# A Review on Paragonimiasis and its Differential Diagnosis Technique

**Vekutolu Resuh[1], Avolu Kotso[1], Viswedenu Kera[1], Lipoksenla Walling[1], Ibasiewdor Mawlein[2] and Wankupar Wankhar[3]***

[1]Department of MLT, Assam down town University, Guwahati, Assam, India.
[2]Department of Operation Theatre Technology, Royal School of Medical and Allied Sciences, The Assam Royal Global University, Guwahati, Assam, India.
[3]Department of Dialysis, Assam down town University, Guwahati, Assam, India.

https://dx.doi.org/10.13005/bbra/3204

(Received: 30 August 2023; accepted: 14 December 2023)

**This review highlights the existence of Paragonimus (PRG) and how they are mistaken for Tuberculosis (TB) during diagnosis. PRG is a parasitic lung fluke (flatworm) that infect the lungs, human serves as the first hosts, crabs, crayfish, and snails as the second intermediate hosts. The north-eastern states of India are endemic to PRG and infection is acquired by consuming uncooked or partially cooked crustaceans. Due to their similar clinical presentation to TB, PRGs are usually misdiagnosed, leading to delayed treatment. Ziehl-Neelsen (ZN) stain, conventional wet film for staining the sputum, pleural fluid, and stool, and lung biopsy are different laboratory tests to determine PRG infection. In addition, efficient technique that can aid diagnosis are immunological assays, like Enzyme-linked immunosorbent assay (ELISA), dot-ELISA, complement fixation test (CFT), intradermal test (ID), Western blot, immunodiffusion and indirect haemagglutination test (IHA). In India, PRG infection is most likely to persist until medical professionals and governing bodies raise awareness to implement adequate management measures.**

**Keywords:** Immunodiagnosis; Paragonimus westermani; Praziquantel; Tuberculosis; Triclabendazole.

Paragonimiasis (PRG) is a food-borne parasitic infection caused by the genus Paragonimus and it mimics pulmonary tuberculosis. This parasite usually requires diagnostic differentiation from the tuberculosis[1]and carcinoma[2]PRG is often caused by *Paragonimus westermani*(*P.westermani*) and they belong to Trematodes and are also called flukes that include the helminths. Gibson and Bray (1994) proposed a systemic classification of trematodes. Trematodes belong to the phylum Platyhelminths, class Trematoda or Dignea. *P.westermani* is classified as a lung trematode (fluke)[3].There are more than 50 distinct species in the genus Paragonimus, and 9 species are known to infect people. Asia's most common species of human pathogen, *P. westermani*, is well recognised[4].PRG poses a risk to more than 293.8 million persons worldwide[5]and regions of South America, Asia, and Africa are plagued by this disease except Australia and Antarctica[6].

Multiple organ system infections have intricated variable clinical presentations. The

*Corresponding author E-mail: wankuparwankhar@gmail.com

"tunnel" sign and serpentine deformations in the brain, spleen, liver, and lung are significant imaging signs of the disease[7].Due to the clinical similarities between PRG and tuberculosis(TB), a differential diagnosis is needed.Lung biopsy can be used in conjunction with microbiological diagnostic methods to confirm PRG diagnosis[8]. Both TB and PRG have been identified in the north-eastern states of India, and multiple endemic foci have been located. The frequency of PRG in the general population varied from 7 to 15% and it was around 50% in TB patients. Nevertheless, PRG is frequently underdiagnosed[9].

## MATERIALS AND METHODS

During the review process, electronic databases such as Scopus, Google Scholar, PubMed, Web of Science, and Science Direct were accessed. Search terms for PRG research and review papers included lung fluke, Paragonimus in Northeast India, P. westermani, praziquantel, and triclabendazole.

