Parasitic (Helminthic) cardiomyopathy: A review and pooled analysis of pathophysiology, diagnosis and clinical management

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Abstract

Neglected tropical diseases form an important component of the burden of cardiac disease in resource-constrained countries. Some diseases resulting from infection by helminthic parasites such as endomyocardial fibrosis, schistosomiasis and hookworm infections are part of the neglected tropical diseases. The neglect has contributed to the under-appreciation and under-research of helminthic cardiac diseases. In contrast, infections by helminthic parasites are prevalent in resource-constrained countries and are among the leading aetiology of cardiac diseases including cardiomyopathy often associated with an ominous prognosis. Infection by a wide variety of helminth parasites, more commonly *Trichinella, Taenia solium, Echinococcus, Schistosoma, Toxocara and Ascaris,* and less commonly, *Heterophyes, Paragonimus, Strongyloides* and *Dirofilaria Immitis* can result in myocardial injury ultimately progressing to cardiomyopathy. However, data on epidemiology, presentation, diagnosis and management of helminthic cardiomyopathy are few and disparate effectively undermining exact understanding. Moreover, expert guidelines specific to the diagnosis and management of helminthic cardiac diseases are also conspicuously lacking. Current clinical practices on management of helminthic cardiomyopathy appear to depend on health centre experience. This paper aims to provide a broadened view of the clinical status of helminthic cardiomyopathy by reviewing published evidence with a particular focus on the causative helminthic parasites, pathophysiology, diagnosis and clinical management.

Abbreviations: CM: Cardiomyopathy; CMR: Cardiac Magnetic Resonance; CSF: Cerebrospinal Fluid; DCM: Dilated Cardiomyopathy; ECG: Electrocardiogram; ECP: Eosinophilic Cationic Protein; ELISA: Enzyme-Linked Immunosorbent Assay; ESC: European Society of Cardiology; GI: Gastrointestinal; HF: Heart Failure; IgE: Immunoglobulin E; IgG: Immunoglobulin G; LBBB: Left Bundle Branch Block; LV: Left Ventricular; MBP: Major Basic protein; MC: Myocarditis; MHC: Major Histocompatibility Complex; MI: Myocardial Infarction; PAIR: Percutaneous Aspiration, Injection of Chemicals and Reaspiration; PCR: Polymerase Chain Reaction; PH: Pulmonary Hypertension; RV: Right Ventricular; VLM: Visceral Larva Migrans; WHO: World Health Organization.

Introduction

Helminth parasites are among the most prevalent infectious agents in the world infecting nearly a third of the global population [1]. Helminthic infections significantly downregulate the host immune response and may lead to many debilitating diseases and syndromes [2]. The heart and the lungs are the most frequently affected thoracic organs. Cardiac involvement may be the consequence of a more generalized illness or a more direct effect on various cardiac structures including the myocardium, pericardium, endocardium or coronary vasculature [3]. Myocardial involvement may result in myocarditis (MC) or cardiomyopathy (CM) whereas pericardial involvement may result in pericarditis, pericardial effusion, cardiac tamponade or constrictive pericarditis. Helminthic infection such as schistosomiasis may lead to pulmonary hypertension in resource-constrained tropical and subtropical settings. Latent helminthic infections may also reactivate and manifest as systemic disease often ultimately affecting the heart in immunosuppressive states such as solid organ transplant,

use of immunosuppressive drugs, or HIV/AIDS [3]. Factors such as a growing migration, population displacement and travel have altered the epidemiology of helminthic infections creating the need for clinicians' awareness of their potential cardiac manifestation. Moreover, eradication of helminthic infection remains a distant goal because of the lack of effective vaccines, limited pharmacological efficacy, emerging drug resistance and rapid re-infection in endemic areas [2]. This paper presents a systematic review of helminthic infections that affect the heart, their epidemiology, pathogenesis and clinical manifestations, ultimately concluding with a meta-analysis of diagnostic and management strategies for helminthic CM.

