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Factors associated with syphilis infection: a comprehensive analysis based on a case-control study

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SUMMARY

This study aimed to comprehensively evaluate factors that influence the likelihood of syphilis infection from risk-taking behaviours and medical conditions. A retrospective case-control study was conducted by enrolling 664 syphilis inpatients (excluding 11 congenital syphilis patients) and 800 sex- and age-matched controls. Medical histories, clinical data and patient interview data were collected and subjected to logistic regression analyses. The prevalence of syphilis in the study population was 3·9% (675/17 304). By univariate analysis, syphilis infection was associated with migration between cities, marital status, smoking, reproductive history, hypertension, elevated blood urea nitrogen (BUN) and infection with hepatitis B virus (HBV) ($P < 0·05$). A high rate of syphilis-HBV co-infection was observed in HIV-negative patients and further research revealed an association between syphilis and specific HBV serological reactivity. Syphilis was also associated with the frequency, duration and status of tobacco use. Multivariate analysis indicated that syphilis infection was independently associated with migration between cities [adjusted odds ratio (aOR) 1·368, 95% confidence interval (CI) 1·048–1·785], current smoking (aOR 1·607, 95% CI 1·177–2·195), elevated BUN (aOR 1·782, 95% CI 1·188–2·673) and some serological patterns of HBV infection. To prevent the spread of infectious diseases, inpatients and blood donors should be tested for HIV, syphilis, HBV and HCV simultaneously.

Key words: HBV infection, medical conditions, risk-taking behaviours, syphilis.

INTRODUCTION

Syphilis, a sexually transmitted disease (STD) caused by *Treponema pallidum*, currently remains a worldwide public health problem, which reflects the failure of syphilis control programmes and the lack of political advocacy [1–3]. Demographic, behavioural and health-related characteristics that increase the risk of syphilis infection have been studied extensively, and co-infection with other STDs is one of the most reliable indicators of syphilis risk. Blocker *et al.* reviewed 30 studies and concluded that infection with syphilis increased the risk of human immunodeficiency virus (HIV) infection with an odds ratio of 8·5 for men and 3·3 for women [4]. Some studies have suggested that co-infection with syphilis increases the risk of

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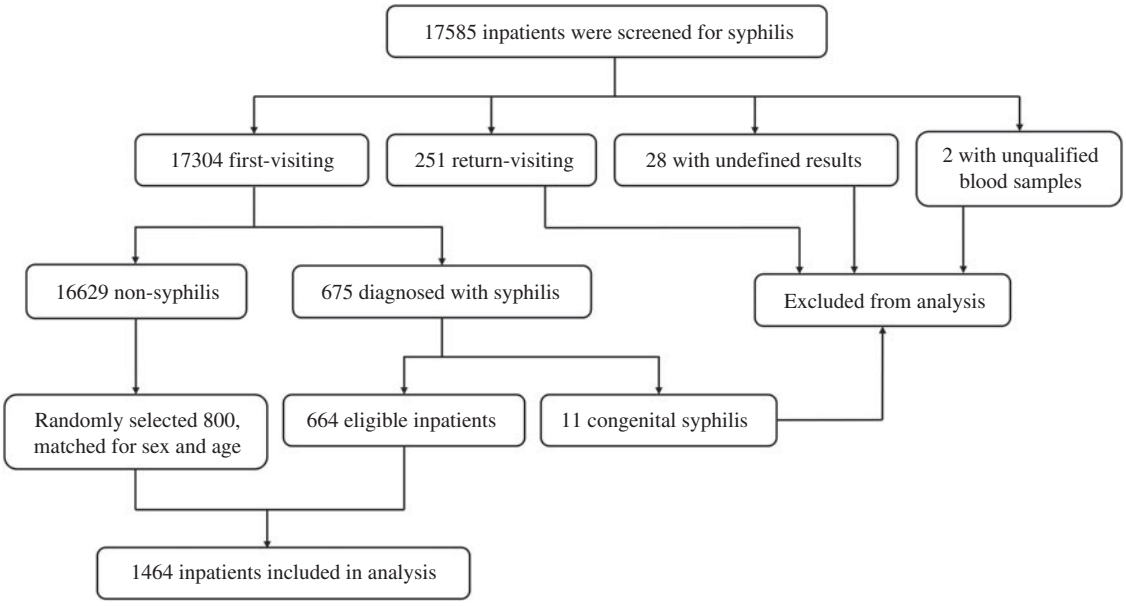

