few epidemiological reports. The published studies of China are mainly regional investigations. We aim to present the overall epidemiological status of HLH in China, and provide Chinese data for the international HLH epidemiological investigation.

Methods. The data of HLH cases in China in 2019 was collected and statistically analyzed.

Findings. Among 1445 cases in 31 areas, EBV accounting for 44.01% is the most common cause. Lymphoma-associated HLH patients are mostly males ($P<0.05$) while rheumatic and immune-associated HLH mostly females ($P<0.001$). Children have mainly primary HLH and EBV-associated HLH ($P<0.001$) while adults mostly tumor-associated HLH. Lymphoma-associated HLH is positively correlated with the age of onset ($P<0.01$). The diagnosis rate of 29 areas has a significant correlation with per capita Gross domestic product ($P<0.05$).

Conclusion. The etiology distribution of HLH in different age and sex is different, assisting clinicians with the diagnosis of HLH; The diagnosis rate of regions with a high incidence of HLH in China is not ideal as the result of the effect of the local economic level indicating the importance of improving the regional medical level.

Background

Hemophagocytic syndrome (HPS), also known as hemophagocytic lymphohistiocytosis (HLH), is a clinical syndrome caused by genetic or acquired immune dysfunction [1]. The disease is dangerous, progressing rapidly, and has a high mortality [2]. At present, most research on HLH focus on etiology and therapy, leaving few epidemiological reports. Japan has studied children and adult cases nationwide, and the annual incidence is estimated to be 1:800,000. A Swedish study reported that the incidence of HLH related to malignant tumors in adults is 0.9% [3]. The published studies of China are mainly regional investigations [4, 5]. Currently, none of them covers multiple regions and the entire population. In this study, we collect data on HLH cases in the whole of China in 2019, analyze the distribution of causes in age and sex, and explore the regional characteristics of incidence across the country as well as the correlation between diagnosis rates and GDP indicators, aiming to present the overall epidemiological status of HLH in China and provide Chinese data for the international HLH epidemiological investigation.

Materials And Methods

1.1 Case selection

Inclusion criteria: New HLH cases diagnosed according to HLH-2004, that is, which meet at least 5 of the 8 diagnostic criteria of HLH-2004: (1) Body temperature ≥ 38.5°C; (2) Splenomegaly; (3) Cytopenia affecting at least 2 of 3 lineages in the peripheral blood: hemoglobin (HB) < 90g/L, platelets (PLT) < 100×10^9/L or neutrophils (N) < 1×10^9/L; (4) Hypertriglyceridemia and/or hypofibrinogenemia: triacylglycerol (TG) ≥ 3mmol/L, or fibrinogen (Fbg) ≤ 1.5g/L; (5) Serum ferritin (SF) ≥ 500μg/L; (6) Hemophagocytosis found in bone marrow or spleen or lymph nodes; (7) Soluble CD25(sCD25) ≥ 2400U/mL; (8) Natural killer (NK) cell activity is low or absent. Besides, cases with at least one of the known genes related to HLH such as PRF1, Unc13D, STX11, STXBP2, RAB27A, CHS1/LYST, AP3β1, SH2D1A, BIRC4, ITK, MAGT1, CD27, etc. positive are diagnosed as primary HLH. Complete clinical data.

1.2 Sources of cases

We collected data of HLH patients registered on the China HLH registration network(www.boshicloud.com) in 2019.

1.3 Organize the data

①General information: age, sex, and place of residence. ②Diagnosis time of HLH. ③Causes of HLH: primary(genetic) or secondary (including infections, tumors, rheumatic immune system diseases, etc.) ④Whether combined with EBV infection.

1.4 Statistical analysis

SPSS21.0 software was used for statistical analysis. The measurement data with normal distribution was represented by $\bar{x} \pm s$, while the non-normal distribution data was represented by the median M (P_{25}, P_{75}); the correlation between the incidence, diagnosis rate and GDP indicators were evaluated by Pearson correlation test. The count data was expressed by [case (%)], and the comparison between groups was performed by $\chi 2$ test. A *P* value < 0.05 was considered statistically significant.

