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Prevalence and risk factors of *Fascioliasis* in China

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ABSTRACT

Fascioliasis has emerged as a significant public health problem among ruminants and humans. Human fascioliasis is a neglected food-borne parasitic disease, which has emerged or reemerged in more than 60 countries worldwide. In China, the first case of human fascioliasis was reported in 1921 in Fujian Province. The first major outbreak of this parasitic disease in 29 patients occurred in 2012 in Yunnan Province. Nonetheless, the prevalence of fascioliasis in China is probably underestimated due to the poor sensitivity of diagnostic tests, limited epidemiological data, and a poor understanding of the impact of subclinical illness. This study aimed to review the prevalence and risk factors of fascioliasis in China so as to improve the prevention and control of this disease.

Key words: China; fascioliasis; prevalence; risk factors

1. Introduction

Fascioliasis is a zoonotic parasitic disease caused by the family Fasciolidae, including *Fasciola hepatica* and *F. gigantica* (Mas-Coma et al., 2009). It has traditionally been recognized as an important veterinary disease, which can cause substantial production and economic losses in livestock (particularly sheep and cattle) (Torgerson and Claxton, 1999). In contrast, human fascioliasis has been typically neglected or misdiagnosed as a liver disease, and is also considered as a secondary disease (Mas-Coma et al., 2005; Mas-Coma et al., 2014).

An increasing number of human fascioliasis cases have been reported in the five continents, including Europe, Africa, Asia, the Americas, and Oceania. Currently, the disease is no longer considered as a secondary zoonotic disease but an important parasitic disease due to a better understanding of its pathogenicity and immunity (Mas-Coma et al., 1999a). It was also included as a food-borne trematode disease priority by the World Health Organization (WHO) (WHO, 2013).

Four clinical phases are identified in fascioliasis (Mas-Coma et al., 1999a, b, c). The incubation phase includes the time from the ingestion of metacercariae to the appearance of initial symptoms. In humans, this phase has not been accurately determined (“a few” days, 6 weeks, 2–3 months, or longer). The invasive or acute phase involves fluke migration to the bile ducts. The latent phase includes maturation of the parasites and starting of oviposition. This phase can last for months or years and the proportion of asymptomatic subjects in this phase is unknown, which is often discovered during family screening after a patient is diagnosed (Arjona et al., 1995). Patients may have prominent eosinophilia suggestive of infection, gastrointestinal complaints, or ≥1 relapse of acute symptoms. Finally, the biliary, chronic, or obstructive phase may develop after several months to years of infection. Of these four phases, the second and fourth are the most important because patients are typically in one of these two phases when diagnosed.

In China, human fascioliasis was first reported in 1921 in Fujian Province (Maxwell, 1921). The first major outbreak of this parasitic disease in 29 patients occurred in 2012 in Yunnan Province (Chen et al., 2013). Currently, 306 cases of human fascioliasis have been reported in China. Nonetheless, the prevalence of fascioliasis in China is probably underestimated because of poor sensitivity of diagnostic tests, limited epidemiological data, and a poor understanding of the impact of subclinical illness. This study aimed to review the prevalence and risk factors of fascioliasis in China so as to improve the prevention and control of this disease.

2. Data retrieval method

The current status and epidemiological characteristics of human fascioliasis in China in the last 97 years were summarized through the literature analysis. The academic papers, including research papers, reviews, and case reports, in the field of human fascioliasis in China from 1921 to 2018 from the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov), China Knowledge Network data platform (http://www. Cnki. net), Wanfang data platform (http://www.wanfangdata.com.cn), and Weipu data platform (http://vip.hbdlib.cn/) were searched with the keywords human, fascioliasis, and China. A total of 71 papers were retrieved, including 60 case reports and 11 investigation reports.

3. Data statistics method

The provinces, number of reported cases, species of *Fasciola*, and references were classified and ranked by applying Microsoft Excel in Table 5. In Table 1, 2, 3, and 4, the statistical test had been done by Chi-square (SPSS R version 3.5.1 (2018-07-02), Platform: x86_64-w64-mingw32/x64 (64-bit), Running under: Windows >= 8 x64 (build 9200)).

4. Epidemiology of human fascioliasis in China

4.1 Epidemiological characteristics of human fascioliasis in China

Currently, fascioliasis presents the widest latitudinal, longitudinal, and altitudinal distribution (Mas-Coma et al., 2003). *F. hepatica* is the main causative agent because of its very wide distribution in Europe, Africa, Asia, Oceania, and the Americas; while *F. gigantica* appears to be of secondary importance because it is restricted to the Old World (Mas-Coma and Bargues, 1997).

In China, the number of cases of human fascioliasis was small as well as with the sporadic character. The first *F. hepatica* infection human case was reported in 1921 in Fujian Province (Maxwell, 1921). Moreover, the first *F. gigantica* human case was in 1984 in Anhui Province (Wang, 1984), as well as the first intermediated form of *Fasciola* human infection in Yunnan Province, 2018 (Zhang, 2018). Furthermore, the first and large-scale human fascioliasis outbreak in China was at the end of 2011, with 29 residents living in Binchuan County, Yunnan, infected with *F. gigantica*.