Helminth parasites (diseases)

Helminths are multicellular worm-like parasites classified into three taxonomical groups: (i) the nematodes also known as roundworms and includes major intestinal worms (or soil-transmitted helminths) and filarial worms that cause lymphatic Filariasis and onchocerciasis. (ii) Cestode (tapeworms), such as the pork tapeworm that causes Cysticercosis. (iii) Trematodes (also known as flukes) such as the schistosomes [4-6]. Fewer helminthic infections that involve the myocardium leading to CM include Trichiniasis, Echinococcosis, Schistosomiasis, Ascariasis, Heterophydiasis, Filariasis, Paragonimiasis, Strongyloidiasis, Cysticercosis, and Visceral larva migrans.

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***Trichinella* (Trichiniasis):** *Trichinella* (or trichina worms) is the genus of parasitic roundworms of the phylum Nematode. Species that infect humans include *T. spiralis* (the most prevalent), *T. pseudospiralis, T. nativa, T. nelsoni, T. bitovi, T. murelli, and T. papuae*. Its portal of entry in humans is oral, through the ingestion of raw or uncooked pork and wild game products infected with *Trichinella* larvae cysts. *Trichinella* infections may leads to Trichiniasis disease (also called trichinosis or trichinellosis), which occurs worldwide although more common in areas where eating of raw or undercooked pork such as ham or sausage is prevalent. Symptoms of trichiniasis in humans vary depending on the number of larvae ingested with some infected individuals remaining asymptomatic. Early signs of infection include muscle soreness, diarrhoea, vomiting, swelling of the eyelids and fever [5]. For mild to moderate infections, most symptoms resolve within a few weeks although fatigue, weakness and diarrhoea may persists for several months. In severe cases, cardiac and neurological complications may occur, which may result in death [4-6].

Pathophysiology: Human infection with *Trichinella* parasite and the resulting CM begins with the ingestion of undercooked meat containing infective *Trichinella larvae in* cyst (encysted larvae). Stomach acidity causes excystation of the ingested larvae cyst to release the worms, which mature and lay eggs [4]. The eggs develop into larvae excyst, which travel via the lymphatics and blood stream finally encysting in striated (cardiac and skeletal) muscle tissue. The larvae induces the striated muscle cell into a nurse cell that supports long-term viability of the encysted larvae [7]. However, the process of encystment and nurse cell formation is unique to the skeletal muscles but absent in cardiomyocytes [8]. Similarly, *Trichinella*-associated CM is not the consequence of direct *Trichinella* larval infection of the myocardium rather a likely consequence of eosinophil-enriched inflammatory response resulting in eosinophilic MC similar to the pathogenic process associated with tropical endomyocardial fibrosis [9-11]. In some patients, trichiniasis may develop organ specific autoantibodies but their pathogenic role in *Trichinella*-associated CM remains unclear [12].

Clinical features: Typical trichiniasis manifestations include the classic diagnostic triad of myalgia, periorbital oedema and eosinophilia. The clinical picture and severity of trichiniasis is proportional to the dose of infection and larval burden in the muscle [3]. The disease manifests with two clinical stages: (i) the intestinal stage, and (ii) the muscular stage [13-15]. Larval migration into the muscles can result into symptoms such as periorbital and facial oedema; subungual, conjunctival and retinal haemorrhages; myalgia; general weakness; and fever [9-11]. The tropism of *Trichinella* for striated muscle involves the myocardium in 21% to 75% of infected patients [9,10]. Migrating *Trichinella* larvae and the resulting inflammatory response may lead to MC, which appears in the third week of infection. Patients with trichiniasis MC may initially present with chest pain mimicking acute myocardial infarction (MI) [10]. Up to 75% of infected patients may present with electrocardiographic (ECG) evidence of myocardial involvement with arrhythmias considered the most common cause of death [9,11]. Some patients may exhibit evidence of pericardial effusion during *Trichinella* infection [10].

