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Geographical variations of risk factors associated with HCV infection in drug users in southwestern China

Y. B. ZHOU[1,2,3]*, Q. X. WANG[4], M. X. YANG[5], Y. H. GONG[4], Y. YANG[6,7], S. J. NIE[1,2,3], S. LIANG[7,8], L. NAN[4], A. COATSWORTH[9], A. H. YANG[1,2,3], Q. LIAO[4], X. X. SONG[1,2,3] AND Q.W. JIANG[1,2,3]*

[1] *Department of Epidemiology, School of Public Health, Fudan University, Shanghai, China;* [2] *Key Laboratory of Public Health Safety, Ministry of Education (Fudan University), Shanghai, China;* [3] *Tropical Disease Research Center, Fudan University, Shanghai, China;* [4] *Center for Disease Prevention and Control of Liangshan Prefecture, Sichuan, China;* [5] *Xuhui Center for Disease Prevention and Control, Shanghai, China;* [6] *Department of Biostatistics, University of Florida, Gainesville, FL, USA;* [7] *Emerging Pathogens Institute, University of Florida, Gainesville, FL, USA;* [8] *Department of Environmental and Global Health, College of Public Health and Health Professions, University of Florida, Gainesville, FL, USA;* [9] *Department of Epidemiology, College of Public Health and Health Professions, University of Florida, Gainesville, FL, USA*

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SUMMARY

Hepatitis C virus (HCV) has become a global public health problem. Many studies have been conducted to identify risk factors for HCV infection. However, some of these studies reported inconsistent results. Using data collected from 11 methadone clinics, we fit both a non-spatial logistical regression and a geographically weighted logistic regression to analyse the association between HCV infection and some factors at the individual level. This study enrolled 5401 patients with 30·0% HCV infection prevalence. The non-spatial logistical regression found that injection history, drug rehabilitation history and senior high-school education or above were related to HCV infection; and being married was negatively associated with HCV infection. Using the spatial model, we found that Yi ethnicity was negatively related to HCV infection in 62·0% of townships, and being married was negatively associated with HCV infection in 81·0% of townships. Senior high-school education or above was positively associated with HCV infection in 55·2% of townships of the Yi Autonomous Prefecture. The spatial model offers better understanding of the geographical variations of the risk factors associated with HCV infection. The geographical variations may be useful for customizing intervention strategies for local regions for more efficient allocation of limited resources to control transmission of HCV.

Key words: Drug users, geographically weighted logistic regression, geographical variation, hepatitis C virus.

INTRODUCTION

Hepatitis C virus (HCV) has become a leading cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma [1, 2] with an estimated 170 million people infected worldwide. It is estimated that 26·4 million people are infected in China alone, representing

* Author for correspondence: Dr Y. B. Zhou, Department of Epidemiology, School of Public Health, Fudan University, 138 Yi Xue Yuan Road, Shanghai, China.
(Email: z_yibiao@hotmail.com) [Y.B.Z.]
(Email: jiangqw@fudan.edu.cn) [Q.W.J.]

~2·2% (range 0·52–3·15) of the general population [3]. Deaths related to HCV exceeded deaths related to HIV in the United States [1]. HCV is hyperendemic in injection drug users (IDUs), and the prevalence can be as high as 90% in this population [3, 4]. A meta-analysis showed that the pooled prevalence of HCV infection in IDUs was 61·4% [95% confidence interval (CI) 55·7–67·2, max 98·7] in China, and its prevalence showed marked geographical variation [3]. There have been many studies that have examined the associations between socioeconomic, demographic and drug-related behavioural factors and HCV infection in drug users; however, some of these results are contradictory [3, 5]. For example, one meta-analysis showed that IDUs sharing needles/syringes had a greater risk of being infected with HCV than non-sharing IDUs [5]. However, another meta-analysis indicated that no significant difference was found in the risk of HCV infection between needle-sharing and non-needle-sharing IDUs [3]. Some studies suggested that level of education was independently associated with HCV infection [6, 7]; however, other studies showed no such association [8, 9]. These inconsistent findings might be the consequence of spatial heterogeneity in the effects or clusters of some risk factors or be related to other potential reasons including the conflicting results from different target populations. Our previous research suggested there was significant global and local geographical autocorrelation in HCV infections [10]. The spatial autocorrelation, if not accounted for, may result in bias in the estimates and incorrect standard errors [11]. Currently, most studies have used non-spatial regression techniques to analyse risk factors of HCV infection making the assumption that the association is stationary across space. Few studies have used spatial regression methods to explore risk factors of HCV infection at the individual level assuming the relationship is non-stationary across space. Therefore, using geographically weighted logistic regression (GWLR), we aim to account for and describe the local variation in the relationship between demographic, socioeconomic and drug-use behavioural characteristics and HCV infection in drug users in an Yi Autonomous Prefecture, Sichuan province, China. This may provide new insights about who is at risk for HCV infection and where. Thus, our analysis is potentially useful for tailoring prevention and healthcare programmes to the needs of diverse groups and for ensuring accessibility of health services to those most in need.