Up to date, of all 306 human fascioliasis cases recorded distributed in 19 provinces (the data from the first important human parasitic infection survey was carried out during 1986–1992 was contained), including Fujian, Guangxi, Guangdong, Hubei, Hunan, Hainan, Guizhou, Sichuan, Yunnan, Jiangxi, Anhui, Shandong, Henan, Hebei, Gansu, Liaoning, Jilin, Inner Mongolia, and Xinjiang (Table 1 and Fig. 1). The disease occurs in both south and north of China. However, based on the information of reported cases, the number in the south (207 cases from Fujian, Guangxi, Guangdong, Hubei, Hunan, Hianan, Guizhou, Sichuan, Yunnan and Jiangxi) is more than that in the north (99 cases from Anhui, Shandong, Henan, Hebei, Gansu, Liaoning, Jilin, Inner Mongolia and Xinjiang) (χ^2 =201; P = 2.2×10^{-16}).

Most human fascioliasis cases were reported in Yunnan Province (Chen et al., 2013), which is located in southwestern China. From 2003 to 2018, 63 human fascioliasis cases were recorded, including 33 infected with *F. hepatica*, 30 infected with *F. gigantica*, and 1 infected with the intermediate form. Besides Yunnan Province, the following provinces also reported high infection: Gansu Province (49 cases, located in northwestern China, major animal husbandry provinces) (Zhang and Chen, 1991; Zhang et al., 1991), Hainan Province (31 cases, the southernmost part of China) (Chen et al., 1994; Wang and Xu, 1995; Xu et al., 1991), Hebei Province (31 cases) (Chen and Mao, 1980; Li et al., 2017), and Hubei Province (25 cases, 1987–1991 survey) (Chen et al., 1991; Du et al., 2010; Luo and Tan, 1988; Qiu et al., 2010; Shi, 1978; Wu et al., 1994; Yang, 2006; Zhang, 1995) (Table 1).

4.2 Proportion of *Fasciola* infection by age groups and gender in China

Among 306 reported cases, there were 240 with known gender as well as detailed age records, including 125 male and 115 female with proportion 52.08% (125/240) and 47.92% (115/240), respectively. 31- to 40-year-old patients were most represented, followed by patients aged 21–30 years in both male and female. It showed that the age distribution of patients was concentrated in young adults (Table 2 and Fig. 2). The infection number of male was higher than that of female (χ^2 =304.13; P = 2.2×10^{-16}). The possible reasons may be rural male have to bear the work of cattle and sheep grazing as well as farming on the fields, which increased the chance to connect with *Fasciola* metacercaria.

4.3 Proportion of *Fasciola* infection in different occupations in China

Among 306 reported cases, there were 225 with known occupation. The occupational distribution was as follows. The infection was found in students, farmers, and preschool children, with the proportion of 55.11% (124/225), 31.56% (71/225), and 9.33% (21/225), respectively. After the chi-square test, the difference in the proportion in different populations was found to be significant (χ^2 =436; P = 2.2×10^{-16}) (Table 3 and Fig. 3).

The possible causes of infection were that farmers were engaged in farming and irritating, which lead to higher chances of exposure to metacercaria than those of urban populations. Moreover, infected students and preschool children in the literatures, live in rural areas, who have drunk raw water, as well as consumed raw aquatic plants or swim in the lake. Above behavior allowed them to attach to metacercaria.

4.4 Proportion of *Fasciola* infection in different ethnic groups, China

Among 306 reported cases, there were 177 with known occupation. The infection was found in three ethnic groups: Han (166/177, 93.79%), Bai (8/177, 4.52%), Li (1/177, 0.56%), Miao (1/177, 0.56%), and Uygur (1/177, 0.56%). After the chi-square test, the infection rate in Han was higher than others (χ^2 =603.31; P = 2.2×10^{-16}) (Table 4).

4.5 Main symptoms

The most common symptom was abdominal pain and indigestion in 86 cases, followed by 63 cases with fever; 57 cases with hepatomegaly and hepatic abscess in B-mode ultrasonography (B-ultrasound), computerized tomography (CT), and Magnetic Resonance Imaging (MRI); 54 cases with an increased number of eosinophils; and 30 cases with abnormal liver function. Moreover, individual cases with ascites (19 cases), yellowing of the skin or sclera (14 cases), liver damage in pathological section (11 cases), pleural effusion (10 cases), cough (10 cases), diarrhea (7 cases), anemia (7 cases), headache (3 cases), and ectopic parasitism (2 cases) were also reported (Table 5). Most people have mixed symptoms.

5. Introduction of important human fascioliasis cases in China

5.1 First human *Fasciola hepatic* infection in China

Human fascioliasis was first reported in Fujian, China in 1921 (Maxwell, 1921). Eggs of *F. hepatica* were found by stool detection from local villagers. However, the information about age, gender, symptoms, and treatment of patient was not described in the document.