Diagnosis: Diagnosis of trichiniasis CM is difficult because of non-specific clinical manifestation. Clinical suspicion rests on the combination of (i) suggestive epidemiology associated with the typical clinical presentation and (ii) the presence of eosinophilia during the second to fourth week of infection of the striated muscle [16]. However, the severity of eosinophilia has no direct relationship with the clinical

course of Trichiniasis. Definitive diagnosis of trichiniasis CM rests on a combination of serology tests for anti-*Trichinella* antibodies and muscle biopsy specimen [14,15]. Definitive diagnosis of trichiniasis rests on detecting larvae in a biopsy muscle samples or specific ant-*Trichinella* antibodies although muscle biopsy is not sensitive to light infections and the early stage of infection [17-19]. Serum specific anti-*Trichinella* antibodies (immunoglobulin E [IgE]) appear first and typify the acute stage of the disease but are only detected in a few cases usually at the onset of the disease because of its relative short half-life in serum [20]. Detection of immunoglobulin G (IgG) by ELISA using excretory-secretory (ES) antigens of *Trichinella* muscle larvae is the most common serodiagnosis methods recommended by the International Commission of Trichinellosis due to ease of collection from experimentally infected animals and preparation of ES antigen by vitro cultivation of larvae [21]. For asymptomatic patients with myocardial involvement, tests for troponin levels may be useful to detect subclinical MC [22]. Although findings of *Trichinella* larvae in muscle biopsy specimen provides a definitive diagnosis, biopsy is rarely necessary [3,22]. ECG abnormalities are common in about 56% of trichiniasis patients, most commonly non-specific repolarization changes without association with poor prognosis [23]. Pericardial effusion is the most common cardiac manifestation of trichiniasis, affecting 10% of the infected patients [14]. Cardiac magnetic resonance (CMR) imaging may provide supportive evidence of myocardial involvement although CMR findings are non-specific to trichiniasis [24].

Treatment: Trichiniasis is usually not serious and often self-limiting within a few months. Symptomatic infection may response to treatment with medication. Anti-parasitic (antihelminthic) medication is usually the first line of treatment against trichiniasis. Prompt treatment using albendazole (Albenza) or mebendazole during the intestinal phase of the disease is efficacious in eliminating the intestinal worms and larvae. However, discover of the disease during the muscle stage, the benefits of anti-parasitic medication is less certain nevertheless usually prescribed in patients with signs and symptoms of CNS, cardiac or respiratory. In severe cases, a dual therapy of anti-parasitic and steroids is advisable [9,10,13-15]. During pregnancy, relative contraindication of albendazole and mebendazole contraindicated have been described nevertheless they have been used in patients without adverse fatal side effects [25]. The use of adjunctive corticosteroids is common for 10 to 15 days to control inflammation [18].

Taenia Solium (Cysticercosis)

Taenia solium is a pork tapeworm belonging to the taxonomical class cestodes. *T. solium* has a complex two-host life cycle: (i) humans, who are the only definitive hosts harbouring the adult tapeworm (taeniasis); and (ii) both humans and pigs acting as intermediate hosts harbouring larvae (cysticerci). Two clinical syndromes caused by *T. solium* are cysticercosis (larvae cysts in various tissues including the brain and the heart) or taeniasis (intestinal tapeworm infection) [26]. Cerebral cysticercosis is the most important clinical manifestations of cysticercosis but encystment of larvae can occur in almost any tissue, including the eye, lung, skeletal muscle, liver, kidney, subcutaneous tissue, and even the heart [27,28]. The prevalence of cysticercosis CM varies and higher in regions where cysticercosis is endemic, pigs are raise and sanitary conditions are lacking [29]. Cysticercosis is more common throughout Latin America, most of Asia, sub-Saharan Africa and parts of Oceania, and the greatest cause of acquired epilepsy worldwide. However, cysticercosis is now increasingly recognized in developed countries die to immigration of tapeworm carries from endemic regions [26].

Pathophysiology: The pathophysiologic mechanisms of cysticercosis CM remains unclear, although the inhibition of the normal host immune response may play a central role. *T. solium* infect humans through ingestion of eggs excreted in the faeces of a human carrier of the pork tapeworm [26,27]. Upon ingestion, oncospheres (larval stage of the tapeworm) invade the intestinal wall and disseminate to the brain, striated muscles and other tissues [3]. Cysticerci can survive in neural and cardiac tissues for years in a state of immune tolerance. Cysticerci disarms host defences by secreting prostaglandins and other compounds (paramyosin, taeniastatin, sulphated polysaccharides) that inhibit or divert complement activation and cytokine production resulting in only minimal host inflammation around the viable cysticerci. Furthermore, humoral antibodies do not kill mature metacestode. Taeniastatin and other poorly defined factors may also interfere with lymphocyte proliferation and macrophage function, inhibiting normal cellular immune defences. Clinical manifestation commonly result when an inflammatory response develops around a degenerating cysticercus after it has died [30]. However, over a period of years, the ability of the cyst to moderate host immune response may be lost [31]. Consequently, an inflammatory response results in degeneration of the cysticercus. As degeneration continues, the parasite becomes encased in a granuloma, which may resolve or lead to scarring and calcification [30,31].