1.5 Funding

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Results

2.1 General information

A total of 1,445 cases of HLH from 31 provinces, municipalities, and autonomous regions (except Taiwan Province, Hong Kong, and Macau Special Administrative Regions) registered on the China HLH registration network (www.boshicloud.com) were collected. Among them, there were 771 males (53.36%) and 674 females (46.64%), with a sex ratio close to 1:1. The median age at diagnosis was 8 years, ranging from 0 to 90 years (a value of 0 means that the diagnosis was made within the first 6 months of life), among which 945 cases (65.40%) were children (≤ 18 years) and 500 cases (34.60%) were adults (> 18 years), with the ratio close to 2:1.

2.2 Etiology analysis

As shown in Table 1 and Table 2, pertaining to the primary cause of disease, among the whole group, heredity accounted for 8.86%. There was no statistically significant difference between males and females ($P > 0.05$). However, there was no significant difference between children under 8 years (including 8) and 9 to 18 years old ($P > 0.05$) while there was a statistically significant difference between children 9 to 18 and adults over 18 years old ($P < 0.001$); EBV accounted for 44.01%, and as same as above, there was no significant difference between males and females ($P > 0.05$) as well as children under 8 (including 8) and 9 to 18 years old ($P > 0.05$), while the difference between children 9 to 18 and adults over 18 was statistically significant ($P < 0.001$); lymphoma accounted for 13.15%. It's worth noting that there was a statistically significant difference between males and females ($P < 0.05$), children under 8 (including 8) and 9 to 18 years old ($P < 0.01$), as well as children 9 to 18 and adults over 18 ($P < 0.001$); other infections accounted for 9.48%, and there was only a statistically significant difference between children under 8 (including 8) and 9 to 18 years old ($P < 0.01$); other tumors accounted for 1.94%, and there was no statistically significant difference on sex and age ($P > 0.05$); rheumatic and immune diseases accounted for 5.40%, and there was a statistically significant difference between men and women ($P < 0.001$). There was also a significant difference between children under 8 (including 8) and 9 to 18 years old ($P < 0.01$), with no significant difference between children 9 to 18 and adults over 18 ($P > 0.05$).

2.3 Infectious disease-associated HLH

In this study, a total of 19 cases of infectious disease-associated HLH, of which 11 cases due to leishmaniasis were from Gansu, 3 cases in Xinjiang, 1 case in Henan, 1 case in Shanxi, and 1 case in Hebei; 1 case of brucellosis from Qinghai, 1 case of Lyme disease from Jilin, the above cases are consistent with the corresponding epidemic areas. In addition, there were 2 cases of typhoid fever respectively from Hubei and Henan. 1 case of tsutsugamushi came from Henan, 1 case of influenza A came from Liaoning, and 2 cases of HIV were from Shanxi and Henan. The above sporadic cases had no obvious regional bias.

2.4 The diagnosis rate, incidence and GDP.

As shown in Table 3, the diagnosis rates and GDP increments of 29 provinces, municipalities, and autonomous regions (except Qinghai, Tibet, Taiwan, Hong Kong, and Macao) were normally distributed. The range of diagnosis rate is 0.43 ± 0.26. The total GDP and GDP per capita were normally distributed after variable conversion. Notably, the diagnosis rate had a significant correlation with GDP per capita but had no significant correlation with GDP and GDP increment. The incidence of 31 areas (except Taiwan, Hong Kong, and Macau) through transforming into normally distributed had no significant correlation with GDP, GDP per capita and GDP increments.

2.5 The incidence

As shown in Fig. 1, the incidence is highest in Gansu, followed by Shaanxi, Hubei and Jiangxi, while Shanghai is the lowest.