5.2 First human *Fasciola gigantica* infection in China

The first human fascioliasis case in China caused by *F. gigantica* was reported in 1984. This was a 12-year-old boy living in Anhui Province. During the stool detection, suspected Fasciolopsis eggs were found. After oral administration of praziquantel (200 mg) for 48 hour, one fluke specimen was collected, which was identified as *F. gigantica* by the morphological method at the Institute of Parasitic Diseases, Chinese Academy of Medical Sciences（Wang, 1984）.

5.3 First human *Fasciola intermediate form* infection in China

The first intermediated form of *Fasciola* human infection was reported in 2018 from Yuxi, Yunnan Province (Zhang, 2018). Two *Fasciola* samples were collected from a 47 year-age female by hepatobiliary surgery. The mitochondrial NADH dehydrogenase subunit 1 (nad1) gene and first internal transcribed spacer (ITS1) of nuclear ribosomal DNA (rDNA) of individual trematodes were amplified by polymerase chain reaction

(PCR). The sequences analyzed by comparing with related sequences of *Fasciola* available in Genbank database. Both *Fasciola* fluckes with the identical nad1 haplotype similar to *F. gigiantica* haplogoup, showed Fg type to sample YXGD01 and Fh type to sample YXGD02 in ITS1 respectively. Moreover, the result between ITS1 and nad1 haplotype of sample YXGD02 infers that it may belong to one special type of intermediate form *Fasciola* between *F. hepatica* and *F. gigantica*.

5.4 First human fascioliasis outbreak in China

The first major outbreak of human fascioliasis was in Binchuan County, Yunnan Province (southwest China), from the end of 2011 to January 2012. A total of 29 human fascioliasis cases with intermittent fever, hepatalgia, and eosinophilia were reported. After morphological, immunological, and molecular detection, *F. gigantica* was identified as the causative pathogen, which led to an initiative from the Chinese government to prevent and control this disease (Chen et al., 2013).

In this outbreak, the characteristics of the disease were as follows: (1) Population distribution: the ratio of male to female was 1:2. The age was 9–63 years (mainly young and middle-aged), with one case less than 10 years old, two cases 11–20 years old, five cases 21–30 years old, six cases 31–40 years old, seven cases 41–50 years old, one case 51–60 years, and three cases more than 61 years old. (2) Regional distribution: The cases were mainly distributed in the towns of Binchuan County (23 cases), one case each in Binju Town, Jinniu Town, and Qiaodian Town. (3) Time distribution: 85% of cases were concentrated in October–December 2011, with one case in March and August 2011, six cases in October, nine cases in November, six cases in December, and two cases in January 2012. The earliest case occurred on March 10, 2011, and the latest case occurred on January 10, 2012. (4) Family aggregation: Two patients were reported in five families and four in two families. (5) Eating habit: all of the patients consumed raw *Houttuynia* (Chen et al., 2013; Dong, 2016; Wang et al., 2015; Zhang et al., 2012).

The possible reasons for the outbreak were as follows. (1) Yunnan is located in the southwestern part of China, with a warm and pleasant climate. The annual temperature is between 19°C and 22°C. (2) The water source is rich, and the water systems such as lakes, rivers, and ponds are widely distributed, providing favorable conditions for the breeding of the intermediate host snails of *Fasciola*. (3) The local villagers raised a large number of cattle and sheep, providing a final host for the prevalence of fascioliasis. (4) Yunnan is a province where ethnic minorities live in concentrated communities. Many ethnic minorities have their own unique eating habits. They generally prefer to eat fresh vegetables, especially cold salads or meat-based seasonings made with plants (green onions, coriander, or *Houttuynia*). If these vegetables are contaminated with metacercaria and are not cleaned, the infection may occur. The reason for the first human fascioliasis outbreak in China was the consumption of *Houttuynia* growing around a pond.

5.5 Familial fascioliasis

In 2016, four cases in the same family were diagnosed with acute fascioliasis. One case was hospitalized with fever, eosinophilia, and hepatic lesions. Magnetic resonance imaging (MRI) revealed hypodense changes in bilateral liver lobes. The other three family members presented with stomachache without other symptoms. *Fasciola* eggs were found in two adult patients during the stool examination. The immunological test of *Fasciola* Immunoglobulin G (IgG) antigen and molecular identification of eggs were performed at the National Institute of Parasitic Diseases, Chinese Center for Disease Control and Prevention, Shanghai, China. Serological tests were positive in all four patients. DNA sequencing of Polymerase Chain Reaction (PCR) products of the eggs showed 100% homology with internal transcribed spacer (ITS) and cytochrome oxidase 1 (cox1) of *F. hepatica* (Ai et al., 2017). The introduction of modern molecular biology technology provides accurate and effective methods for diagnosing parasitic diseases.

6. Infection route

The ingestion of infective metacercariae by humans may occur in different ways according to the reports: (1) ingestion of freshwater wild plants, important in animal endemic areas; (2) ingestion of freshwater cultivated plants, mainly watercress; (3) ingestion of terrestrial wild plants collected from dry habitats but submerged in water a few weeks or months earlier; (4) drinking of contaminated water; and (5) ingestion of dishes and soups made with contaminated water.

