Review Article

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Current Understanding on Opisthorchiasis: A Neglected Tropical Helminthic Zoonosis

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Abstract

Helminthic zoonoses are significant from public health and economic point of view. Opisthorchiasis, caused by liver flukes from the Opisthorchiidae family, represents a significant global public health challenge, particularly in Southeast Asia. With an estimated 80 million individuals at risk, the primary transmission route is the consumption of raw or undercooked freshwater fish harboring metacercariae. This review provides a comprehensive overview of the etiology, life cycle, transmission dynamics, clinical manifestations and epidemiological patterns of opisthorchiasis. The infection is primarily linked to severe hepatobiliary complications, including cholangiocarcinoma, classified as a Group 1 carcinogen by the International Agency for Research on Cancer. Current diagnostic methods rely on stool examination for eggs and praziquantel remains the treatment of choice. Given the intricate life cycle involving freshwater snails and fish, effective control measures must focus on public health education, safe food practices and enhanced surveillance.

Keywords: Foodborne infection, Opisthorchiasis, Transmission, Zoonotic disease

Introduction:

Parasitic diseases caused by protozoa, cestodes, nematodes, trematodes and ectoparasites are implicated as the cause of morbidity as well as morbidity in humans and animals throughout the world (Pal, 2007; Pal et al., 2020; Pal et al., 2022; Pal et al., 2023). Opisthorchiasis is a significant foodborne parasitic disease caused by liver flukes in the Opisthorchiidae family. These parasites, particularly *Clonorchis sinensis*, *Opisthorchis viverrini* and *Opisthorchis felineus*, pose substantial public health concerns globally, affecting both developing and developed countries. Approximately, 80 million people are at risk of infection. The transmission of this zoonotic disease occurs primarily through the consumption of raw or undercooked freshwater fish harboring infectious larvae (Pal et al., 2020). Historically, *Clonorchis sinensis* was first discovered in 1874 in India (McConnell, 1875); *Opisthorchis felineus* was identified in cats and humans in Russia by 1884 (Cox, 2002); and *Opisthorchis viverrini* was documented in civet cats and later in humans in Thailand in 1915 (Sripa et al., 2012a). These liver flukes can cause severe infection, leading to chronic liver diseases and even cancer in endemic regions (Torgerson et al., 2015; WHO, 2023).

The three liver fluke species (*Clonorchis sinensis*, *Opisthorchis viverrini* and *Opisthorchis felineus*) have intricate life cycles involving multiple hosts. Their life cycle includes two intermediate hosts: freshwater snails and freshwater fish, where the parasites undergo asexual reproduction, followed by a definitive host (humans or certain animals), where sexual reproduction occurs (Qian and Zhou, 2021). These liver flukes infect various natural hosts, including humans and animals such as cats, cetaceans, civets, dogs, foxes, pigs and wild boars. The ability of these parasites to infect multiple species and their complex life cycles contribute to their persistence and spread in endemic regions (Pal, 2007).

Human infection with *Opisthorchis felineus* occurs through consuming raw or undercooked freshwater fish harboring the parasite's metacercariae. Once ingested, the larvae develop and migrate to the bile ducts through chemotaxis, where they mature into adult worms. These adult flukes feed on the biliary epithelium and bile contents. They shed eggs that pass through the gastrointestinal tract and are excreted with the feces into the external environment.

In freshwater, snails from the family *Bithyniidae* ingest the eggs and within the snail, the miracidia hatch and undergo several developmental stages, eventually maturing into cercariae. These cercariae are released from the snails and penetrate freshwater fish, where they encyst in the skin or flesh, becoming the infective metacercariae. This life cycle is a key factor in the transmission of *Opisthorchis felineus* and the continuation of parasitic zoonosis in endemic areas (Sripa et al., 2012b).

Opisthorchis felineus is recognized as the species with the highest zoonotic potential within the Opisthorchis genus, posing a significant risk even in environments

with high hygienic standards and minimal freshwater contamination by human feces (Saltykova et al., 2014). The morbidity associated with opisthorchiasis is primarily hepatobiliary, with conditions such as bile duct fibrosis, cholangitis, obstructive jaundice, hepatomegaly, abdominal pain and nausea (Keiser and Utzinger, 2009).