Fig. 1. Selection criteria of the study subjects.

infection with hepatitis C virus (HCV) [5, 6]. Association between infection with syphilis and hepatitis B virus (HBV) has also been observed [7], with some variation in different population subgroups [8, 9].

At present, studies about other factors associated with syphilis infection, such as risk-taking behaviours and medical conditions, which potentially affect the immune system and susceptibility, are limited. Syphilis and HBV infection are both endemic in China [1, 10], thus further research on the association between syphilis and HBV exhibits great value both academically and practically. Here, we conduct a retrospective case-control study to identify behavioural factors and medical conditions associated with syphilis infection.

METHODS

Study population and data collection

A retrospective case-control study was performed in Zhongshan Hospital, Medical College of Xiamen University from January 2013 to June 2014. A total of 17 585 inpatients were screened for syphilis infection by serological tests. Patients excluded from the study were 251 returning patients, 28 patients with undefined test results and two patients with unqualified blood samples. Of the remaining 17 304 patients, 675 had positive serological tests for syphilis and were ultimately diagnosed with syphilis based on clinical presentation, clinical data and medical history. Eleven patients with congenital syphilis were excluded leaving 664 patients to be included in subsequent analysis. Eight hundred age- and sex-matched controls were selected at random from the 16 629 non-syphilis inpatients at the hospital (Fig. 1). The study design was approved by the Institutional Ethics Committee of Zhongshan Hospital, Medical College of Xiamen University, and was found to be in compliance with national legislation and the Declaration of Helsinki guidelines.

All study participants were interviewed by physicians and data were collected on demographic and geographical variables (e.g. ethnicity, city of origin), health history and behavioural variables including tobacco use and alcohol consumption. Non-local residents were regarded as migrants. Current co-infection with other STDs (e.g. HIV, HBV infection) and liver and renal functions were assessed clinically.

Clinical diagnosis

According to the European guideline on the management of syphilis [11], syphilis was clinically diagnosed in this study by combining the serodiagnosis and disease history (including clinical characteristics and/or the patient's sexual history), in line with our previous studies [2, 3]. Laboratory tests for syphilis were performed using the *Treponema pallidum* particle agglutination assay (Fujirebio, Japan), and an automated chemiluminescence immunoassay (Boson Biotechnology,

China) according to the manufacturers' instructions and as previously reported [12]. The fluorescent treponemal antibody absorption (Euroimmun Medizinische Labordiagnostika, Germany) test was used to discriminate the discordant results. Enzyme-linked immunosorbent assay (ELISA) for HBV was performed for determination of hepatitis B surface antigen (HBsAg), antibody to HBsAg (anti-HBs), hepatitis B e antigen (HBeAg), antibody to HBeAg (anti-HBe) and antibody to hepatitis B core antigen (anti-HBc) (In Tec, China). Subjects were considered HBV-positive if they had a positive test for HBsAg and/or anti-HBc [13]. ELISA methods were also performed for HCV antigens (In Tec, China) and for exposure to HIV (HIV1 + 2 antigens/antibodies; Beijing Wantai Biological Pharmacy Enterprise Co. Ltd, China). Serum alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin, blood urea nitrogen (BUN) and creatinine were quantitated using a Roche Cobas 8000 automatic biochemistry analyser (Roche Diagnostics, F. Hoffmann-La Roche Ltd, Switzerland).

Statistical analysis

All statistical analyses were performed using SPSS v. 19·0 for Windows (SPSS Inc., USA). Univariate and multivariate logistic regression analyses were performed and crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. A two-sided P value $< 0{\cdot}05$ was considered to be statistically significant.