Living habit and cultural traditions prove to be highly essential in endemic areas. During the first human fascioliasis outbreak in Yunnan, the local residents preferred consuming salad cooked with freshwater plants, such as *Houttuynia*, watercress, and radish. The link of fascioliasis risk with the consumption of raw vegetables other than *Houttuynia* should be highlighted because it suggests contamination when washing terrestrial vegetables with untreated water and/or in plant cultures using natural water for irrigation (Chen et al., 2013).

However, no difference in the viability and infectivity of metacercariae was found between isolates from different reservoir species, demonstrating that flukes from secondary reservoirs, such as pigs and donkeys, contributed to the same potential risk as those from the main reservoirs, such as sheep and cattle (Mas-Coma et al., 1999c).

7. Detection methods

Four clinical periods were distinguished in human fascioliasis (Mas-Coma and Bargues, 1997). The incubation period is from the ingestion of metacercariae to the appearance of first symptoms. However, this period may be only "a few" days to 2–3 or even more months. The second period of *Fasciola* migration up to the bile ducts is defined as an invasive or acute period. The symptoms in this period include fever, abdominal pain (especially in the right hypochondrium or below the xiphoid) or nausea, diarrhea, cough, dyspnea, chest pain, and also urticaria. The third period includes maturation of *Fasciola* and oviposition, which may last for months or years (Arjona et al., 1995). Patients may have prominently increased eosinophilia, gastrointestinal complaints, or other acute symptoms. In the last period, the biliary, chronic, or obstructive symptoms may develop after months to years. Diagnosis can be carried out during the second or fourth period.

Although some suggestive clinical presentation aspects may be useful, this parasitic disease has not received attention due to a few cases of concentrated outbreaks, leading to a the lack of familiarity among clinical doctors in China. Consequently, it is often misdiagnosed as liver cancer as the main symptom is liver damage. Moreover, verification needs the use of at least one among the direct parasitological techniques or indirect immunological tests, in which operations are professional and require the knowledge of relevant technical personnel.

Noninvasive diagnostic techniques, especially medical imaging, for instance, radiology, radioisotope scanning, ultrasound, computed tomography, and magnetic resonance, may be additionally helpful (Carnevale et al., 2016). It is nonspecific in this early phase in ultrasonography (US) detection. The US features of *Fasciola* lesions may be variable until 8 weeks after infection. Focal hypoechoic or hyperechoic lesions or diffuse involvement of the liver is always found in the parenchymal period (Dusak et al., 2012; Gonzalo-Orden et al., 2003). Computed tomography (CT) findings of the parenchymal phase include multiple, small, round, or oval clustered hypodense lesions with peripheral contrast enhancement (Gonzalo-Orden et al., 2003). MRI can establish liver parenchymal involvement. Hypointense and hyperintense lines are demonstrated in the subcapsular area on T1W and T2W MRI scans, respectively, in the early migration of *Fasciola* (Gonzalo-Orden et al., 2003). In this study, 8 cases were detected by US (Ding et al., 2016; Fan et al., 2006; Huang et al., 2009; Lv et al., 1987; Tang et al., 2005; Yao et al., 1989; Zhang, 1995; Zhang et al., 2002), 67 cases by CT (Chen, 1995; Chen et al., 2013; Du et al., 2010; Du et al., 2011; Fan et al., 2006; Lin et al., 2017; Jiang et al., 2014; Qiu et al., 2010; Wang et al., 2007; Zeng and Li, 2006; Zhang et al., 2002;), and 25 cases by MRI (Du et al., 2010; Huang et al., 2006; Lin et al., 2017; Qiu et al., 2010; Wen et al., 2009; Yang, 2006; Zhang et al., 2004) (in Table 2).

The most appropriate diagnostic method to detect infection and estimate intensity is to analyze *Fasciola* eggs in stool sample, duodenal contents, or bile. Direct smear method, sedimentation techniques, and Kato–Katz technique are most commonly used in detecting human fascioliasis. The sedimentation techniques appear to be more accurate and sensitive compared with the direct smear method due to its concentration principle. Five cases were detected by direct smearing methods (Yang, 2006; Wang et al., 1981; Chen ＆ Mao, 1980; Guo ＆ Zhou, 1989; Huang, 18) and 55 cases by the stool sedimentation method (Ai et al., 2017; Chen et al., 1991; Chen et al., 2013; Du et al., 2011; Fan et al., 2006; Hu and Ding, 2016; Huang et al., 2006; Huang et al., 2009; Zhang et al., 2002; Zhang et al., 2002). Moreover, quantitative coprological analyses have become important in epidemiological surveys and post-treatment monitoring. The Kato–Katz technique appears to be appropriate because of its simplicity, very low cost, and reproducibility. Its low sensitivity may be solved by the repeated application (Mas-coma et al., 1999). This method was used mainly in the first important parasitic disease survey and other large-scale investigations (Hu and Ding, 2016; Wu et al., 1994; Zhang and Chen, 1991).