METHODS

Study area and population

The Yi Autonomous Prefecture, located in the southwest of China, is on one of the main drug-trafficking routes from the 'Golden Triangle' to northwest and central China. It is one of the largest illicit drug production and distribution centres of China. A population of 4·9 million people live in this prefecture composed of 16 counties and a city and 618 townships. Approximately 50% of the population belongs to the Yi ethnic group. HIV/AIDS has been endemic in this region since the first HIV case was identified in drug users in 1995. Since late 2012, ten regular methadone clinics and one mobile methadone clinic have been established, the first of which was established in 2004. All patients attending the 11 clinics from 2004 to 2012 were selected as the study population, and detailed information on the infrastructure and procedures of these clinics and the patients has been reported elsewhere [10, 12–16]. All these patients were tested for HCV infection 1 month after first entry into the clinic. Meanwhile, all these drug users were asked to take part in a questionnaire investigation. The questionnaires were administered face-to-face in a private room by a same-sex interviewer who was trained in administration of questionnaires. The information on residency of drug users was collected from their identification card.

Data collection and measurement

Data regarding HCV infection, demographic and socioeconomic factors, drug-use behaviours and residency of all subjects treated in the 11 national clinics during the period 2004–2012 were collected from the national methadone database [5, 14]. Our outcome variable was HCV infection.

Our independent variables cover three domains of interest. The first domain was drug-use behaviours which include injection, sharing syringes and drug rehabilitation. The second involves demographic factors including gender, age, ethnicity, and marital status. Gender is a dummy variable with female as the reference group. Age was divided into four age groups (<30, 30–39, 40–49, ⩾50 years) where the <30 years group serves as the reference group, and three dummy variables are created. Ethnicity is classified as Yi, Han (reference group) and other using two dummy variables. Marital status was categorized into single (reference), married, divorced and

Table 1. *The characteristics and prevalence of HCV infection of the national methadone clients in southwest China*

Study variable	No. of clients examined	Infection prevalence (%)	χ^2	*P*
Drug-use behaviours				
History of injection drug use				
Yes	2407	46·2	545·8	<0·001
No	2994	16·9		
History of sharing syringes				
Yes	909	42·8	85·3	<0·001
No	4492	27·4		
History of drug rehabilitation				
Yes	2523	42·6	358·8	<0·001
No	2878	18·9		
Demographic factors				
Gender				
Males	4583	30·0	0·0	0·911
Females	818	29·8		
Age, years				
<30	2369	30·2	12·2	0·007
30–39	2323	31·3		
40–49	633	25·8		
⩾50	76	18·4		
Marital status				
Single	1156	42·4	145·1	<0·001
Married	3998	25·6		
Divorced	185	45·4		
Widowed	62	38·7		
Ethnicity				
Yi	4364	26·1	166·1	<0·001
Han	994	46·5		
Other	43	46·5		
Socioeconomic factors				
Employment				
Farming	4192	25·9	185·2	<0·001
Service sector	187	42·2		
Unemployed	800	49·0		
Other	222	29·3		
Educational attainment				
No school	1196	25·3	66·7	<0·001
Primary school	2417	27·2		
Junior high school	1257	38·3		
Senior high school or above	531	33·9		

widowed. The third domain focuses on socioeconomic factors, including occupation and education. Occupation was classified into farmer, service sector, unemployed, and other (reference) such as factory worker, government employee, etc. Educational achievement was divided into four levels (three dummy variables): no school (reference group), elementary school, junior high school and senior high school or above. Our independent variables also include 'methadone clinic' which was divided into 11 levels.