## DISCUSSION

### Historical review of *Paragonimus*

Paragonimus ova were first discovered in the stool and sputum of a Chinese patient in Mumbai, 1919 and it was believed that the infection may have originated outside India. Singh et al. (1981) reported the first instance of paragonimiasis in Manipur. Epidemiological survey of PRG was first carried in the east district of Manipur, India between 1986 and 1987. In November 1990, Manipur hosted the first Indo-Japan joint research on Paragonimus and paragonimiasis. This research focused on the morphological characterisation, pathobiology, and life cycle of Paragonimus species. This has led to the identification of crustaceans as second intermediate hosts, the structural features of Paragonimus species from Manipur and the detection of endemic paragonimiasis sites[4].The primary cause of human paragonimiasis in these states has been determined to be *P.heterotremus*[6]. The clinical manifestations such as *tightness and pain in the chest, coughing up blood-stained sputum or haemoptysis and dyspnoea, can often misdiagnosed as tuberculosis*. The differential diagnosis such as the radiologic findings, Dot-immunogold filtration assay (DIGFA), Intradermal test and ELISA were used for differential diagnosis of paragonimiasis[4].

### Life Cycle

To complete the life cycle, mammals act as a definitive host for the Paragonimus species where sexual reproduction occurs, snails and crustaceans serve as the intermediate hosts [10].

### First intermediate hosts

The life cycle begins with the generation and release of fertilised, operculate ova from sexually developed adult trematodes that are present in the lungs of the host. The eggs are ingested and subsequently either released or excreted in the stool after being coughed out [1].The first intermediate host (the snail) is invaded when Paragonimus eggs produced in the sputum or stool of definitive hosts hatch and release ciliated miracidia. In the snail, the miracidium changes into a mother sporocyst[4]. The sporocysts, are simple sac-shaped structures containing germ cells, create the first generation of rediaea larvae phase which develops in the

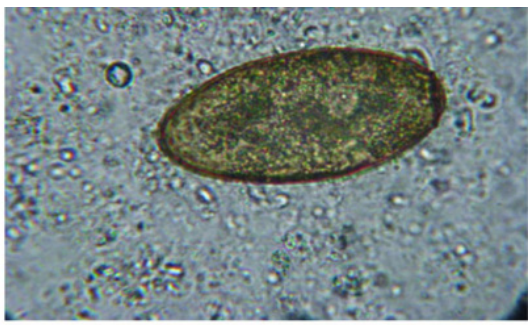

**Fig. 1.** Direct wet mount of sputum showing operculated egg of *P. westermani* at 40X.[19]

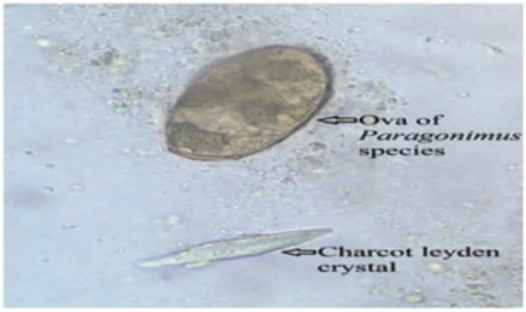


**Fig. 2.** Charcot-Leyden crystals seen in the pleural fluid.[1]

intermediate host asexually. Similar germinal cells are present in both the first and second generations of rediae, which are then responsible for producing the stumpy-tailed cercariae that eventually emerge from the snail [10].As a result, in the snail, it takes between 9 and 13 weeks for miracidium to grow into cercariae. An appropriate crustacean host is where the cercariae continue to develop[4].

**Second intermediate hosts**

The second intermediate host for the cercaria are snails and Crustaceans (Anterior stylet and a stumpy tail) they are infected by ingestion of infected snail or by direct penetration of the cercaria[10].Metacercariae from different Paragonimus species may coexist in a single crab. The cercariae transformed into metacercariae and stayed encysted in the crab host's skeletal muscles, intestines, gills, liver, and possibly heart. The metacercariae must be ingested by an appropriate final mammalian host in order for the life cycle to continue[4].