Besides eggs found in stool testing analyses, adults and eggs may be found using other detection techniques: obtaining duodenal fluid and duodenal and biliary aspirates; surgery (laparotomy, cholecystectomy, and sphincterotomy); and histological examination of liver and/or other organ biopsy materials. In this study, 8 cases were detected using eggs from the bile duct drainage (Chen, 1984; Duan and Wei, 1988; Liu and Han, 1989; Lv et al., 1987; Sun and Chai, 1981; Sun and Chai, 1983; Wu et al., 1982; Yao et al., 1989), 35 cases by pathological section (Zeng ＆ Li, 2006; Jiang et al., 2014; Shi, 1978; Zhang, 1995; Li et al., 2017), and 22 cases diagnosed and treated by surgery (Chen et al., 1997; Dong et al., 2000; Fu and Ding, 2004; Hou, et al., 2003; Huang, 1978; Lin et al., 1990; Luo and Tan, 1988; Miu and Zhu, 1988; Qiu et al., 2010; Tang, 1954; Tang et al., 2005; Xie et al., 2014; Yu, 1987; Wang and Xu, 1995; Wang and Yang, 2011; Zhang et al., 2002; Zhang et al., 2004; Zhang et al., 2005; Zhang et al., 2018; Zheng et al., 1986; Zheng, 1997; Zhu et al., 2014).

Immunological techniques, namely serological, intradermal, and stool antigen detection, can be applied during all periods of the disease, but fundamentally during the invasive or acute period. These techniques can also be used in other situations in which coprological techniques may present problems.. However, immunological techniques offer other types of problems related mainly to sensitivity and specificity (Sarkari and Khabisi, 2017). Different serological tests have been used for human diagnosis. Almost all these techniques are used for detecting circulating antibodies, and only a very few are designed to detect circulating antigens and immune complexes (Mas-Coma et al., 2014). Currently, the commercialized DRG *Fasciola hepatica* IgG (human) ELISA kit produced in Germany, which is highly sensitive and specific, has a high negative predictive value but a low positive predictive value. This test could be used both as an individual serodiagnostic test for human fascioliasis when backed up by a compatible clinical history and a second diagnostic technique for other cross-reactive helminth infections and in future large-scale epidemiological studies of human fascioliasis worldwide (Valero et al., 2012). Among the human fascioliasis reports in China, DRG ELISA kits have been used in serum detection in the first human fascioliasis outbreak in Yunnan, family cases in Fujian, and patients from Guizhou (Chen et al., 2013; Ai et al., 2017; Chen, unpublished).

Furthermore, infection by *F. hepatica* and *F. gigantica* cannot be differentiated by clinical, pathological, coprological, or immunological methods. This is a problem in overlapping areas because this differential diagnosis is important owing to the different pathological, transmission, and epidemiological characteristics of the two fasciolids, as well as due to intermediate forms in which egg measurements may overlap. PCR amplification (PCR–RFLP, PCR–SSCP, multiplex PCR, specific PCR, and TaqMan real-time PCR-based assay) and DNA marker sequencing are appropriate to distinguish *F. hepatica*, *F. gigantica*, and hybridization in intermediate forms. For such a purpose, the complete sequences of the two rDNA spacers ITS-2 and ITS-1 together with those of the mtDNA genes cox1 and nad1 have so far proved to be the markers of choice, and a complete baseline and nomenclature for these four markers have already been provided (Ai et al., 2011). By the molecular methods, 29 patients were infected with *F. gigantica* in Yunnan, 3 with *F. hepatica*, and 1 with the intermediate form (Ai et al., 2017; Chen et al., 2013; Chen, unpublished; Zhang et al., 2018).

8. Treatment

Many drugs have been used to treat human fascioliasis. The most useful and commonly used one is triclabendazole (Fasinex). However, cases of human fascioliasis were rare in China, and no triclabendazole was available for humans. Effective drugs to treat this parasitic disease were lacking, with only praziquantel and albendazole, which did not work in the outbreak in Yunnan. The patient's condition was controlled after triclabendazole was urgently procured from the WHO. Moreover, triclabendazole resistance has been observed in concerned livestock in animal endemic areas and also reported in a highly endemic area for humans, such as Cajamarca, Peru (Gonzalez et al., 2011). Currently, no resistance has been reported among humans in China. However, during a return visit to the patients in Binchuan, Yunnan (June to July, 2013), one patient was found to have no fever and abdominal pain after taking the drug, but eggs were still discharged in feces. Whether this is drug resistance remains to be investigated. In addition, the understanding of the mechanism underlying the resistance to triclabendazole remains far from complete and unknown (Fairweather, 2005; Fairweather, 2009).