In order to explore the local associations between HCV infection and risk factors (as mentioned above) at the individual level, the location of each individual was defined as the geographical coordinate (i.e. latitude/longitude) of the centre of the township in which he/she resided; township is the smallest geographical unit in the present analysis.

Statistical analysis

Non-spatial logistical regression

Using SPSS software (SPSS Inc., USA), the prevalence of infection and characteristics of the patients in the methadone clinics were analysed, and multivariable non-spatial logistical regression was employed to analyse the association between HCV infection and risk factors and interactions between variables.

GWLR

A GWLR model was used to analyse the local associations between HCV infection and risk factors adjusting for spatial autocorrelation. The model is figured by [17]:

$$\log\left(\frac{P(y_i = 1)}{1 - P(y_i = 1)}\right) = \beta_0(u_i, v_i) + \sum_{j=1}^{k} \beta_j(u_i, v_i)x_{ij},$$

where y_i and x_{ij}, denote the HCV infection status and explanatory variables for individual i with location coordinates(u_i, v_i), and $\beta_0(u_i, v_i)$ and $\beta_j(u_i, v_i)$ are the location-specific intercept and coefficients.

The GWLR model was implemented with GWR 4·0 software (https://geodacenter.asu.edu/software/downloads/gwr_downloads). The kernel function used for geographical weighting to estimate local coefficients is 'adaptive bi-square'. The bandwidth is the number of nearest neighbours to be included in the bi-square kernel. The 'golden section search' method was used to automatically determine the best bandwidth size based on Akaike's Information Criterion (AIC) corrected for small sample size bias, where the bandwidth with the lowest AIC was used in the final analysis. Geographical variability for each coefficient can be assessed by comparing the AICs between the GWLR model and the global logistic regression model assuming invariant model coefficients [17]. The coefficient of an independent variable in the model represents the change in log odds of the response given a unit change in that variable. Taking the exponentiation of the coefficient yields the odd ratio (OR) corresponding to a unit change in the variable. The local estimates (OR) and P values are visualized in maps to demonstrate the geographical variations in the association between HCV infection and individual factors. The results are relatively insensitive to the choice of kernel functions (e.g. bi-square and Gaussian) for geographically weighted regression [17]. All variables were entered first into the GWLR regression model, then the variable with the largest P value was removed from the model until only the variables with some local P values <0·1 remained within the GWLR model.

RESULTS

Prevalence of HCV infection

A total of 5401 patients with complete information regarding risk factors, home address, name of methadone clinic attended and results of their HCV test were obtained from the national database. These patients came from 405 of the 618 townships of the Yi Autonomous Prefecture. The prevalence of HCV infection in the population was 30·0% (1620/5401). Table 1 presents the infection prevalence of HCV in different characteristics of the national methadone clients. Clients with a history of IDU, or of sharing syringes or of drug rehabilitation had a higher prevalence of HCV infection than those without such a history. Patients who were married, of Yi ethnicity, employed in farming or had no schooling had a lower prevalence of HCV infection than those who were not (Table 1). Additionally, 44·6% of the patients had injection history, and 16·8% (909/5401) shared syringes (Table 1).

Univariable and multivariable non-spatial logistical regressions

For the univariable non-spatial logistic regression, other factors were associated significantly with HCV infection except for gender (Table 2).