RESULTS

Description of syphilis patients

From January 2013 to June 2014, 675 inpatients at Zhongshan Hospital were diagnosed with syphilis, showing a prevalence of 3·9% (675/17 304). After excluding 11 congenital syphilis cases, 664 syphilis patients were enrolled for further analysis. The median age of syphilis patients in the study was 58 years (range, 20–93 years), including 417 males (62·8%) and 247 females (ratio 1·69:1). However, the male:female ratio varied by 10-year age group as follows: 0·44:1 (age 20–29), 0·56:1 (age 30–39), 1·14:1 (age 40–49), 2·18:1 (age 50–59), 2·18:1 (age 60–69), 2·53:1 (age 70–79), 2·38:1 (age 80–89), 0·5:1 (age 90–93) (Fig. 2).

Univariate analysis

The characteristics of the 664 syphilis patients were compared to the characteristics of non-syphilis patients. Migrants between cities in Fujian Province had increased odds of syphilis infection, compared to local residents. An increased odds of syphilis infection was also evident for married participants and divorced/widowed participants, compared to those unmarried. Apparently, tobacco use was significantly associated with syphilis infection, while alcohol consumption was not. No significant association was observed between syphilis infection and ethnicity, employment status or drug use (Table 1). Interestingly, an increased odds of syphilis infection was observed for participants with elevated BUN levels (>8·2 mmol/l). Participants with hypertension or female participants with a reproductive history also had increased probability of syphilis infection. However, other renal function parameters, liver function parameters, history of surgery, transfusion or diabetes mellitus were not significantly associated with syphilis infection (Table 1).

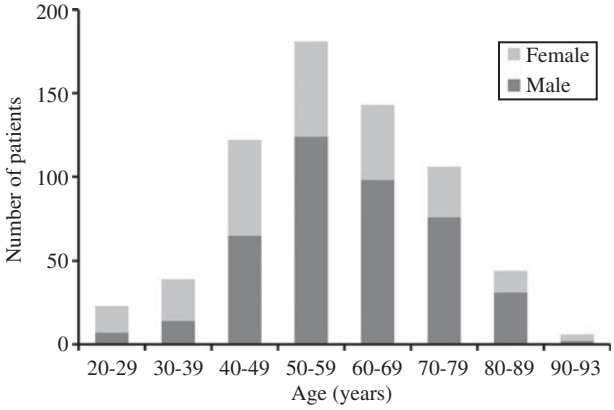

Fig. 2. Age and gender of 664 syphilis patients.

Of 1464 subjects, HIV status was determined to be negative for 1213 study subjects but 251 patients were lacking HIV test results. There were 1165 HIV-negative study subjects tested for HBV and 1114 HIV-negative study subjects tested for HCV. HBV infection was associated with increased risk of syphilis infection (OR 2·073, $P < 0{\cdot}001$), while HCV infection was not (Table 1).

Further multiple-level investigation was performed on the associations between syphilis infection and tobacco use, as well as alcohol consumption by stratifying the participants into different groups (Table 2). Results indicated that current smokers had increased odds of syphilis infection, while no significant difference was observed between former smokers and non-smokers. Furthermore, whether current or former smokers who consumed tobacco for >20 pack-years or for >15 years were associated with increased