Discussion

HLH is a critical disease of the blood system with rapid progress and high mortality [6]. With the deepening of understanding, the diagnosis technology of the primary cause of HLH (including the underlying disease) is daily increasingly improved, and definite progression has been made on the prognosis of patients [7]. Therefore, to present the overall epidemiological status of HLH in China, and provide Chinese data for the international HLH epidemiological investigation, this study was the first one to collect data on all cases registered in China's HLH registry network in 2019 and analyzed their incidence, diagnosis rate, and characteristics of the etiological distribution.

According to foreign reports, adult cases account for 40% of the total. The sex ratio of children with HLH is close to 1:1, but adults are more common in males [8]. In this study, the ratio of children to adult patients was about 1.9:1. The number of male and female patients was similar. The ratio of male to female (M/F) in children was about 1.05:1, while in adults it was about 1.3:1, which is consistent with previous reports. As it is known, 90% of patients with primary HLH are younger than 2 years old, and patients over 8 years old are rare. When common triggers such as infections and tumors stimulate the silent status with atypical mutations (e.g., subtype mutations) of HLH-associated genes, the patient may manifest as late-onset primary HLH [9]. In this study, there were 128 cases of primary HLH, including 55 children aged 2 years and younger, 43 children between 2 and 8 years old, 30 cases over 8 years old, and the median age was 3 years old (P_{25} was 2 and P_{75} was 8). The maximum age was 44, suggesting that with the maturity and popularization of genetic testing technology, the ability to identify late-onset primary HLH has improved.

It was reported in South Korea that the most common cause of secondary HLH was hematological malignancies, followed by EBV infection [10]. It was also reported in China that adult HLH malignancies were dominant, especially non-Hodgkin's lymphoma [11]. These results may be related to the age distribution of the patients in both studies with the median age close to 50 years old. In our study, EBV as the primary cause accounted for nearly 45% of the total. It suggests that the most common primary cause of HLH in China is the infection of EBV, which may also be related to the prevalence of EBV in our country. The most common subtype of HLH in Japan is EBV-HLH (approximately 40% of the total), suggesting that EBV-HLH may have an ethnic genetic background [12]. However, it is worth noting that cases of unknown cause in our study accounted for 15%, exceeding the proportion of lymphoma and primary HLH. On the one hand, it may be due to the complex manifestations of HLH and the uneven diagnosis level in different regions. The diagnosis level of the primary cause of HLH needs to be improved; on the other hand, it may be related to the course of HLH because HLH progresses rapidly, making it more difficult to diagnose the cause.

It has been reported in China that the proportion of EBV infection in adult HLH patients is lower than that in children, while the incidence of fungal infection and NK/T cell lymphoma in adults is higher [12]. In this study, the overall median age of patients is 8 (P_{25} is 3, P_{75} is 30) years old, so 8 and 18 are used as age stratification. Pertaining to EBV-HLH, there was no statistically significant difference between children under 8 (including 8) and 9 to 18 years old ($P > 0.05$), while there was statistically significant difference between children 9 to 18 and adults over the age of 18 ($P < 0.001$). The proportion of EBV infection in adults was 33.4%, while in children it was 49.6%, which was consistent with the previous report. Among patients with lymphoma-associated HLH (LAHS), there was a statistically significant difference between children under 8 (including 8) and 9 to 18 years old ($P < 0.01$) as well as children 9 to 18 and adults over 18 ($P < 0.001$), suggesting that the incidence of LAHS is positively correlated with the age of onset.

Previous studies have found that the frequency of gene mutations is inversely proportional to the age of onset of HLH [3]. In this study, we found that among patients with primary HLH, there was no significant difference between children under 8 years old (including 8) and 9 to 18 years old ($P > 0.05$) while there was between children 9 to 18 and adults over 18 years old ($P < 0.001$), which is inconsistent with previous studies. However, it still reflects that genetic mutations are more common in children.