For multivariable non-spatial regression, both IDU and drug rehabilitation were significantly ($P < 0·001$) positively associated with HCV infection [adjusted OR (aOR) 3·04, 95% CI 2·65–3·48; aOR 1·76, 95% CI 1·53–2·03, respectively] in drug-use behaviours (Table 2). Compared to others, both unemployed and service-sector work were significantly ($P < 0·01$) related to HCV infection (aOR 1·20, 95% CI 1·33–1·91; aOR 1·73, 95% CI 1·25–2·39, respectively) (Table 2). Being married was significantly ($P < 0·001$) negatively associated with HCV infection (aOR 0·70, 95% CI 0·61–0·81) compared to being single. Having senior high-school education or above was significantly ($P = 0·039$) positively related to HCV infection (aOR 1·28, 95% CI (1·03–1·59) compared to no school (Table 2).

Multivariable spatial logistical regression

The optimal bandwidth size was 170 (individuals) in this study. The value of AIC in the global regression was 5894·0, whereas AIC = 5707·2 for GWLR. Table 3 presents the factors which were significantly and locally associated with HCV infection. For a

Table 2. *The association of HCV infection and risk factors from univariable and multivariable non-spatial logistical regressions*

Study variable	Univariable regression			Multivariable regression		
	OR	95% CI	*P* value	aOR	95% CI	*P* value
Constant	—	—	—	0·22	—	<0·001
Drug-use behaviours						
Injection history (1 = yes, 0 = no)	4·22	3·73–4·78	<0·001	3·04	2·65–3·48	<0·001
Drug rehabilitation history (1 = yes, 0 = no)	3·18	2·81–3·59	<0·001	1·76	1·53–2·03	<0·001
Sharing syringes (1 = yes, 0 = no)	1·98	1·71–2·30	<0·001	—	—	—
Demographic factors						
Gender (ref. = female)						
Male (1 = yes, 0 = no)	1·01	0·86–1·19	0·911	—	—	—
Marital status (ref. = single)						
Married (1 = yes, 0 = no)	0·46	0·41–0·53	<0·001	0·70	0·61–0·81	<0·001
Divorced (1 = yes, 0 = no)	2·00	1·48–2·68	<0·001	—	—	—
Widowed (1 = yes, 0 = no)	1·48	0·89–2·45	0·134	—	—	—
Age (ref. <30)						
30–39 (1 = yes, 0 = no)	0·90	0·80–1·01	0·070	—	—	—
40–49 (1 = yes, 0 = no)	0·79	0·65–0·95	0·013	—	—	—
⩾50 (1 = yes, 0 = no)	0·52	0·29–0·94	0·029	—	—	—
Ethnicity (ref. = Han)						
Yi (1 = yes, 0 = no)	0·41	0·35–0·47	<0·001	—	—	—
Other (1 = yes, 0 = no)	2·04	1·12–3·73	0·020	—	—	—
Socioeconomic factors						
Employment (ref. = other, e.g. factory worker, government employee, etc.)						
Farming (1 = yes, 0 = no)	0·44	0·38–0·50	<0·001	—	—	—
Unemployed (1 = yes, 0 = no)	2·64	2·26–3·08	<0·001	1·60	1·33–1·91	<0·001
Service sector (1 = yes, 0 = no)	1·74	1·30–2·35	<0·001	1·73	1·25–2·39	<0·01
Educational attainment (ref. = no school)						
Primary school	1·28	1·14–1·44	<0·001	—	—	—
Junior high school	1·64	1·43–1·87	<0·001	—	—	—
Senior high school or above (1 = yes, 0 = no)	1·22	1·01–1·48	0·039	1·28	1·03–1·59	<0·05

OR, Odds ratio; aOR, adjusted odds ratio; CI, confidence interval.

factor, the spatial regression model can achieve many local ORs. The minimum, medium and maximum presented in Table 3 were the lowest local ORs, the median local ORs and the highest local ORs among these local ORs, respectively. Of drug-use behaviours, IDU was significantly ($P < 0.001$) positively associated with HCV infection for all study individuals (Fig. 1), and drug rehabilitation was significantly ($P < 0.05$) positively related to HCV infection for 94·4% of study individuals in 94·5% of townships (Fig. 1).