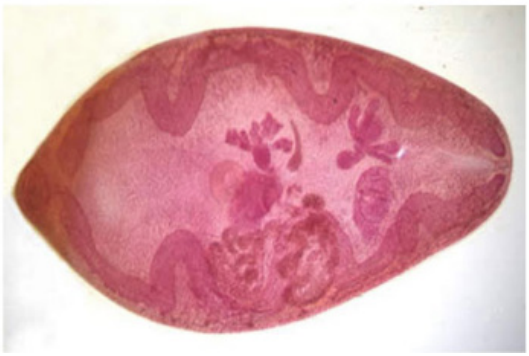

**Fig. 3.** *P. Westermani* adult taken from a lung biopsy specimen.[3]

**Definitive hosts**

The metacercariae excyst larvae, which were ingested by the definitive hosts, penetrate the intestinal wall of the small intestine and travel 3–6 hours to the abdominal cavity. The larvae subsequently migrate into the abdomial cavity through the diaphragm leaving back of hemorrhagic and rusty-brown inflammatory exudates [4].Following this, the worms enter the lung parenchyma to develop into matured worms that lay ova. The unembronated ova damage the bronchial wall, causing to cough up sputum that is laden with ova or, if consumed, excreted through stools. Consequently, the life cycle continues [1].

**Route of exposure**

PRG is a significant contributor to lung disease on a global scale. When freshwater crabs or crayfish are consumed raw or improperly prepared, humans become infected. An alternate way to contract infection is through the consumption of raw flesh from a paratenic animal host, in which

**Table 1.** Common medication for Paragonimiasis

| Name of the drug | Mode of action | Side Effects | Reference |
|---|---|---|---|
| Praziquantel | The permeability of the worm musculature to mono and divalent cations, especially $Ca^{2+}$, is rapidly increased by praziquantel. Muscle contraction is brought on by a rapid increase in $Ca^{2+}$ and takes place within 10-20 seconds, causing the flukes to become spasticly paralysed. | Abdominal pain, headache, dizziness, and diarrhea,Allergic reactions to praziquantel are very rare | 26,27 |
| Triclabendazole | The tegument of immature and adult worms absorbs triclabendazole and its active metabolites (sulfoxide and sulfone), which causes a decrease in resting membrane potential, suppression of tubulin function, and inhibition of protein and enzyme synthesis. These changes in metabolism are associated with spermatogenesis and vitelline cells being inhibited, as well as alteration of the surface and ultrastructure. | Biliary colic, include abdominal, hypochondrial and epigastric pain, often accompanied by sweating, in some cases with associated obstructive jaundice and elevations in serum levels of hepatic enzymes, most commonly alkaline phosphatise. | 28,29 |

matured worms frequently live in groups in lung cysts and release their eggs through air passages [11].Additionally, the parasite migrates from the gut to the lungs and finally to the brain, skin, and subcutaneous tissues[12].

**Clinical Manifestations in humans**

Human with paragonimiasis typically experienced symptoms of cough concurrently with the presentation of hemoptysis, chest discomfort, dyspnea with occasional fever and eosinophilia[1].One to two months or more may be needed for incubation. Clinical manifestation of a modest bronchopneumonia, bronchiectasis, pneumonitis, or pleural effusion may also accompany paragonimiasis[13].Common symptoms of persistent infections include weakness, weight loss, anaemia, and fever. In general, lung infections have a high rate of morbidity and a low rate of fatality, unless they are compounded by infections of important organs like the heart and brain. From a clinical perspective, the three types of paragonimiasis are: pulmonary pleuropulmonary, and extra-pulmonary. Contrarily, Paragonimiasis has been divided into three categories by Procop et al. (2009): Ectopic Paragonimiasis, Chronic Pleuropulmonary Paragonimiasis, and Acute Paragonimiasis[4].In India's north-eastern states, paragonimiasis and tuberculosis are widespread and paragonimiasis is infrequently included in the distinctive diagnosis of TB. Due to its similarity to the clinical presentation of TB, diagnosis is typically delayed [14].Paragonimiasis can be misdiagnosed and neglected and often treated with anti-TB medication when it mimics smear-negative pulmonary TB, especially in high-prevalence countries[30].