Table 1. *Univariate analysis for association with syphilis infection*

Factor	Syphilis ($N = 664$)[a] *n* (%)	Non-syphilis ($N = 800$)[a] *n* (%)	OR	*P* for OR
Demographic characteristics				
Origin				
Local	442 (67·2)	564 (71·1)	Ref.	
Other city in Fujian Province	209 (31·8)	212 (26·7)	1·258	**0·049**
Other city outside Fujian Province	7 (1·1)	17 (2·1)	0·525	0·156
Marital status				
Unmarried	24 (3·6)	49 (6·2)	Ref.	
Married	620 (93·9)	737 (92·9)	1·718	**0·034**
Divorced/widowed	16 (2·4)	7 (0·9)	4·667	**0·003**
Ethnicity[b]				
Han	660 (99·8)	794 (100)	Ref.	
Minority	1 (0·2)	0	n.a.	n.a.
Employment status				
Employed	119 (18·0)	150 (18·9)	Ref.	
Retired	49 (7·4)	83 (10·5)	0·744	0·175
Unemployed	181 (27·4)	190 (23·9)	1·201	0·255
Unknown	312 (47·2)	371 (46·7)	1·060	0·687
Risk-taking behaviours				
Tobacco use				
No	493 (74·2)	639 (79·9)	Ref.	
Yes	171 (25·8)	161 (20·1)	1·377	**0·010**
Alcohol use				
No	565 (85·1)	700 (87·5)	Ref.	
Yes	99 (14·9)	100 (12·5)	1·227	0·180
Drug use				
No	661 (99·5)	798 (99·8)	Ref.	
Yes	3 (0·5)	2 (0·3)	1·811	0·664
Medical condition				
Surgery				
No	482 (72·6)	599 (74·9)	Ref.	
Yes	182 (27·4)	201 (25·1)	1·125	0·322
Blood transfusion				
No	658 (99·1)	796 (99·5)	Ref.	
Yes	6 (0·9)	4 (0·5)	1·815	0·526
Vaginal delivery or abortion[c]				
No	7 (2·8)	24 (8·0)	Ref.	
Yes	240 (97·2)	276 (92·0)	2·981	**0·009**
Hypertension				
No	399 (60·1)	532 (66·5)	Ref.	
Yes	265 (39·9)	268 (33·5)	1·318	**0·011**
Diabetes mellitus				
No	565 (85·1)	703 (87·9)	Ref.	
Yes	99 (14·9)	97 (12·1)	1·270	0·119
Elevated ALT (M > 50 U/l, F > 40 U/l)				
No	579 (89·1)	731 (92·1)	Ref.	
Yes	71 (10·9)	63 (7·9)	1·423	0·052
Elevated AST (M > 40 U/l, F > 35 U/l)				
No	559 (87·5)	691 (88·7)	Ref.	
Yes	80 (12·5)	88 (11·3)	1·124	0·478
Elevated total bilirubin (>17·1 μmol/l)				
No	506 (85·2)	608 (82·8)	Ref.	
Yes	88 (14·8)	126 (17·2)	0·839	0·247

Table 1 (*cont.*)

Factor	Syphilis ($N = 664$)[a] *n* (%)	Non-syphilis ($N = 800$)[a] *n* (%)	OR	*P* for OR
Elevated BUN (>8·2 mmol/l)				
No	564 (87·9)	729 (92·3)	Ref.	
Yes	78 (12·1)	61 (7·7)	1·653	**0·005**
Elevated sCr (M > 115 μmol/l, F > 97 μmol/l)				
No	573 (89·3)	718 (90·9)	Ref.	
Yes	69 (10·7)	72 (9·1)	1·201	0·302
HIV infection				
No	525 (100)	688 (100)	Ref.	
Yes	0	0	n.a.	n.a.
HBV infection[d]				
No	76 (15·1)	179 (27·0)	Ref.	
Yes	426 (84·9)	484 (73·0)	2·073	**<0·001**
HCV infection[e]				
No	468 (98·5)	635 (99·4)	Ref.	
Yes	7 (1·5)	4 (0·6)	2·374	0·221

OR, Odds ratio; n.a., not applicable; M, male; F, female; ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; sCr, serum creatinine; HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus.

[a] The sum of numbers in some subgroups may not add up to the total number of subjects because of missing values.

[b] Fisher's exact test *P* value was 0·454.

[c] Data for the history of vaginal delivery or abortion are for women only.

[d] Data for hepatitis B virus infection are for HIV-negative patients only.

[e] Data for hepatitis C virus infection are for HIV-negative patients only.