Of demographic factors, being married was significantly ($P < 0.05$) negatively associated with HCV infection for 92·8% of individuals compared to those who were single in 81·0% of townships; these townships were mainly distributed in the northeastern counties (Fig. 2). Yi ethnicity was significantly ($P < 0.05$) negatively related to HCV infection for 71·7% of individuals compared to Han ethnicity in 62% of townships; these townships were mainly distributed in the southeastern counties (Fig. 2). Being female was significantly ($P < 0.05$) positively associated with HCV infection only in 11·2% of townships, located mainly in counties E and F.

For socioeconomic factors, working in the service sector and unemployment (relative to factory workers and governmental employees) were significantly ($P < 0.05$) positively associated with HCV infection for only 5·8% of individuals in 14·3% of townships and 3·0% of individuals in 8·1% of townships, respectively; these townships are located mainly in the southern counties (Fig. 3). Senior high-school education or above (relative to no school) was significantly ($P < 0.05$) positively associated with HCV infection

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Table 3. *The local association of HCV infection and risk factors from the geographically weighted logistic regression model*

Study variable	Minimum		Medium		Maximum		Significant (%)	
	B	OR	*B*	OR	*B*	OR	Increased risk	Decreased risk
Constant	−2·79	0·06	−0·97	0·38	−0·63	0·53	0·0	99·5
Drug-use behaviours								
Injection history (1 = yes, 0 = no)	0·79	2·21	1·02	2·77	1·46	4·29	100·0	0·0
Sharing syringes (1 = yes, 0 = no)	−0·14	0·87	0·02	1·02	0·31	1·36	0·5	0·0
Drug rehabilitation (1 = yes, 0 = no)	0·02	1·00	0·58	1·79	1·17	3·22	94·5	0·0
Demographic factors								
Marital status (ref. = single)								
Married (1 = yes, 0 = no)	−0·49	0·61	−0·36	0·70	0·31	1·36	0·0	81·0
Gender (1 = males, 0 = females)	−1·06	0·35	−0·11	0·90	0·04	1·04	0·0	11·2
Ethnicity (ref. = Han)								
Yi (1 = yes, 0 = no)	−0·64	0·53	−0·32	0·73	0·28	1·32	0·0	62·0
Other (1 = yes,0 = no)	−0·44	0·64	0·40	1·49	3·45	31·50	0·8	0·0
Socioeconomic factors								
Employment (ref. = other, e.g. factory worker, government employee, etc.)								
Farmer (1 = yes, 0 = no)	−0·56	0·57	−0·20	0·82	0·47	1·60	0·0	3·4
Service sector (1 = yes, 0 = no)	−0·26	0·76	0·30	1·35	2·13	8·39	14·3	0·0
Unemployed (1 = yes, 0 = no)	−0·11	0·90	0·23	1·26	1·56	4·76	8·1	0·0
Educational attainment (ref. = no school)								
Primary school (1 = yes, 0 = no)	−0·18	0·84	−0·05	0·95	0·80	2·23	5·7	0·0
Junior high school (1 = yes, 0 = no)	−0·30	0·74	−0·12	0·89	0·75	2·12	1·3	0·0
Senior high school or above (1 = yes, 0 = no)	0·98	0·38	0·34	1·40	0·99	2·69	55·2	0·0

OR, Odds ratio.