The epidemiological survey of lymphoma in Japan shows that the overall sex ratio of lymphoma (M/F) is 1.17. Some subtypes of lymphoma patients are mainly males (M/F > 3:1), but there is no statistical difference in the sex of patients with the main subtypes of lymphoma such as diffuse large B cells lymphoma (DLBCL) [13]. In this study, LAHS was significantly different between males and females ($P < 0.05$). The sex ratio (M/F) of total case number was 1.1, while for the LAHS, the ratio was 1.5, suggesting that patients of LAHS are mainly males; Rheumatic immune diseases are complex, such as systemic lupus erythematosus (SLE), osteoarthropathy (OA), and Sjogren's syndrome (SS) are more common in females, while ankylosing spondylitis and gout are more common in males [14]. Among them, the most common diseases related to HLH are systemic juvenile idiopathic arthritis (sJIA) and adult still's disease (AOSD). It has been reported that sJIA complicated by macrophage activation syndrome (MAS) is more common in women [15]. Similarly, AOSD is more common in women than men. Reports of male patients with AOSD-HLH are rare [16]. In this study, there were 78 cases of rheumatic immune-associated HLH, including 20 males and 58 females. The difference of sex was statistically significant ($P < 0.001$), suggesting patients of rheumatic immune-associated HLH are mainly women, which is consistent with previous reports.

In addition to EBV, other infection factors include cytomegalovirus (CMV), human herpesvirus type 6 (HHV-6), influenza virus, Mycobacterium tuberculosis, parasites, fungi, and common infectious diseases consist of HIV, leishmaniasis, brucellosis, tuberculosis, etc. [17]. Leishmaniasis [18] is mainly distributed in Gansu, Shanxi, Shaanxi, Sichuan and Xinjiang, etc. In this study, Gansu has the highest incidence and is one of the main endemic areas of leishmaniasis. Therefore, there are more cases of HLH related to Leishmania infection than other infectious diseases. Brucellosis is mainly distributed in pastoral areas [19] such as Qinghai, and Lyme disease is mainly distributed in forest areas such as Northeast, Northwest and North of China [20]. Other infectious diseases have no obvious regionality. Therefore, when considering the primary cause of HLH, the local epidemiological situation should be considered, and the contact history of the affected area should be emphatically asked to avoid missing rare infections other than EBV. About other infectious diseases with no obvious geographical bias, it is important to note that malignant tumors and opportunistic infections are important triggers of HLH in HIV patients, and acute HIV infection itself can cause HLH. To make matters worse, the treatment of HIV-associated HLH is still challenging and the use of steroid therapy can not improve the prognosis of patients [21], which reminds us that we should enhance the prevention and education of HIV.

According to reports, the incidence of HLH in children has increased to (1 to 225)/300,000, and it is related to geographical factors [8]. In this study, the overall incidence of HLH in China in 2019 was about 1.04/1000,000 (excluding Taiwan Province, Hong Kong and Macau Special Administrative Region do not provide data). The incidence is highest in Gansu with 4.684/1000,000 followed by Shaanxi, Hubei, Jiangxi, etc. Compared with other areas, the incidence is lower in the Yangtze River Delta and lowest in Shanghai with 0.083/1000,000. The overall incidence has shown a downward trend from inland to coastal and border areas. It is worth noting that the incidence in Beijing and Tianjin is relatively high. Since the epidemiological investigation of HLH mainly relies on case reports, the incidence obtained by statistics depends on the diagnostic level of the local area. Therefore, this study further explored the diagnosis rate in various regions and its correlation with the local economic level. It found that the diagnosis rate had a significant correlation with the local GDP per capita ($P < 0.05$).