Table 2. *Multiple-level analysis about the association between syphilis and tobacco use, alcohol use and HBV serological data*

Factor	Syphilis ($N = 664$)[a] *n* (%)	Non-syphilis ($N = 800$)[a] *n* (%)	OR	*P* for OR
Tobacco use				
Current or former use[b]				
No	493 (74·2)	639 (79·9)	Ref.	
Former	30 (4·5)	32 (4·0)	1·215	0·456
Current	141 (21·2)	129 (16·1)	1·417	**0·010**
Duration of tobacco use[c]				
0 years	493 (77·5)	639 (81·7)	Ref.	
1–15 years	11 (1·7)	22 (2·8)	0·648	0·246
>15 years	132 (20·8)	121 (15·5)	1·414	**0·013**
Tobacco consumption[d]				
None	493 (77·9)	639 (82·1)	Ref.	
1–20 pack-years	38 (6·0)	43 (5·5)	1·145	0·556
>20 pack-years	102 (16·1)	96 (12·3)	1·377	**0·038**
Alcohol use				
Current or former use[e]				
None	565 (85·1)	700 (87·5)	Ref.	
Former	23 (3·5)	19 (2·4)	1·500	0·198
Current	76 (11·4)	81 (10·1)	1·162	0·374

Table 2 (*cont.*)

Factor	Syphilis ($N = 664$)[a] *n* (%)	Non-syphilis ($N = 800$)[a] *n* (%)	OR	*P* for OR
Duration of alcohol use[f]				
0 years	565 (91·3)	700 (91·3)	Ref.	
1–15 years	3 (0·5)	12 (1·6)	0·310	0·070
>15 years	51 (8·2)	55 (7·2)	1·149	0·493
Alcohol consumption[g]				
None	565 (91·0)	700 (90·8)	Ref.	
1–28 drinks/week	20 (3·2)	38 (4·9)	0·652	0·129
>28 drinks/week	36 (5·8)	33 (4·3)	1·352	0·224
Serological patterns of HBV infection				
HBsAg-, anti-HBs-, HBeAg-, anti-HBe-, anti-HBc-	39 (7·8)	84 (12·7)	Ref.	
HBsAg-, anti-HBs+, HBeAg-, anti-HBe-, anti-HBc-	37 (7·4)	93 (14·0)	0·857	0·574
HBsAg-, anti-HBs-, HBeAg-, anti-HBe-, anti-HBc+	60 (12·0)	60 (9·0)	2·154	**0·004**
HBsAg-, anti-HBs+, HBeAg-, anti-HBe-, anti-HBc+	175 (34·9)	190 (28·7)	1·984	**0·002**
HBsAg-, anti-HBs-, HBeAg-, anti-HBe+, anti-HBc+	24 (4·8)	29 (4·4)	1·782	0·086
HBsAg+, anti-HBs-, HBeAg+, anti-HBe-, anti-HBc+	7 (1·4)	5 (0·8)	3·015	0·074
HBsAg+, anti-HBs-, HBeAg-, anti-HBe+, anti-HBc+	53 (10·6)	59 (8·9)	1·935	**0·015**
HBsAg-, anti-HBs+, HBeAg-, anti-HBe+, anti-HBc+	96 (19·1)	127 (19·2)	1·628	**0·039**
Others[h]	11 (2·2)	16 (2·4)	1·481	0·369

HBV, hepatitis B virus; OR, odds ratio; HBsAg, hepatitis B surface antigen; anti-HBs, antibody to HBsAg; HBeAg, hepatitis B e antigen; anti-HBe, antibody to HBeAg; anti-HBc, antibody to hepatitis B core antigen.

[a] The sum of numbers in some subgroups may not add up to the total number of subjects because of missing values.

[b] No tobacco exposure indicates never having smoked cigarettes. Former tobacco exposure indicates having smoked cigarettes daily or irregularly in the past and having quit smoking for ⩾3 months. Current tobacco exposure indicates having smoked cigarettes daily or irregularly in the past 3 months.

[c] Non-smokers acknowledged smoking for 0 years. Current or former smokers who acknowledged smoking <1 year were recorded as smoking for 1 year.