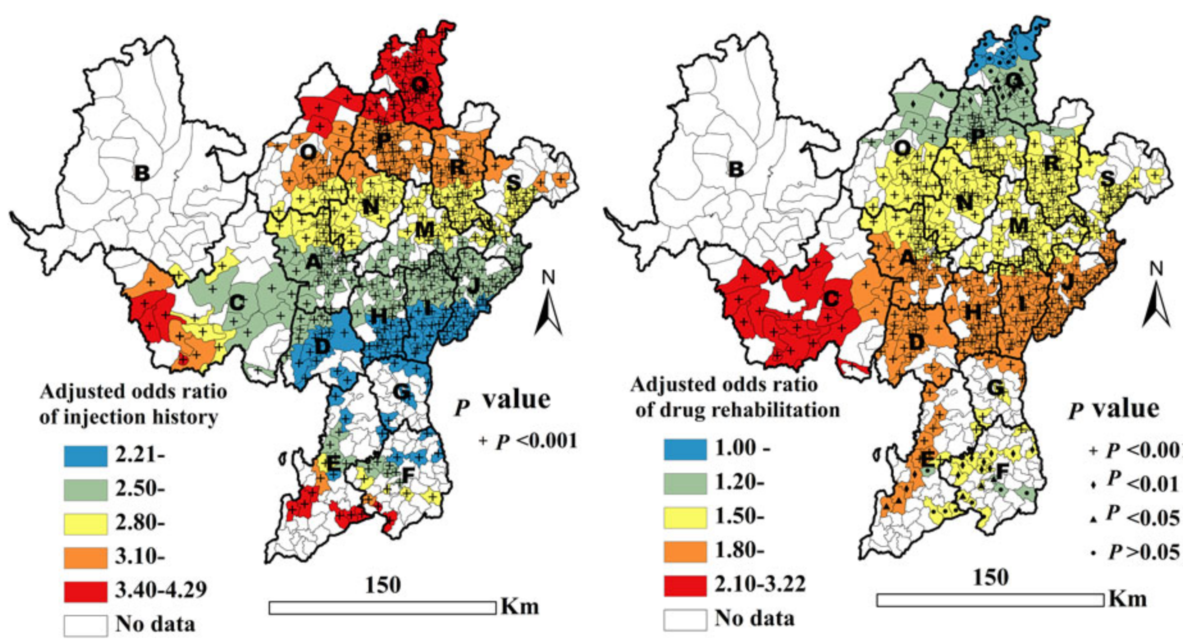

Fig. 1. Geographical distribution of adjusted odds ratios of injection history and drug rehabilitation history associated with HCV infection from the geographically weighted logistic regression model.

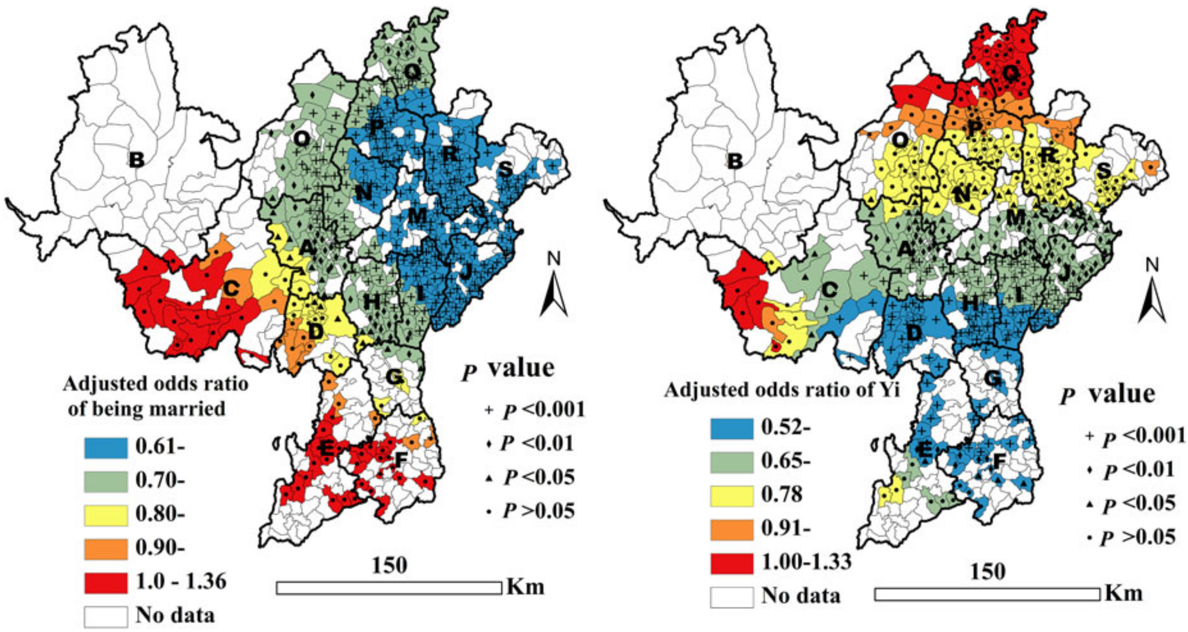

Fig. 2. Geographical distributions of adjusted odds ratios of being married and Yi ethnicity associated with HCV infection from the geographically weighted logistic regression model.