Clinical features: Clinical manifestation of cysticercosis often develop at the time of cyst degeneration although the trigger is unknown [31]. Myocardial inflammatory response varies resulting in granuloma formation and fibrosis, which may consequently lead to arrhythmias and conduction abnormalities spontaneously or during treatment [32-35]. Cardiac involvement in cysticercosis was believed to be rare but autopsy studies reveal a prevalence of 20% to 25% in patients with concomitant diagnosed neurocysticercosis [33-35]. Cardiac cysticercosis is often asymptomatic and discovered during surgery or post-mortem. Cysticerci are usually multiple and randomly distributed in cardiac tissues including sub-pericardium, sub-endocardium and myocardium. It is rare for a single cardiac cyst to be present [33,34].

Diagnosis: Diagnosis of cysticercosis rests on clinical presentation, abnormal findings on cardiac and neuro-imaging, and serology. Occasional more invasive procedures such as biopsy may be required to confirm diagnosis [36]. The extent of diagnostic evaluation depends on the severity of clinical presentation. In the case of a leaking cyst, routine blood tests may reveal marked peripheral eosinophilia. The sensitivity and specificity of serology depends on the site and stage of infection. An enzyme-linked immune-electrotransfer blot assay is the test of choice for the detection of antibodies [37]. Polymerase chain reaction (PCR)-based tests have an emerging role in the epidemiological examination of taeniasis and are available for diagnosis of cysticercosis [38-40]. During the intestinal stage, most infected individuals lack viable *T. solium* in their intestines [3]. Echocardiography evaluation may be useful in detecting cardiac cyst and occasionally detect cardiac cyst consistent with cysticercosis on routine screening for other purposes [27,41]. CMR imaging may demonstrate cystic lesions that are hypo-intense on T1-weighted images and hyper-intense on T2-weighted images. Rounded scolices when visible are of intermediate to low-signal intensity on T2-weighted images and of intermediate to hyper-intense signal intensity within low-signal fluid on T1-weighted images [42,43].

Treatment: Clinical management of cysticercosis depends on the clinical picture of the patient. There is no clinical evidence that administering anti-parasitic medication for asymptomatic patients with non-viable cysticercal lesions found incidentally in the brain is beneficial. Patients with cysticerci only in subcutaneous or intramuscular sites generally do not require specific surgical or anti-helminthic therapy. If a single lesion is discovered, excision may be considered. Patients with subcutaneous or intramuscular cysticercosis who develop symptoms resulting from inflammation may be treated with cysticerci excision or anti-inflammatory agents. Patients with extra-neural cysticercosis should be evaluated for possible neural involvement using brain imaging. The role of anti-helminthic treatment (albendazole and praziquantel) or surgery in cardiac cysticercosis has not been directly evaluated; however, they may be effective given their efficacy on other sites [33-35]. Adjunctive corticosteroid therapy is sometimes administered during neurocysticercosis [44,45]. The potential benefit of reducing treatment related to inflammation in cardiac cysticercosis has not been defined but theoretically plausible [3].

Echinococcus (Echinococcosis)

Human echinococcosis is a zoonotic infection caused by infection of metacestodes (the larval forms) of tapeworms of the genus *Echinococcus* found in the small intestines of carnivores. Four taxonomically relevant species of *Echinococcus*: *E. granulosus, E. multilocularis, E. oligarthrus* and *E. vogeli* are recognized but only the first two are pathogenic in humans and may result in echinococcal disease [46]. *Echinococcus* species have a worldwide distribution. The World Health Organization (WHO) proposed the designation cystic echinococcosis for the disease caused by *E. granulosus* (the type most frequently encountered) and Alveolar Echinococcosis for the disease caused by *E. multilocularis* [46]. Humans become accidental intermediate host when they ingest eggs from the faeces of dogs and other canidae but direct human-to-human transmission does not occur [3].