**Laboratory diagnosis**

Diagnosis is based on microscopic demonstration of *Paragonimus* eggs in sputum, pleural fluid, and stool or by serological test. The presence of distinctive ellipsoidal, golden-brown, operculated paragonimus eggs in body fluids, sputum or faeces allows for the precise diagnosis of paragonimiasis. A mature worm may occasionally be discovered in biopsy samples, autopsies, pleural fluid, or sputum[15].

**Sputum**

Ziehl-Neelsen (ZN) stain is a popular stain, for identifying Paragonimus eggs in sputum. When conventional Wet film (WF) and ZN stains are compared, the ZN Stain examine is preferred since it completely excludes the possibility of TB transmission during the standard WF examination for paragonimiasis. According to Slesak et al. (2011), the ZNS approach provides potential for paragonimiasis epidemiological research. Hence, sputum is frequently screened for Paragonimus eggs [16].On the contrary, a direct wet mount fecal test for the parasite egg is ideal for specimens of sputum collected in the early morning. In most cases, blood-stained or the rusty brown sputum have many Paragonimus eggs and Charcot-Leyden crystals [4].

**Pleural Fluid**

Approximately 10% of pleural effusion cases may possibly contain paragonimus eggs in the centrifuged deposit of pleural fluid[4].Pleural fluid is the most suitable specimen to determining if anti-Paragonimus-specific antibody is present. The fibrous tissue removed during decortication may contain several eggs and they are typically not visible in the pleural fluid.The pleural fluid usually consists of leukocytes, eosinophils, and Charcot-Leyden crystals that are birefringent and easily visualised with plane-polarized [10].In PRG, pneumothoraxor pleural effusion is a significant finding [17].

**Stool**

The formalin-ether sedimentation method uses two to three stool samples taken on consecutive days. In children, the sputum samples likely negative for eggs, stool examination for Paragonimus eggs is often suggested[4].A single stool test has sensitivity between 11 to 15%, which is lower than sputum test sensitivity. However, the sensitivity increases to 25% when three stool samples are examined[10]. In addition, it is also possible to observe ova of Trichuris trichiura and Enterobius vermicularis in stools samples[18].

**Biopsy**

The ova of PRG are far more likely to be discovered than the adult worm during histological and cytologic processing of respiratory samples[10]. However, in a carefully dissected cystic lesion or nodular we may find immature adult helminths. As an alternative, a histological analysis will also reveal eosinophils, inflammatory cells, fibro collagenous tissue, sections of the helminths, and deformed eggs[4].Following the failure of histological and cytologic procedures, a lung

biopsy can be performed to ensure a diagnosis of PRG [14].