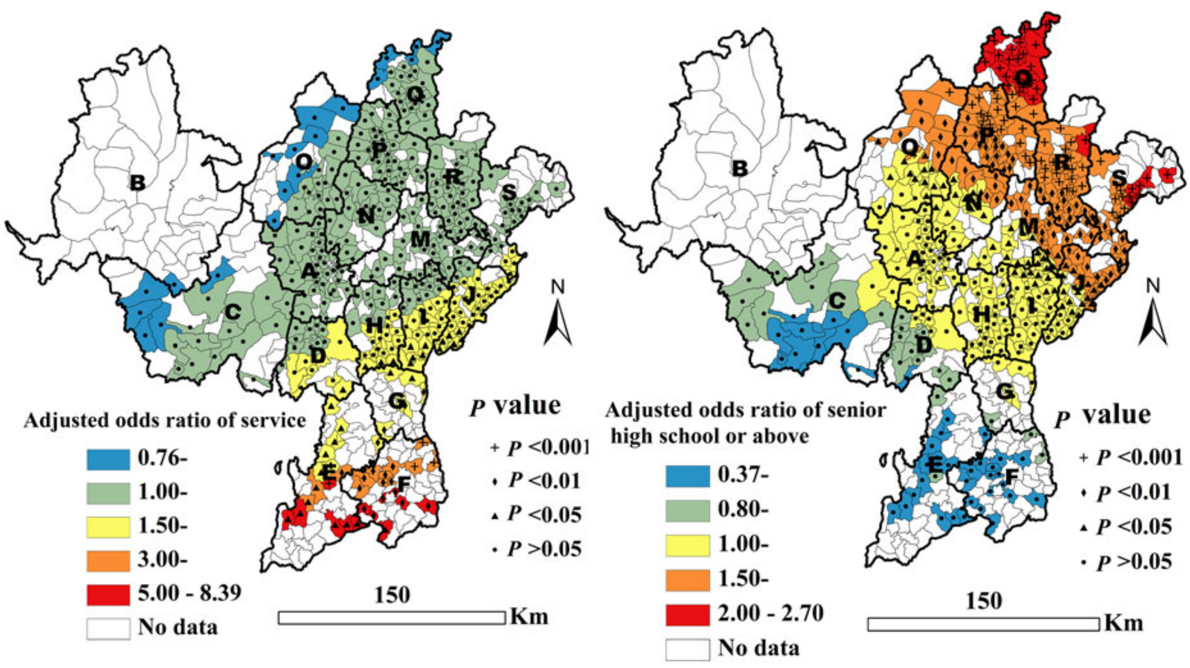

Fig. 3. Geographical distributions of adjusted odds ratios of HCV infection for service sector and senior high-school education or above from the geographically weighted logistic regression model.

for 57·1% of individuals in 55·2% of townships located in the northeastern counties (Fig. 3).

DISCUSSION

The non-spatial and the spatial analyses agreed on the role of IDU as a global (i.e. in the whole Yi Prefecture rather than in a specific township or county) high-risk factor for HCV infection, consistent with previous findings [3, 5, 6, 13, 18]. Both models also suggested that sharing syringes might be not an independent predictor of HCV infection in this study population, in accordance with previous studies [3, 19]. It seemed that the most likely factor affecting the significance of needle-sharing as a risk factor for HCV might be the prevalence of HCV in a given area. Some studies showed that sharing of injection paraphernalia (e.g. cookers, cotton) other than syringes may be an important cause of HCV transmission, and responsible for some proportion of new HCV infections [19–21]. These might partly explain why sharing syringes were not associated with the prevalence of HCV infection in half of the observed townships of the Yi Autonomous Prefecture in our previous study [13]. Interestingly, drug rehabilitation appeared to be a risk factor in both non-spatial and spatial analyses, confirming previous findings [13, 22, 23]. One plausible explanation for this is that the detoxification programmes might increase the frequency of the sharing use of drug injection paraphernalia (cookers, cotton, rinse water, drug solutions) [24]. However, such speculation requires further studies to confirm.