Pathophysiology: In primary echinococcosis, metacestodes develop from oncospheres following peroral infection with E. *granulosus* eggs whereas in secondary echinococcosis, larval tissue proliferates after disseminating from the primary site of metacestode by spontaneous trauma such as induced rupture during medical intervention [46]. Oncospheres cross the small intestinal walls and spread to encyst in various visceral organs including the liver, lungs and heart. Both humoral and cellular immune response act against the oncospheres and metacestodes. The *Echinococcus* parasite evades the host immune response by using a number of mechanisms including cyst-laminated cuticle as a barrier to host cells, polyclonal activation of lymphocytes nu parasite soluble antigens and depression of host immune response [47]. Chronic stimulation of the host by cyst fluid antigens result in elevated levels of specific IgG production suggesting host response immune-modulation [47]. Th1 cell activation appears critical for protective immunity while Th2 response correlated with progressive disease [48].

Clinical features: Hydatid cysts develop over months to years mostly remaining asymptomatic but some cysts may grow sufficiently large to cause symptoms [3,46]. Echinococcal disease is often an incidental diagnosis during imaging for other reasons. The common location of cysts is the liver and the lung, and only 10% may occur in other visceral organs [49]. Cardiac hydatid cysts occur in between 0.5% and 3.0% of echinococcosis patients and in most cases are univescular [50-54]. Echinococcal patients may present with arrhythmias, MI, cardiac tamponade, pulmonary hypertension, syncope, purulent pericarditis and sudden cardiac death [50,51,53,54]. Isolated cardiac hydatid cysts is uncommon in the absence of liver involvement and can mimic ST segment elevation MI on ECG [50,51]. Most cases of pericardial echinococcosis occur in the setting of disseminated

infection from the initial liver infection [50,51,54]. In rare cases, atrial or ventricular thrombus may mimic a hydatid cyst [55,56].

Diagnosis: Cystic echinococcosis is one of the few parasitic infection in which the basis for laboratory diagnosis is serology [57]. Indirect hemagglutination test and ELISA are the most widely used tests for the detection of anti-*Echinococcus* antibodies (IgG). Depending on the serology test and other parameters, about 10% of patients with hepatic cysts and 40% with pulmonary cysts do not produce detectable serum IgG antibodies and exhibit false negative results [57]. The sensitivity and specificity of serology in patients with liver involvement are > 80% but less sensitive when echinococcosis is isolated at other sites [58]. False positives in serology tests are more common in children and pregnant women than in other populations [59]. Detection and identification of antigens in cyst fluid or serum may assist in diagnosis [60,61]. Less than 15% of echinococcosis may exhibit peripheral eosinophilia. At present, DNA tests may prove useful for diagnosis but are only available in research settings. Cardiac imaging using echocardiography is the most appropriate in assessing potential myocardial or pericardial hydatid cysts [62]. Other imaging modalities such as computer tomography (CT) and CMR may also demonstrate specific signs such as calcification of the cyst walls and the presence of daughter cysts and membrane detachment [63,64].

Treatment: The only medical therapy (antihelminthic) with proven efficacy against cystic echinococcosis is benzimidazolic drugs – mebendazole or albendazole, which are well tolerated but exhibit difference efficacy. A single therapy of benzimidazole requires prolonged administration over many weeks, with unpredictable outcomes in terms of response rates in individuals [65]. Treatment duration of 3 to 6 months is common to both mebendazole and albendazole since efficacy increases with courses of up to 3 months in the more common cyst sites [66,67]. Although chemotherapy, cyst puncture and percutaneous aspiration, injection of chemicals and reaspiration (PAIR) show potential to replace surgery as efficacious treatment for cystic echinococcosis (cardiac hydatidosis), surgery (when feasible) remains the most efficacious treatment to remove cyst and can lead to a complete cure. For surgical patients, commencement of benzimidazolic drugs should be four days before surgery and continued for at least one month for albendazole and three months for mebendazole after surgery [68-71]. Benzimidazolic drugs for surgical patients reduce the risk of cyst dissemination and response to therapy may be monitored with serology and imaging [3,46]. However, WHO does not recommend surgery for pregnant women and patients with multiple or difficult to access cysts or patients with dead or totally calcified cysts. Asymptomatic cysts, if heavily calcified and presumed non-viable, may be monitored without specific therapy [3].