**Immunodiagnosis**

The most accurate technique of diagnosis is a serological test. Clinical samples from patients with early-onset (asymptomatic), chronic (inactive), or ectopic paragonimiasis may not show eggs. However, serological techniques are unable to distinguish between serum antibodies for previous and present infections, which frequently linger afteranti-helmintic therapy. Different serologic assays have been established, and they differ slightly from one another in terms of their sensitivity and specificity. Most serologic assays are extremely sensitive, frequently surpassing 95% sensitivity[10].Numerous immunological assays have been examined, including, Enzyme-Linked Immunosorbent Assay (ELISA), Indirect Haemagglutination Test (IHA), Complement Fixation Test (CFT),Western blot, Intradermal (ID) test, and Immunodiffusion[5].Based on these, the immunoserologic enzyme-linked immunosorbent assay test, which detects IgG antibodies specific to paragonimus, is generally regarded as sensitive and precise in the examination of paragonimiasis. IHA is a quick and sensitive test that revealed a sensitivity of 88 per cent in the diagnosis of *P.heterotrema*. CFT is used to confirm cases of ID positivity and to diagnose current infections. Western Blot is for sero-diagnosis of human *P. heterotrema*and specific diagnosis of PRG. ID test is used to distinguished pulmonary PRG from pulmonary tuberculosis.Immunodiffusion are accurate test and can be used for speciation by demonstration of specific precipitin bands[4].The availability of serologic tests is constrained, and given the rarity of the condition, they are frequently used as confirmation testing after pathology has identified the organisms[19].A rapid test kit called dot-immunogold filtration assay (DIGFA), can detect anti PRG antibodies in less than 10 minutes. The kit's sensitivity and specificity were up to 99 and 92 percent, respectively [20].

**X-rays and other imaging technique**

The life cycle of PRG through human infection result in a variety of imaging findings that are non-specific and diverse. Common features include Ground-glass opacity(GGO), migration track, worm cyst, nodule, pleural effusion, pleural thickening on chest CT scans, ring-enhancing lesions on brain MRI. In computerised tomography (CT) scans features like mixed density lesions or patchy low, serpentine lesions or conglomerated small cystic and migration worm cyst and migration track [21].Pulmonary parenchymal abnormalities and bilateral effusion in chest radiography we also detected[22].In the cerebral cortex, clusters of numerous ring-structure shadows known as "grape cluster," "soap bubble appearance," or "isodense lesion" that resemble tuberculomas can be seen on brain scans using and MRI in individuals with cerebral paragonimiasis. In comparison, CT scans was a more effective method for observing lung lesions than unlike the chest X-ray[4].

**Treatment**

Early diagnostic and efficient treatment is essential to prevent the onset of paragonimiasis. In pulmonary paragonimiasis, praziquantel (325 mg/kg/d for 3 days) cleared ova from sputum after 90 days medication. Triclabendazole at 5 mg/kg/d is necessary to effectively remove ova from sputum. World Health Organization (2012) recommended PZQ and TCZ medications for treatment of human paragonimiasis**(Table: 1)**. PZQ has also been approved by the American Academy of Paediatrics as the first line of treatment for paragonimiasis. The recommended course is a total of 150 mg/kg administered orally three times per day for three days [23].However, PZQ has side effect which causes abdominal pain, headache, dizziness, and diarrhea [26]. On the other hand, TCZ causes side effect such as biliary colic, which include abdominal, hypochondrial and epigastric pain, often accompanied by sweating.[28].Depending on the clinical and epidemiological setting, so far it has shown that if one medication is ineffective, the other has proven to be effective and vice versa [24].

**Prevention and control**

Avoiding non-boiled stream water, raw or undercooked river crabs or crawfish, pickled or liquor-soaked crabs, and non-cooked or undercooked river water, paragonimiasis can be avoided. Patients who exhibit symptoms of suspected paragonimiasis need to receive active [24].Mass drug administration, increased public knowledge, and health education are frequently mentioned in paragonimiasis prevention techniques[25].Although vaccination is a possibility,

it is unlikely to happen given the more urgent demand against illnesses that are more common and their impact on the economy[10].

## CONCLUSION

PRG is a foodborne lung infection common in northeast, India, and it was first documented in Manipur. The cause of paragonimiasis has been associated to be P. heterotremus. PRG resemblance to pulmonary tuberculosis in clinical presentation,Chest radiographs shows definitive role in differentiating one disease from the other,which results in misdiagnosis.Examination of eggs in sputum and stool is the most routine diagnostic protocol. However, the most accurate diagnostic technique is the immunodiagnostic test. PRG infection can be prevented by avoiding uncooked meals and thoroughly preparing food can help prevent the disease. Praziquantel is the preferred medication for paragonimiasis, while triclabendazole is also an option. PRG infection is most likely to persist until there is increased public knowledge on the effects of consuming uncooked crabs and crayfish, and awareness among medical professionals and governing bodies to implement adequate management measures.