The GWLR model revealed the geographical variations of some risk factors associated with HCV infection which cannot be detected by the non-spatial logistic model. For example, the non-spatial logistic regression analysis suggested that being married was negatively associated with HCV infection, consistent with some studies [25, 26]. However, other studies suggested that marriage could be a risk factor for, or not related to, HCV infection [6, 9 27]. The spatial model showed that being married was negatively related to HCV infection for individuals primarily of Yi ethnicity living in the northeastern counties [10], but it was not significantly associated with HCV infection in southern counties where the majority of residents are of Han ethnicity (Fig. 2) [10]. This geographical variation of marital status associated with HCV infection might be related to the distribution of ethnicity. Whether the effect of marital status depends on ethnicity or culture needs future investigation. Examples of conflicting conclusions in previous studies that are possibly explained by spatial heterogeneity are also seen for the effects of ethnicity [3, 28] and gender [3, 5, 8, 9].

The non-spatial analysis indicated that senior high-school education or above was an independent risk factor for HCV infection, and the spatial analysis also showed that drug users with senior high-school education or above were more likely to be infected with HCV than those with no school in the northeastern counties of the Yi Autonomous Prefecture. These findings indicated that drug users with senior high-school education or above might be the priority population for intervention, especially in the northeastern counties of the Yi Autonomous Prefecture, like P, Q and R counties where drug users had high HCV infection prevalence [10].

Our findings have some important implications. First, geographical variations of risk factors associated with HCV infection might provide some guidance for tailoring site-specific intervention strategies to better control or prevent HCV transmission with limited resources. For example, drug users who are single and live in the northeastern counties, where marriage was negatively related to HCV infection, could be prioritized for intervention. Second, it is necessary to conduct health education in IDUs, making them aware of the potential risk of sharing injection paraphernalia in HCV transmission. Third, spatial correlation and heterogeneity should not be ignored in future studies of risk factors for HCV infection.

This study had several limitations. First, it is difficult to confirm whether patients of the methadone clinics are truly representative of the overall population of drug users. There was, however, a study reporting that the HIV prevalence in patients attending methadone clinics is not significantly different from that in drug users who do not attend methadone clinics [5], and the prevalence of HIV and HCV infections were significantly correlated across townships in the study area [10]. Second, the information regarding sexual behaviours was not available, and therefore we were unable to estimate or control for the effects of sexual behaviours on HCV infection. However, homosexuality (especially gay men) was rarely found in this study population, and an aggregate analysis indicated that there is no increased risk of sexual transmission of HCV in heterosexual couples in regular relationships [29]. The association of HCV infection with IDU may be confounded by increased number of multiple sexual partners with increased likelihood of IDU; however, the significant geographical variation of IDU in the association with HCV infection was not found in our study. Third, the interactions between variables were not analysed in this study because the spatial model cannot currently analyse the interaction. Finally, assigning the same coordinates to everyone in a township might be increase multicollinearity and reduce variance; however, an average of 13·3 patients per township has little impact on both multicollinearity and variance. For example, for injection drug history, the aOR (95% CI 2·65–3·48) from the non-spatial model is also very close to the aOR (95% CI 2·21–4·29) from the spatial model.

CONCLUSION

The geographical variations of some factors like marital status and educational attainment associated with HCV infection were found in drug users in this study area. These geographical variations of risk factors associated with HCV infection might provide some guidance for tailoring site-specific intervention strategies to better control or prevent HCV transmission in areas with limited resources. Spatial correlation and heterogeneity should not be ignored in future studies of risk factors for HCV infection.

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DECLARATION OF INTEREST

None.

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