9. Risk factors for fascioliasis in China

Human fascioliasis is not a notifiable and serious parasitic disease in China because most Chinese usually consume cooked food and boiled water, which can kill living metacercaria. Another reason is the limitation of medical detection methods. This disease may be asymptomatic or non-pathognomonic for a long time after infection. Clinicians were not familiar with this parasitic disease, leading to misdiagnosis or missed diagnosis. Hence, the prevalence of human fascioliasis may be underreported comprehensively. Moreover, community-based or epidemiological surveys for fascioliasis were rarely recorded, except for the first important parasitic disease survey and the outbreak in Yunnan.

The following are the risk factors for this disease in China:

Natural factors: (1) infection rate and terrain. China has eight basic terrains, including plains, water networks, swamps, beaches, mountains, hills, basins, and river valleys. The prevalence of *F. hepatica* in water network areas is higher than that in other seven terrains (Xu et al., 2000). (2) Drinking water. It has been cited as the source of human infection, whether directly by drinking or indirectly through contaminated vegetables or kitchen utensils (Chen et al., unpublished). Infection by ingestion of salads contaminated with metacercariae-carrying water used for irrigation has been reported (Ai et al., 2017; Chen et al., 2013). (3) The infection of domestic animal reservoir hosts and intermediate snail hosts. In the humid low-lying swamps, excretion of feces by cattle and sheep pollutes the environment. Also, the existence of members of the family Lymnaeidae increases the susceptibility of livestock while grazing. Among the fascioliasis cases reported in China, most cases were distributed in the south due to the warm and humid climate, which facilitated the growth of freshwater snails and release of cercariae.

Social factors: (1) Economic factors: (a) Social development level. The disease mostly occurs in poor areas, and the infection has a significant negative correlation with the social structure scores of the provinces in China. (b) Population quality. According to the proportion of the population with the secondary school education in each province (autonomous regions and municipalities) in 1990, the whole country (except Taiwan Province) can be divided into the following five parts: the first cultural level was 45% (including Beijing, Shanghai, and Tianjin). The second cultural level was 35% (including Heilongjiang, Jilin, Liaoning, Inner Mongolia, Shanxi, and Jiangsu). The third cultural level was 25% (including Hebei, Shandong, Henan, Anhui, Zhejiang, Jiangxi, Hubei, Hunan, Guangdong, Hainan, Guangxi, Shaanxi, Ningxia, Sichuan, Qinghai, and Xinjiang). The fourth cultural level was 10% (including Gansu, Fujian, Guizhou, and Yunnan). The fifth cultural level was <10% (including Tibet). The infection rate of *F. hepatica* also increased in the first to the fourth part with the decrease in the proportion of the population with the secondary school education level (Xu et al., 2000). (2) Human factors: Eating habits play an essential role in the transmission of this disease. In South China, people prefer consuming freshwater plants, such as *Oenanthe benghalensis*, *Zizania latifolia*, and *Houttuynia cordata*. The reported cases from Yunnan and Fujian had consumed salads made with freshwater plants. Interestingly, the infection rate was higher in women than in men, perhaps because women preferred to eat raw vegetables for maintaining health and lowering body weight. Moreover, women typically prepared meals in households, which might involve freshwater plants potentially carrying metacercariae (Chen et al., 2013). In the fascioliasis outbreak in Yunnan Province, the reform of man-made irrigation systems in Binchuan County led to the increase in the number of lymnaeid snails and the unexpected emergence of human fascioliasis (Chen et al., 2013).

10. Prevention and control of human fascioliasis

China is not endemic for human fascioliasis. The parasite distribution appears to be scattered, and misdiagnosis is common. The following measures should be undertaken to prevent and control this zoonotic parasitic disease:

(1) Reduce misdiagnosis and increase timely treatment. Most cases have acute-onset fever, liver pain, mixed nausea, vomiting, physical examination with or without jaundice, liver percussion pain, leukocytosis and eosinophilia, as well as a low-density shadow in liver CT detection. No pathogen is found in a fecal examination. Many cases were misdiagnosed as cholangitis, liver abscess, amoebic liver abscess, or liver cancer. Moreover, the detection methods often lead to a missed diagnosis. The direct smear method is most often used, with high a rate of missed diagnosis. The Kato–Katz method also has a high rate of missed detection, and washing–sedimentation is not clinically useful. However, the latter has the highest detection rate among all methods. Most patients who visit the hospital during the acute phase of the disease are often misdiagnosed. Immunological methods are better for detecting serum antibodies in patients, but no commercial diagnostic reagent supplier is available in China. Therefore, it is necessary to strengthen research and development. Furthermore, when the fluke was removed by surgery or autopsy from the liver and gallbladder, it was undiagnosed.

(2) Strengthen health education and prevent ingestion of parasites. Prevention and control of human fascioliasis should involve controlling the source of infection, disrupting the route of transmission, treating patients and sick animals, improving sanitation, and other comprehensive measures. Regular inspection, diagnosis, and timely treatment of patients and livestock are crucial to control infection sources. Proper

treatment of human and livestock excrement is essential to prevent water pollution. People should avoid consuming raw water and raw aquatic plants. Improvements in the environment and killing the intermediate host are essential to reduce the chances of human infection.