Of particular concern is the link between *Opisthorchis viverrini* and *Clonorchis sinensis* infections and the development of cholangiocarcinoma, a highly fatal form of bile duct cancer. Studies in animal models and epidemiological data have confirmed this association, classifying these parasites as Group 1 carcinogens by the International Agency for Research on Cancer (De Martel et al., 2012; Thunyaharn et al., 2013). The growing public health concern surrounding opisthorchiasis highlights its status as an emerging foodborne zoonosis with significant implications for both human and veterinary health. The current review delineates the impact of opisthorchiasis on global health, emphasizing the need for heightened awareness, surveillance and control measures.

Opisthorchiasis:

Etiology:

Opisthorchiasis is caused by trematodes, including Opisthorchis novorca, Opisthorchis tenuicollis and most notably Opisthorchis viverrini (Southeast Asian liver fluke) and Opisthorchis felineus (cat liver fluke). These liver flukes can cause serious health complications, particularly affecting the liver and bile ducts, as they complete their life cycle within human hosts (Pal, 2007). Humans acquire the infection by consuming raw or undercooked freshwater fish containing the infectious metacercariae, the encysted larval stage of the parasite (MSD, 2023).

Life cycle of parasitic Opisthorchis:

The life cycle of *Opisthorchis* involves multiple hosts with complex developmental stages. Adult flukes lay fully developed eggs, which are excreted in the feces of the definitive host. When these eggs are ingested by a suitable snail (the first intermediate host), the miracidia are released and undergo several developmental stages: sporocysts, rediae and cercariae. The cercariae then leave the snail and penetrate a freshwater fish (the second intermediate host), where they emerge as metacercariae, typically within the muscles or under the scales (CDC, 2023).

Mammalian hosts, including cats, dogs and fish-eating mammals such as humans, become infected by consuming undercooked or raw fish containing metacercariae. Once ingested, the metacercariae excyst in the duodenum and travel through the ampulla of Vater into the biliary ducts. There, they mature into adult flukes within 3 to 4 weeks. The adult flukes (Opisthorchis viverrini: 5–10 mm long by 1–2 mm wide; Opisthorchis felineus: 7–12 mm long by 2–3 mm wide) attach to the mucosa of the biliary and pancreatic ducts, where they reside and continue their reproductive cycle by laying eggs. This multi-host life cycle is crucial for the transmission and persistence of Opisthorchis in endemic regions, underscoring the importance of controlling snail and fish reservoirs to break the cycle of infection (CDC, 2023).