[d] Non-smokers acknowledged no tobacco use. Pack-years are calculated by multiplying the average number of packs (1 pack = 20 cigarettes) smoked per day by the number of years a person smoked. Current or former smokers who consumed tobacco at <1 pack-year were recorded as having consumed 1 pack-year.

[e] No alcohol exposure was defined as never having consumed ⩾1 drink per month. Former alcohol exposure was defined as having consumed ⩾1 drink or more daily or irregularly per month in the past and having stopped drinking for ⩾3 months. Current alcohol exposure was defined as having consumed ⩾1 drink daily or irregularly per month in the past 3 months.

[f] Non-drinkers were regarded as drinking for 0 year. Current or former drinkers who having been drinking for <1 year were regarded as drinking for 1 year.

[g] Non-drinkers were regarded as having consuming no alcohol. A drink-equivalent (hereafter called 'drink') was defined as one 12-oz beer, one 6-oz glass of wine, one 3-oz mixed drink, or one 1·5-oz shot of liquor. Current or former drinkers who consumed <1 drink on average per week were regarded as having consumed 1 drink per week.

[h] Others including 1 (HBsAg-, anti-HBs-, HBeAg-, anti-HBe+, anti-HBc-), 5 (HBsAg+, anti-HBs-, HBeAg-, anti-HBe-, anti-HBc+), 1 (HBsAg-, anti-HBs+, HBeAg-, anti-HBe+, anti-HBc-), 2 (HBsAg+, anti-HBs+, HBeAg-, anti-HBe-, anti-HBc+), 2 (HBsAg+, anti-HBs+, HBeAg+, anti-HBe-, anti-HBc+), 11 (HBsAg+, anti-HBs+, HBeAg-, anti-HBe+, anti-HBc+), 5 (HBsAg+, anti-HBs-, HBeAg+, anti-HBe+, anti-HBc+).

probability of syphilis infection. Compared to no alcohol consumption, the duration or frequency of alcohol use was not associated with syphilis infection. It should be noted that current or former drinkers who consumed alcohol for >15 years had more than threefold increased odds of syphilis infection compared to those with 1–15 years of alcohol consumption (data not shown). Similarly, participants who consumed alcohol (>28 drinks/week) had a twofold increased odds of syphilis infection compared to those consuming 1–28 drinks/week (data not shown). An intensive study of the association between syphilis and serological reactivity to HBV is also shown in Table 2. Compared to the pattern negative for all HBV serological markers, an isolated anti-HBc + pattern, an anti-HBs + /anti-HBc + pattern, an HBsAg + /anti-HBe + /anti-HBc + pattern, and an anti-HBs + /anti-HBe + /anti-HBc + pattern were all associated with

Table 3. *Multivariable analysis for association with syphilis infection*

Factor	aOR	95%CI	*P* for aOR
Origin			
Local	Ref.		
Other city (same province)	1·368	1·048–1·785	**0·021**
Other city (different province)	0·449	0·158–1·274	0·132
Tobacco use			
Never	Ref.		
Former	1·063	0·587–1·923	0·840
Current	1·607	1·177–2·195	**0·003**
HBV infection			
HBsAg-, anti-HBs-, HBeAg-, anti-HBe-, anti-HBc-	Ref.		
HBsAg-, anti-HBs+, HBeAg-, anti-HBe-, anti-HBc-	0·901	0·517–1·569	0·712
HBsAg-, anti-HBs-, HBeAg-, anti-HBe-, anti-HBc+	2·230	1·297–3·833	**0·004**
HBsAg-, anti-HBs+, HBeAg-, anti-HBe-, anti-HBc+	2·029	1·298–3·172	**0·002**
HBsAg-, anti-HBs-, HBeAg-, anti-HBe+, anti-HBc+	1·906	0·970–3·745	0·061
HBsAg+, anti-HBs-, HBeAg+, anti-HBe-, anti-HBc+	2·797	0·818–9·563	0·101
HBsAg+, anti-HBs-, HBeAg-, anti-HBe+, anti-HBc+	1·983	1·146–3·432	**0·014**
HBsAg-, anti-HBs+, HBeAg-, anti-HBe+, anti-HBc+	1·791	1·112–2·885	**0·017**
Others*	1·520	0·632–3·653	0·350
Elevated BUN (>8·2 mmol/l)	1·782	1·188–2·673	**0·005**

aOR, Adjusted odds ratio; CI, confidence interval; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; anti-HBs, antibody to HBsAg; HBeAg, hepatitis B e antigen; anti-HBe, antibody to HBeAg; anti-HBc, antibody to hepatitis B core antigen; BUN, blood urea nitrogen.