## ACKNOWLEDGEMENT

The author is grateful to Assam down town University for the assistance provided during the study.

**Conflict of interest**

The authors affirm that they have no conflict interests to disclose.

**Funding source**

There are no funding sources.

**Authors' contributions**

Vekutolu Resuh: Writing – original draft, Investigation, Methodology, Avolu Kotso: Data curation; Viswedenu Kera: Data curation; Lipoksenla Walling: Data curation; Ibasiewdor Mawlein: Data curation; Wankupar Wankhar: Conceptualization, Validation, Formal analysis, Writing; review & editing.

**Ethics Approval Statement**

Not applicable.

**Data Availability Statement**

Not applicable.

## REFERENCES

1. Sah, R, Khadka S. Case series of paragonimiasis from Nepal. *Oxford Medical Case Reports*. 2017 (11):omx083.
2. Luo J, Wang MY, Liu D, Zhu H, Yang S, Liang BM, Liang ZA. Pulmonary paragonimiasis mimicking tuberculous pleuritis: a case report. *Medicine*. 2016 ;95(15).
3. Apurba SS, Sandhya BK .Essential of Medical Parasitology,1st edition.2014; pp 215-219.
4. Singh TS, Sugiyama H, Rangsiruji A. Paragonimus & paragonimiasis in India. *The Indian Journal of Medical Research*. 2012;136(2):192.
5. Hanprom J, Lapphra K, Tontiwattanasap W, Papwijitsil R, Copeland K, Chokephaibulkit K. Case Report: Reemerging Paragonimiasis in Umphang District, Thailand. *The American Journal of Tropical Medicine and Hygiene*. 2023;108(4):738.
6. Yadav A, Kumar A, Agarwal D, Kumar A. A curious case of hemoptysis. *Medical Journal Armed Forces India*. 2022; *78*:S266-S268
7. Li-Ping SH, Xian-Bing KO, You-Song DE, Jing-Bo WA, Xiao-Kai B, Cheng L. Clinical and imaging features of thirty cases of paragonimiasis westermani. Zhongguo xue xi Chong Bing Fang zhi za zhi= *Chinese Journal of Schistosomiasis Control*. 2019;31(2):200-3.
8. Singh TN, Kananbala S, Devi KS. Pleuropulmonary paragonimiasis mimicking pulmonary tuberculosis—a report of three cases. *Indian J Med Microbiol*. 2005(2):131-4. doi: 10.4103/0255-0857.16056. PMID: 15928446.
9. Das M, Doleckova K, Shenoy R, Mahanta J, Narain K, Devi KR, Konyak T, Mansoor H, Isaakidis P. Paragonimiasis in tuberculosis patients in Nagaland, India. *Global Health Action*. 2016;9(1):32387.
10. Procop GW. North American paragonimiasis (caused by Paragonimus kellicotti) in the context of global paragonimiasis. *Clinical Microbiology Reviews*. 2009;22(3):415-46.
11. Blair D. Paragonimiasis. *Digenetic Trematodes*. 2019:105-38.
12. Oh MY, Chu A, Park JH, Lee JY, Roh EY, Chai YJ, Hwang KT. Simultaneous Paragonimus infection involving the breast and lung: a case report. *World Journal of Clinical Cases*. 2019;7(24):4292.
13. Lane MA, Barsanti MC, Santos CA, Yeung M, Lubner SJ, Weil GJ. Human paragonimiasis in North America following ingestion of raw crayfish. *Clinical Infectious Diseases*. 2009;49(6):e55-61.
14. Cong CV, Anh TT, Ly TT, Duc NM. Paragonimiasis

diagnosed by Ct-guided transthoracic lung biopsy: literature review and case report. *Radiology Case Reports*. 2022;17(5):1591-7.