HLH is a syndrome of pathological immune activation. Common symptoms are persistent fever, splenomegaly, and pancytopenia, but these symptoms are not specific [1], which increases the difficulty in distinguishing other symptoms-overlapping inflammatory diseases with HLH. At present, HLH is mainly diagnosed based on HLH-2004 [23]. At present, it is known that primary HLH is a gene defect that causes the cytotoxicity of NK cells and cytotoxic T lymphocytes (CTL) to be weakened or even absent (mainly NK cells), which leads to the accumulation of antigen-presenting cells (APC). Then CD8 + CTL is continuously stimulated to release a large number of cytokines to trigger a "cytokine storm" [24]. NK cytotoxicity is determined by cytotoxicity test, and sCD25 concentration is related to T cell activation [22]. The above two detection methods are more sensitive than other indicators of HLH-2004 [25] but have higher requirements for laboratories. For example, the NK cytotoxicity test requires the use of radioactive ^{51}Cr and the results are affected by the number of NK cells [26], so it has not been universal yet [3]. In this study, data from Taiwan, Hong Kong and Macao was not available. The incidence of the other 31 provinces, municipalities and autonomous regions has no statistical correlation with GDP indicators ($P > 0.05$). Qinghai and Tibet has a small number of cases and they all come from the local area, considering the geographical occlusion affects the medical habits of local people. In order to avoid making additional effect on the statistical results of the diagnosis rate, they were not included in the analysis. Excluding the above five regions, the diagnosis rate has no significant correlation with GDP and GDP increment but has a significant correlation with GDP per capita ($P < 0.05$), and the Pearson correlation coefficient is positive (value is 0.403), indicating that the local diagnosis level is positively correlated with the local economic level. Relatively economically developed areas have better medical resources, higher levels of diagnosis and treatment, and the ability to develop new diagnostic technologies. However, the medical level of economically underdeveloped areas is relatively backward. This study shows that areas with high incidence are concentrated in the northwest inland of China, which is also an economically underdeveloped area. Improving the diagnosis level in this area is of great significance to improve the prognosis of patients and enhance health of national people. The supply of medical resources to the underdeveloped region should be increased, medical talents and technology should be introduced, and the construction of laboratories as well as the use of Internet medical platforms should be strengthened. At the same time, research on new and easy-to-obtain detection methods should be carried out to make early diagnosis and early treatment of suspected cases in areas with high HLH incidence in China.

Declarations

Availability of Data and Materials

The datasets used during the current study are available from the corresponding author on request.

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Author's Contributions

Y.W. and Z.W. designed and performed research; Y.W., Z.W., Y.S., L.L.R.Z., J.F., R.J., J.Y., F.L., J.B., Y.Z., C.Z., H.T., F.Z., Y.C., Q.Z. provided the materials and interpreted the data; Y.W. and S.Y. performed statistical analysis and wrote the manuscript. All the authors approved the final manuscript.

Ethics declarations

Ethic approval and consent to participate

Written informed consent was obtained from each patient or his (or her) guardian.

Consent for publication

Not applicable.

Conflict of interest statement

The authors declare that they have no competing interests.

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Tables

Table 1

Gender distribution of the etiology of patients [cases (%)]

Primary cause	Male	Female	χ^2	P
Genetic	78(60.94)	50(39.06)	3.243	0.072
EBV	350(55.03)	286(44.97)	1.281	0.258
Lymphoma	115(60.53)	75(39.47)	4.519	0.034*
Other infections	75(54.74)	62(45.26)	0.117	0.732
Other tumors	17(60.71)	11(39.29)	0.621	0.431
Rheumatic	20(25.64)	58(74.36)	25.448	< 0.001***
Other disease	14(43.75)	18(56.25)	32.856	< 0.001***
Unknown	102(47.22)	114(52.78)	3.840	0.050

* P < 0.05 Significantly different; *** P < 0.001 Significantly different

Table 2

The age distribution of the etiology of patients (cases)