* Others including 1 (HBsAg-, anti-HBs-, HBeAg-, anti-HBe+, anti-HBc-), 5 (HBsAg+, anti-HBs-, HBeAg-, anti-HBe-, anti-HBc+), 1 (HBsAg-, anti-HBs+, HBeAg-, anti-HBe+, anti-HBc-), 2 (HBsAg+, anti-HBs+, HBeAg-, anti-HBe-, anti-HBc+), 2 (HBsAg+, anti-HBs+, HBeAg+, anti-HBe-, anti-HBc+), 11 (HBsAg+, anti-HBs+, HBeAg-, anti-HBe+, anti-HBc+), 5 (HBsAg+, anti-HBs-, HBeAg+, anti-HBe+, anti-HBc+).

the increased probability of syphilis infection, with *P* values 0·004, 0·002, 0·015 and 0·039, respectively.

Multivariate analysis

Multivariate analysis was performed on 490 syphilis patients and 652 controls, 322 participants were eliminated because of missing values (e.g. lack of HIV results) (Table 3). Migrants between cities in Fujian Province, relative to local residents, remained positively associated with syphilis infection [adjusted odds ratio (aOR) 1·368, 95% CI 1·048–1·785]. An increased odds of syphilis infection was observed in current smokers (aOR 1·607, 95% CI 1·177–2·195). Elevated BUN levels (>8·2 mmol/l) resulted in increased odds in favour of syphilis infection (aOR 1·798, 95% CI 1·188–2·673). Associations between syphilis and different serological patterns of HBV infection were noted. Compared to the HBV-negative pattern, an isolated anti-HBc + pattern, an anti-HBs + /anti-HBc + pattern, an HBsAg + /anti-HBe + /anti-HBc + pattern and an anti-HBs + /anti-HBe + /anti-HBc + pattern were all positively associated with the probability of syphilis infection.

DISCUSSION

To date, syphilis infection is increasingly prevalent in China. Although individual risk factors for syphilis infection have been well described (unprotected sex, etc.), some potential determinants are less well studied. In this study, we comprehensively evaluated the factors that may influence the likelihood of syphilis infection regarding risk-taking behaviours and medical conditions. Through rigorous analyses, our research indicated that migration, tobacco use, elevated BUN levels and HBV infection were associated with syphilis infection.

Xiamen city is one of the coastal urban regions in China where the syphilis burden is greatest [14]. Our study showed a prevalence of syphilis of 3·9%, nearly as high as the prevalence in other high-risk groups, such as female sex workers (2·4–3·2%) [15], male students who have sex with men (5·0%) [16], and males with commercial sex partners (5·3%) [17]. The male:female ratio of syphilis patients was 1·69:1, higher than reported in the national survey [18], and disproportionate in different age groups. Migration between cities in the same province increased the risk of syphilis

infection. Migrants reported more sexual activity, and appeared to be less knowledgeable about STDs and less aware of voluntary counselling and testing services reported in previous studies [19].

HBV infection was prevalent in all subjects, but significantly more common in syphilis than in non-syphilis study subjects. Syphilis and HBV are primarily transmitted by sexual contact, vertical transmission, or unsafe injections (i.e. blood transfusions or dialysis) [20]. Syphilis and HBV are also more prevalent in the same high-risk subpopulations, including men who have sex with men, drug users, and persons with multiple sexual partners [20]. Because it is an ulcerative infection, syphilis may also directly facilitate acquisition of HBV [8].