15. Kalhan S, Sharma P, Sharma S, Kakria N, Dudani S, Gupta A. Paragonimus westermani infection in lung: A confounding diagnostic entity. *Lung India*: *Official Organ of Indian Chest Society*. 2015;32(3):265.
16. Slesak G, Inthalad S, Basy P, Keomanivong D, Phoutsavath O, Khampoui S, Grosrenaud A, Amstutz V, Barennes H, Buisson Y, Odermatt P. Ziehl-Neelsen staining technique can diagnose paragonimiasis. *PLoS neglected tropical diseases*. 2011;5(5):e1048.
17. Vijayan VK. Diagnosis of Pulmonary Parasitic Diseases. *Parasitic Diseases of the Lungs*. 2013:1-4.
18. Roy JS, Das PP, Borah AK, Das JK. Paragonimiasis in a child from Assam, India. *Journal of Clinical and Diagnostic Research: JCDR*. 2016;(4):DD06.
19. Eapen S, Espinal E, Firstenberg MS. Delayed diagnosis of paragonimiasis in Southeast Asian immigrants: a need for global awareness. *International Journal of Academic Medicine*. 2018;4(2):173.
20. Gan X, Shi X, Wang Y. Development of rapid diagnostic Kit (Dot Immunogold Filtration Assay) for detection of antibodies angainst Paragonimus westermani. *Chinese Journal of Zoonoses*. 2005;21(11):988.
21. Sah SK, Du S, Liu Y, Yin P, Ganganah O, Chiniah M, Yadav PK, Guo YY, Li Y. Imaging findings of Paragonimus westermani. *Radiology of Infectious Diseases*. 2016;3(2):66-73.
22. Vidamaly S, Choumlivong K, Keolouangkhot V, Vannavong N, Kanpittaya J, Strobel M. Paragonimiasis: a common cause of persistent pleural effusion in Lao PDR. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 2009;103(10):1019-23.
23. Qian M, Li F, Zhang Y, Qiao Z, Shi Y, Shen J. A retrospective clinical analysis of pediatric paragonimiasis in a Chinese children's hospital from 2011 to 2019. *Scientific Reports*. 2021;11(1):2005.
24. Richter J.Current status of the treatment of paragonimiasis.*One Health Implement Res.*2022;2:96-107
25. Liang T, Liang G, Du Y, Wang X, Wang Y, Chen A, Chen Z, Du J, Li H, Yu L. Scrotal Paragonimiasis in adults: two case reports and review of literature. *Medicine*. 2018;97(14).
26. Kyung SY, Cho YK, Kim YJ, Park JW, Jeong SH, Lee JI, Sung YM, Lee SP. A paragonimiasis patient with allergic reaction to praziquantel and resistance to triclabendazole: successful treatment after desensitization to praziquantel. *The Korean Journal of Parasitology*. 2011;49(1):73.
27. Keiser J, Odermatt P, Becker SL, Utzinger J .Paragonimus species (Paragonimiasis). *Antimicrobe.*2002;2.
28. Pi H, Ogunniyi AD, Savaliya B, Nguyen HT, Page SW, Lacey E, Venter H, Trott DJ. Repurposing of the fasciolicide triclabendazole to treat infections caused by Staphylococcus spp. and vancomycin-resistant Enterococci. *Microorganisms*. 2021;9(8):1697.
29. Gandhi P, Schmitt EK, Chen CW, Samantray S, Venishetty VK, Hughes D. Triclabendazole in the treatment of human fascioliasis: a review. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2019;113(12):797-804.
30. Kim KE, Jung SS, Park HS, Lee JE, Chung C, Lee SI, Koh JS, Park D. The first case report of Paragonimus westermani infection diagnosed by transbronchial lung cryobiopsy. International Journal of Infectious Diseases. 2023: 1;128:184-6.