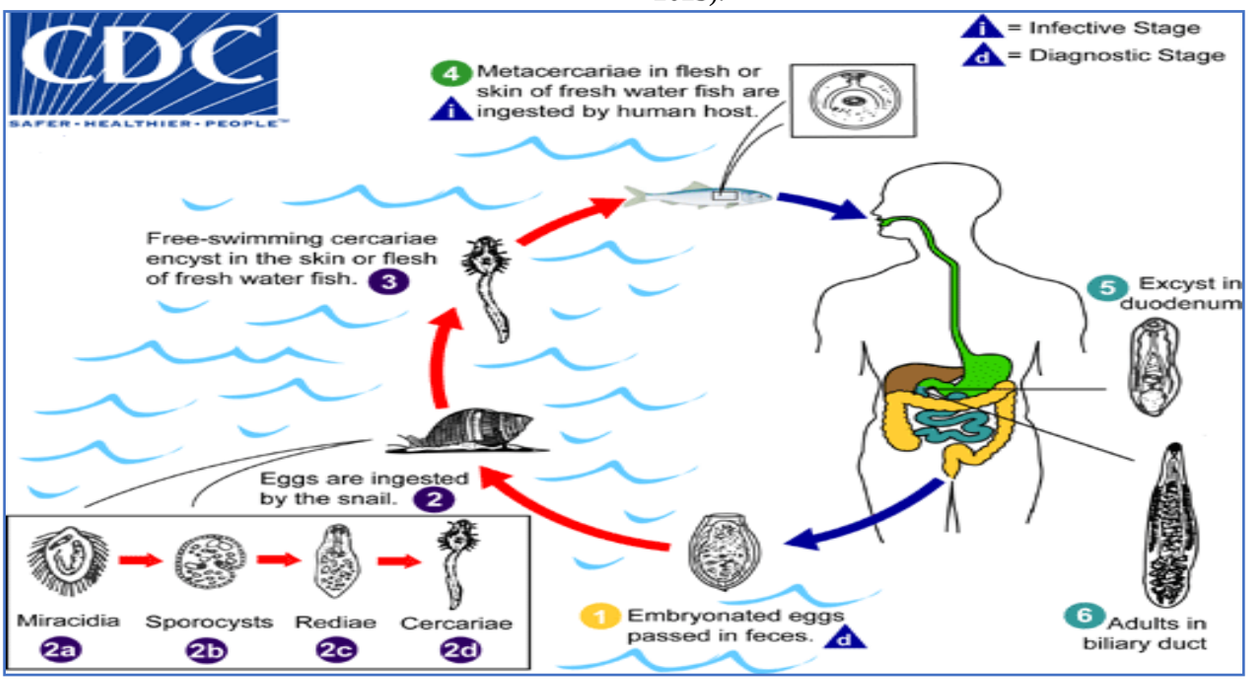

Figure 1: Life cycle of *Opisthorchis* (CDC, 2023)

Transmission:

The source of opisthorchis infection is exogenous, with ingestion of contaminated fish being the primary mode of transmission. Humans typically acquire the infection by consuming raw or undercooked freshwater fish containing the infective metacercariae. In many cases, the infection remains asymptomatic (Pal et al., 2020). However, consuming sub-dried or slightly salted fish may also lead to infection, as these preservation methods do not effectively eliminate the parasite's infective stage (Pal, 2007).

The transmission cycle involves freshwater snails as the first intermediate host, followed by freshwater fish as the second intermediate host. Humans and other fish-eating mammals, such as cats and dogs, become infected by eating fish that harbor the metacercariae. These animals also act as reservoirs, helping to maintain the transmission cycle of opisthorchis (Pal, 2007; CDC, 2018).

Symptoms:

In humans, *Opisthorchis* infections can range from asymptomatic cases to more severe clinical manifestations. Symptoms may include fever, cephalalgia (headache), chills, flatulence, diarrhea, jaundice (icterus), hepatomegaly (enlarged liver) and skin eruptions (Pal, 2007). Notably, *Opisthorchis viverrini* has been strongly linked to cholangiocarcinoma (bile duct cancer). A study conducted in Thailand by Parkin et al. (1991) found that 75% of cholangiocarcinoma cases in 103 patients were attributable to *Opisthorchis viverrini* infection. However, more comprehensive studies are needed to definitively establish the parasite's role in causing this fatal cancer.

In animals, affected species may exhibit symptoms, such as fever, diarrhea, jaundice and carcinomatous growths in the lymph nodes, liver and lungs (Pal, 2007).

Epidemiology:

Opisthorchiasis has been reported in various countries, including China, Germany, India, Japan, Laos, Poland, Russia and Thailand (Pal, 2007). Epidemiological studies primarily focus on infections caused by *Opisthorchis viverrini* and, to a growing extent, *Opisthorchis sinensis*. Comprehensive data are being collected in Southeast Asia, particularly in Thailand, Laos, Cambodia and Vietnam, to map endemic regions and understand the burden of morbidity associated with these infections (Petney et al., 2013).

Peter Odermatt from the Swiss Tropical and Public Health Institute has emphasized the significance of opisthorchiasis in rural areas of these countries (Sithithaworn et al., 2012). In Laos, the infection is especially widespread, with over half of the population affected and in highly endemic villages, as many as 70% of residents are infected. Studies have shown that in some Lao villages, 50% of the population is infected with *Opisthorchis viverrini*, with infection prevalence increasing with age (Forrer et al., 2012).

A strong correlation has been observed between fish consumption and the prevalence of *Opisthorchis viverrini* in rural Lao communities, where up to 23 species of fish can carry the infective metacercariae. In some villages, 60% of certain fish species are found to be infected, underscoring the role of local dietary habits in the transmission of this parasitic zoonosis (Sayasone et al., 2007).

Studies have shown that domestic animals, such as cats and dogs, which often cohabit with humans, can play a significant role in the transmission of *Opisthorchis viverrini*. Around 30% of these animals were found to be infected with the parasite, highlighting their contribution to the intensification of transmission to humans. This zoonotic risk is exacerbated by cultural practices, particularly the consumption of raw fish dishes, which remains a deeply ingrained habit in many communities. This presents a major public health challenge in regions where *Opisthorchis viverrini* is endemic, as it sustains the cycle of infection between humans and animals (Vinogradov et al., 2013).