(3) Strengthen scientific research and focus on technical talent reserves. The current detection methods for *Fasciola* infection include direct smear of stools, washing–precipitation method, or Kato–Katz method to identify eggs. However, in the early stages of infection or the acute phase of the disease, the parasites remain in the sperm stage or in the liver parenchyma so that no egg is discharged. Fast and effective immunodiagnostic methods are required to detect the parasite at this stage. However, no such diagnostic reagent suppliers exist in China.

(4) Medicine storage: China has a shortage of triclabendazole; it is currently purchased from abroad. Hence, it is crucial to strengthen the development and registration of triclabendazole in China.

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Figure legend

Figure 1 The distribution of human fascioliasis cases in China

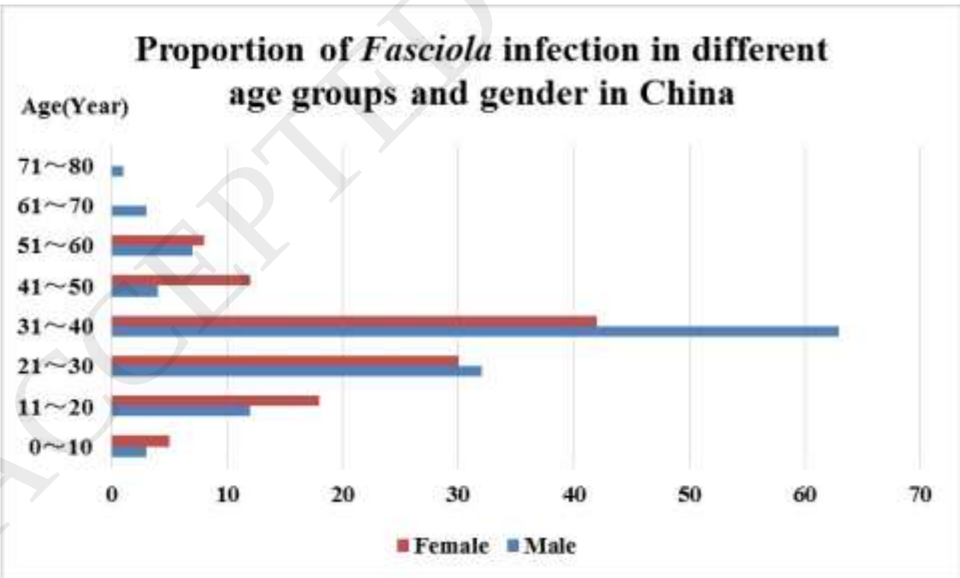

Figure 2 Proportion of *Fasciola* infection by age groups and gender in China

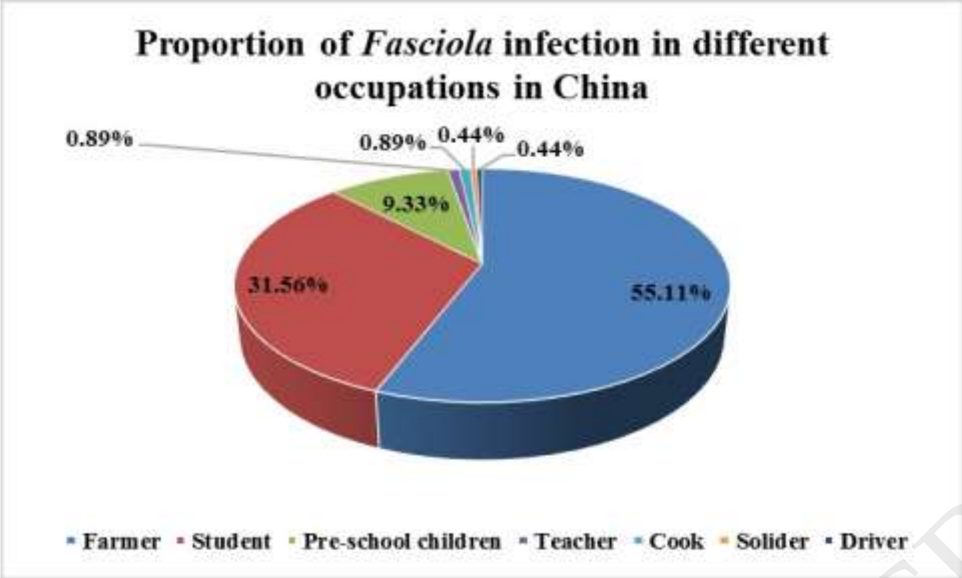

Figure 3 Proportion of *Fasciola* infection in different occupations in China

Table

Table 1 Human fascioliasis cases in China from 1921 to 2018

Table 1
Human fascioliasis cases in China from 1921 to 2018

Province	**Number of reported cases**	**Species of Fasciola**	**Reference**
Fujian	10	*Fasciola hepatica*	Maxwell, 1921; Wang et al., 1997; Zhang et al., 2002; Zeng and Li, 2006; Jiang et al., 2014; Ai et al.,2017; Xu et al., 2000
Guangxi	3	*F. hepatica*	Tan and Zheng, 1997; Xie et al., 2014
Guangdong	2	*F. hepatica*	Lin et al., 1990; Chen et al., 1995
Hubei	37	*F. hepatica*	Shi, 1978; Luo and Tan, 1988; Wu et al., 1994; Chen et al., 1991; Zhang, 1995; Yang, 2006; Du et al., 2010; Qiu et al., 2010; Xu et al., 2000
Hunan	3	*F. hepatica*	Pan and Huang, 1954; Miu and Zhu, 1988; Yu, 1987
Hainan	22	*F. hepatica and F. gigantica*	Wang and Xu, 1995 (*F. hepatica*); Chen et al., 1994; Xu et al., 2000 Xu et al., 1991(*F. gigantica*)
Guizhou	4	*F. hepatica*	Tang, 1954; Lv et al., 1987; Chen et al.(accepted by Tropical Biomedicine); Wang et al., 2014; Zhu et al., 2014
Sichuan	6	*F. hepatica*	Zhang et al., 2002; Wang et al., 2007; Wang and Yang , 2011; Du et al., 2011; Quan et al., 2011; Li et al., 2017
Yunnan	63	*F. hepatica*; *F. gigantica*; Intermediate form; *Fasciola* spp.	*F. hepatica*: He et al., 2009; Hou, et al., 2003; Zhang et al., 2005; Fu and Ding, 2004; Zhang et al., 2004; Tang et al., 2005; Huang et al., 2006; Fan et al., 2006; Huang et al., 2009 *F. gigantica*: Chen et al., 2013; Dong, 2016; Wang et al., 2015; Zhang et al., 2012; Hu and Ding, 2016 Intermediate form: Zhang et al., 2018 *Fasciola* spp.: Wen et al., 2009