Primary cause	≤ 8y	9 to 18y	≥ 19y	$\chi_1{}^2$	$\chi_2{}^2$	P_1	P_2
Genetic	98	19	11	1.941	18.559	0.164	< 0.001△△△
EBV	363	106	167	1.153	23.069	0.283	< 0.001△△△
Lymphoma	16	13	161	10.041	50.516	0.002**	< 0.001△△△
Other infections	85	10	42	7.163	2.401	0.007**	0.121
Other tumors	7	4	17	1.541	0.962	0.214	0.327
Rheumatic	27	20	31	13.562	3.054	< 0.001***	0.081
other	14	5	13	0.308	0.006	0.579	0.940
unknown	135	23	58	4.964	0.001	0.026*	0.970

χ_1 is the comparison between ≤ 8 years old and 9 to 18 years old, P_1 is the probability; χ_2 is the comparison between 9 to 18 years old and ≥ 19 years old, P_2 is the probability; * P < 0.05 Significantly different; ** P < 0.01 Significantly different; *** P < 0.001 Significantly different; △△△P < 0.001 Significantly different

Table 3
The relationship between the diagnosis rate, incidence and GDP index

	diagnosis rate	Incidence /100,000	GDP/100 million(¥)	GDP per capita (100 million(¥)/100,000)	GDP increment/100 million(¥)
Gansu	0.63	0.4684	8718.30	33.20	472.20
Shaanxi	0.65	0.2998	25793.17	67.25	1354.85
Hubei	0.81	0.2197	45828.31	77.45	6461.76
Jiangxi	0.57	0.1947	24757.50	53.56	2772.70
Tianjin	0.61	0.1859	14104.28	90.44	-4705.36
Ningxia	0.00	0.1760	3748.48	54.98	43.30
Beijing	1.00	0.1705	35371.30	162.95	5051.30
Shanxi	0.35	0.1513	17026.68	45.99	208.57
Guizhou	0.44	0.1480	16769.34	46.84	1962.89
Hebei	0.09	0.1244	35104.50	46.46	-905.80
Chongqing	0.86	0.1214	23605.77	77.44	3242.58
Inner Mongolia	0.10	0.1144	17212.50	67.93	-76.70
Hunan	0.42	0.0962	39752.12	57.95	3326.34
Liaoning	0.60	0.0941	24909.50	57.14	-405.90
Guangdong	0.87	0.0917	107671.07	94.90	10393.30
Shandong	0.23	0.0826	71067.50	70.73	-5402.20
Yunnan	0.26	0.0792	23223.75	48.38	5342.63
Anhui	0.33	0.0727	37114.00	58.66	7107.18
Fujian	0.32	0.0710	42395.00	107.57	6590.96
Henan	0.25	0.0635	54259.20	56.49	6203.34
Sichuan	0.16	0.0528	46615.82	55.89	5937.69
Guangxi	0.22	0.0471	21237.14	43.47	884.63
Jilin	0.25	0.0442	11726.80	43.15	-3347.82
Heilongjiang	0.07	0.0396	13612.70	35.93	-2748.90
Zhejiang	0.37	0.0331	62352.00	108.68	6155.00
Jiangsu	0.27	0.0324	99631.52	124.08	7036.12
Hainan	0.50	0.0216	5308.94	57.35	476.89
Shanghai	0.50	0.0083	38155.32	157.42	5475.45
Xinjiang	0.71	0.0573	13597.11	55.62	1398.03

* $P < 0.05$ Significantly different

	diagnosis rate	Incidence /100,000	GDP/100 million(¥)	GDP per capita (100 million(¥)/100,000)	GDP increment/100 million(¥)
Qinghai	1.00	0.2173	2965.95	49.57	100.72
Tibet	1.00	0.0593	1697.82	50.36	220.19
Pearson correlation		diagnosis rate incidence	-0.048 -0.264	0.403 -0.242	0.283 -0.180
P		diagnosis rate incidence	0.804 0.152	0.030* 0.189	0.137 0.331
* P < 0.05 Significantly different					