Diagnosis:

Diagnosing liver fluke infections, including opisthorchis, involves examining not only humans but also intermediate and animal hosts (Qian et al., 2016; Saijuntha et al., 2018). In humans, microscopic detection of fluke eggs in fecal samples using the sedimentation method is a standard diagnostic tool for opisthorchiasis (Pal, 2007). Molecular approaches, such as the polymerase chain reaction (PCR), have also been explored for detecting *Opisthorchis felineus* in hospital-based studies in Europe, where infections are sporadic (Pozio et al., 2013). Additionally, Wongratanacheewin et al. (2002) demonstrated that PCR can effectively detect *Opisthorchis viverrini* in human stool specimens, suggesting the potential for using molecular tools to diagnose infections from other opisthorchis species.

Serologic tests, including the enzyme-linked immunosorbent assay (ELISA), can aid in diagnosing opisthorchis infections by detecting specific antibodies (Pal, 2007). Serological markers, such as eosinophilia (up to 40%), elevated sedimentation rates, increased liver enzymes and specific antibodies (IgM, IgG and IgE), are valuable indicators. Moreover, sonography is particularly helpful in detecting early carcinoma changes and bile duct cancer associated with opisthorchis infections. This combination of diagnostic methods enhances the

detection and monitoring of opisthorchiasis in both clinical and epidemiological settings (Garedaghi, 2020).

Treatment:

Praziquantel is the recommended drug for treating liver fluke infections, including those caused by opisthorchis. It is a broad-spectrum, safe and highly effective anthelmintic for trematode and cestodes infections (Chai, 2013). The standard dosage for humans is 25 mg/kg administered orally three times a day after meals. The World Health Organization (WHO) suggests either this regimen for two to three consecutive days or a single dose of 40 mg/kg (WHO, 2022). High efficacy has been demonstrated with the 25 mg/kg dose three times daily over two to three days, though for ease of administration, a total dose of 75 mg/kg divided into three doses in one day, or a 50 mg/kg loading dose followed by 25 mg/kg later in the same day, is often used (Qian et al., 2022).

In animals, hexachlorophene may be tried as an alternative treatment (Pal, 2007), though praziquantel remains the primary drug of choice due to its effectiveness in controlling liver fluke infections across species.

Prevention and Control:

Prevent contamination of fish ponds by feces, sanitary disposal of faecal and other waste materials, freezing of fish at -10 ℃ for 5 minutes for killing metacercariae, dipping the fish in a 15% salt solution for 3 days to destroy the infective stage of parasites (metacercariae), avoiding consuming raw or uncooked fish and stopping to feed raw fish to carnivores are some of the measures that will mitigate the incidence of opisthorchiasis (Pal, 2007). In addition, health education of people in endemic areas about the hazards of eating raw fish is highly imperative (Pal, 2007). Consumption of thoroughly cooked fish, protection of water bodies, decontamination of sewage, dehelminthization of domestic carnivores, proper washing of hands and kitchen utensils after processing raw fish and education of the people about the hazards of eating raw or undercooked fish are the practical strategies for the prevention of this emerging zoonotic helminthiasis (Pal et al., 2020). It is pertinent to mention that the improvement of hygienic defecation can be very helpful in the interruption of the transmission cycle.

Conclusion:

Opisthorchiasis is a significant foodborne zoonotic disease that poses considerable health risks globally, particularly in endemic regions. The complex life cycle of the liver flukes, primarily *Opisthorchis viverrini* and *Opisthorchis felineus*, contributes to the disease's persistence and transmission. The associated morbidities, particularly hepatobiliary complications and the risk of cholangiocarcinoma, highlight the urgent need for effective public health interventions. Despite the availability of treatment options like praziquantel, the ongoing transmission of opisthorchiasis indicates that preventive measures are insufficiently implemented in many affected communities.

Based on the above conclusion, the following recommendations were forwarded:

- ✓ Educational campaigns should emphasize safe food handling practices and the importance of cooking fish thoroughly to eliminate metacercariae.
- ✓ Establish robust surveillance systems to monitor the prevalence of opisthorchiasis in both human and animal populations.
- ✓ Implement stringent regulations for fish preparation and sale, including guidelines for freezing or salting fish to kill parasites before consumption.
- ✓ Reduce the risk of freshwater contamination by promoting proper sewer disposal methods and improving sanitation facilities in endemic areas.

There is an urgent need for increased awareness and intervention strategies to mitigate the health burden associated with this neglected tropical disease.

Conflict of interest:

There was no conflict of interest among the authors.

Contribution of authors:

All the authors contributed equally in the preparation of the manuscript.

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