China is one of the countries where HBV is most highly endemic globally, with an estimated 120 million people carrying HBsAg [10]. Meanwhile, syphilis has been ranked as the third most prevalent notifiable infectious disease in China, with >0·4 million new infections each year (www.stats.gov.cn). HBV serological tests of 1165 HIV-negative subjects in this study demonstrated an association between syphilis and HBV infection. Furthermore, there are several types of HBV infection status in clinical practice. Compared to an HBV-negative status, syphilis infection was positively associated with specific HBV serological reactivity. Therefore, this study suggests that HBV-syphilis co-infection may become or already be a serious public health problem.

Syphilis patients are also often co-infected with HIV [4]. The latter can lead to immunosuppression, which could potentially increase the risk of developing syphilis [21]. However, the HIV infection rate in this study was fairly low, and the association between syphilis and HIV infection was not analysed. Although HCV-syphilis co-infection was common in previous studies [5, 6], no association between syphilis and HCV infection was observed in the present study, again, possibly because of a low prevalence of HCV infection. HIV/syphilis/HBV/HCV tests are compulsory in China for inpatients and blood donors to prevent the spread of infectious diseases [22]. This practice also identifies individuals infected with HIV/syphilis/HBV/HCV.

Smoking has been considered a marker of high-risk for syphilis infection, especially when associated with increased sexual activity, more lifetime sexual partners, less condom use, and earlier age at first intercourse and pregnancy [23, 24]. Consistent with this, current smoking and duration and frequency of smoking were associated with higher risk of syphilis infection in the present study. In addition, higher risk of syphilis infection was associated with duration and frequency alcohol consumption. As early as 1901, a study concluded that alcohol use was associated with newly diagnosed syphilis infection [25]. It may also be associated with risky sexual behaviour or casual selection of sex partners [26], as well as suppression of the immune system or promotion of other biological changes that increase susceptibility to STDs [27].

In the current study, elevated BUN level was positively associated with syphilis infection, suggesting that reduced renal function may contribute to syphilis infection. Kidney disease may affect general immunity, resulting in persistent systemic inflammation and acquired immunosuppression, which facilitate the infection [28]. Conversely, syphilis may negatively impact renal function. Renal manifestations of syphilis have been recognized since the 18th century [29]. A variety of renal conditions have been reported in secondary syphilis, ranging from nephrotic syndrome to acute nephritic syndrome, rapidly progressive glomerulonephritis and renal failure [30]. Nevertheless, BUN can be elevated by many extra-renal factors, such as high protein diet, hypovolaemia, congestive heart failure and gastrointestinal haemorrhage [31].

The retrospective case-control study allowed a better identification of associated factors than a cross-sectional study. However, for associations reported here, it is not known whether factors associated with syphilis infection were present before subjects were exposed to and became infected with *T. pallidum*. Thus, no causal relationships can be inferred. Furthermore, the current study is hospital-based and nearly 22·0% (322/1464) of the study subjects were excluded from multivariate analysis because of missing data, raising the concern of selection bias. Another limitation is that the sample size may be too small, and statistical power too low, to compare syphilis prevalence in patient subgroups with different patterns of HBV seroreactivity. Additionally, this study was conducted in a highly endemic area for both syphilis and HBV, further research is needed to explore the syphilis-HBV co-infection in populations with moderate or low prevalence.

In conclusion, this study demonstrated a high prevalence of syphilis in the study subjects and a high rate of syphilis-HBV co-infection in HIV-negative patients. Individuals who migrate between cities are at higher risk of infection with syphilis than non-migrants, suggesting that political advocacy, counselling and testing services could be valuable. Abstinence from smoking

and limited consumption of alcohol may reduce the risk of infection with syphilis. In addition, syphilis infection may be more prevalent in individuals with elevated BUN levels. To prevent the spread of infectious diseases, inpatients and blood donors should continue to be tested for exposure to and/or infection with HIV, syphilis, HBV and HCV at the same time.

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DECLARATION OF INTEREST

None.

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