Figures

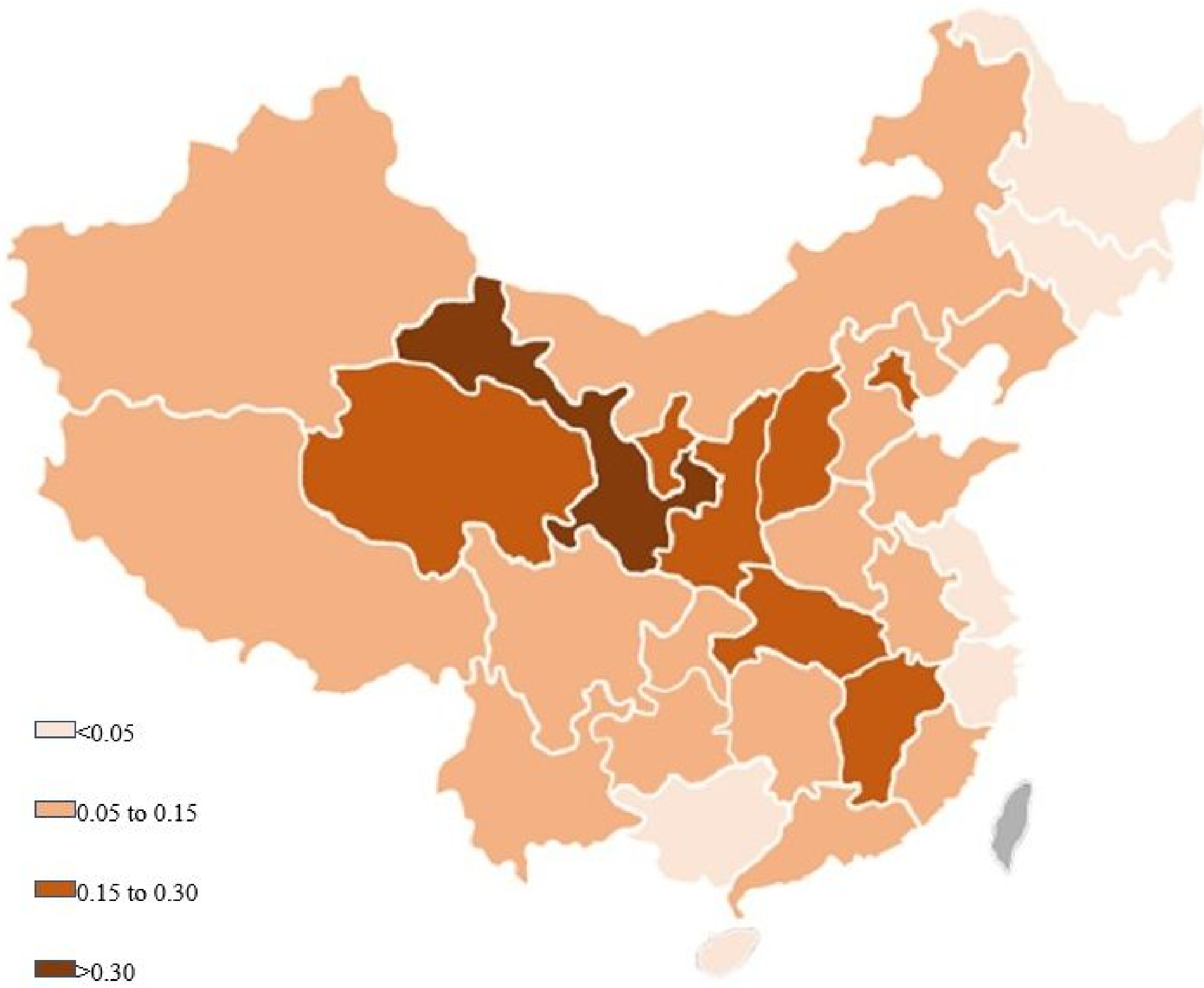

Figure 1

The incidence nationwide. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.