Jiangxi	53	*F. hepatica*	Zhang et al., 2002; Xu et al., 2000
Anhui	2	*F. hepatica* and *F. gigantica*	Wang, 1984; Xu et al., 2000
Shandong	4	*F. hepatica*	Liu and Han, 1989; Wang et al., 1981; Dong et al., 2000; Chen et al., 1997; Zhang et al., 1999
Henan	5	*F. hepatica*	Wu et al., 1982; Zhang et al., 1983; Yao et al., 1989; Xu et al., 2000
Hebei	31	*F. hepatica and F. gigantica*	*F. hepatica*: Chen and Mao, 1980; *F. hepatica and F. gigantica:* Li et al., 2017
Gansu	49	*F. hepatica*	Zhang and Chen , 1991; Zhang et al., 1991
Liaoning	5	*F. hepatica*	Lu and Li, 1965; Chen, 1984; Zheng et al., 1986; Guo and Zhou, 1989
Jilin	3	*F. hepatica*	Huang, 1978 a, b
Inner Mongolia	3	*F. hepatica*	Sun and Chai, 1983; Cheng, 1981; Sun and Chai, 1981; Duan and Wei, 1988
Xinjiang	1	*F. hepatica*	Xu et al., 2000
Total	**306**		

Table 2 Proportion of *Fasciola* infection by age groups and gender in China

Table 2 Proportion of *Fasciola* infection by age groups and gender in China

Age (year)	**Male**		**Female**	
	No. of infection	**Proportion (%)**	**No. of infection**	**Proportion (%)**
0～10	3	2.4	5	4.35
11～20	12	9.6	18	15.65
21～30	32	25.6	30	26.09
31～40	63	50.4	42	36.52
41～50	4	3.2	12	10.43
51～60	7	5.6	8	6.96

61～70	3	2.4	0	0
71～80	1	0.8	0	0
Total	**125**		**115**	
χ^2 **=304.13**				
P **= 2.2×10**$^{-16}$				

Table 3 Proportion of *Fasciola* infection in different occupations in China

Table3 Proportion of *Fasciola* infection different occupations in China

Occupation	No. of infection	Proportion (%)
Farmer	124	55.11
Student	71	31.56
Pre-school children	21	9.33
Teacher	2	0.89
Cook	2	0.89
Solider	1	0.44
Driver	1	0.44
Total	225	
χ^2 **=436**		
P **= 2.2×10**$^{-16}$		

Table 4 Proportion of *Fasciola* infection in 37 nationalities, China

Table 4 Proportion of *Fasciola* infection in 37 nationalities, China

Nationality	No. of infection	Proportion (%)
Han	166	93.79
Bai	8	4.52
Li	1	0.56
Miao	1	0.56
Uygur	1	0.56
Total	177	
χ^2 **=603.31**		
P **= 2.2×10^{-16}**		

Table 5 Symptoms of human fascioliasis in China

Figure 5 Main symptoms of human *Fasciola* infection

Symptoms of human *Fasciola* infection	**No. of cases**
abdominal pain and indigestion	86
fever	63
hepatomegaly and hepatic abscess in B-ultrasound, CT, and MRI	57
increased number of eosinophils	54
abnormal liver function	30
ascites	19
yellowing of the skin or sclera	14
liver damage in pathological section	11
pleural effusion	10
cough	10
diarrhea	7
headache	3
ectopic parasitism	2