Schistosoma (Schistosomiasis)

Human schistosomiasis (originally known as bilharzia) is a freshwater snail-transmitted intravascular disease caused by infection with parasitic dimorphic *Schistosoma* trematode worms (flukes), which live in the blood stream of humans [72-74]. More than 200 million people from Africa, Asia and South America are infected with the disease and a further 732 million are vulnerable to infection worldwide [75,76]. Humans acquire infection with *Schistosoma* when they make contact with water contaminated with the skin penetrating cercariae [72]. Five *Schistosoma* species pathogenic to humans are *S. mansoni, S. haematobium, S. japonicum, S. mekongi,* and *S. intercalatum* but the main disease burden is usually attributable to the first two species, referred to as the major human *Schistosoma* [77]. The acute form of schistosomiasis occurring after three to six weeks after exposure is

generally self-limiting and benign whereas the chronic form can cause severe health impairment. Hepatosplenic disease affects about 25% of chronic schistosomiasis and of clinical interest because of the potential to cause liver fibrosis, portal hypertension and parasite migration to the lungs causing pulmonary hypertension and ultimately right ventricular (RV) failure [78].

Pathophysiology: Myocardial or pericardial involvement by *Schistosoma* species is rare and may occur due to the accumulation of *Schistosoma* eggs, which induce a local granulomatous response [81-83]. In the life cycle of *Schistosoma*, the host releases the produced eggs into the environment via the gastrointestinal (GI) tract but a number of eggs remain within the portal venous system. These eggs become the target of the host immune system resulting in localized inflammatory lesions, which often progress into micro abscesses and subsequently granulomas [78]. Eventually, collagen deposition ensues and fibrotic lesions replace granulomas. Depending on the topography of these fibrotic lesions, periportal fibrosis manifests in 4% to 8% of chronically infected patients leading to portal venous system destruction and portal hypertension [84]. Increased portal pressure causes portosystemic shunts believed to be a key component of the less common but severe complications of chronic hepatosplenic schistosomiasis.

The involvement of portal hypertension may produce a hepatopulmonary syndrome manifested as dyspnoea upon exertion, RV hypertrophy and ultimately *cor pulmonale* [85,86]. Additionally, endothelial damage to the pulmonary circulation in the setting of shunting of *Schistosoma* eggs via portosystemic shunts. *S. mansoni* is able to survive in the pulmonary circulation by molecular masking by coating with ABO blood group glycolipids and major histocompatibility complex (MHC) molecules in the human host [81-83]. *Schistosoma*-associated pulmonary hypertension (PH) has an ominous prognosis associated with advanced stage of hepatosplenic schistosomiasis [81,87]. Thrombosis *in situ* particularly of the right pulmonary artery as well as cardiac arrhythmias and sudden death syndrome may occur [83,87].

While the pathophysiology of hepatic and pulmonary involvement in schistosomiasis is known, that of myocardial involvement remains controversial but may be related to the immunoallergic phenomena, which may be caused by the presence of *Schistosoma* in the blood circulation and tissue [88]. Eosinophils may play an essential role in the regulation of allergy and in the protection against helminthic infection with the support of proteins contained in their granules such as the Major Basic protein (MBP) and Eosinophilic Cationic Protein (ECP) [89]. Besides the beneficial role of eosinophils may be toxic for the host and especially the heart. MBP and ECP are pathophysiologically relevant because of their cytopathogenic effect on endothelial cells and cardiomyocytes, myocardial interstitial fibrosis, development of parietal thrombi and then fibrosis of the endocardium and the myocardium [90].

Clinical features: Data on clinical manifestation of schistosomiasis disproportionately focuses on general acute or chronic form of the disease with a scant mention of cardiac involvement. Acute schistosomiasis typically manifests in non-immune individuals 3 to 6 weeks following the exposure in endemic regions. It is usually self-limiting and resolves over a few weeks although life-threatening complications that are mainly neurological have been described [91,92]. Cardiac complications have been observed in two patients with acute schistosomiasis, which differ from those observed during the chronic phase of the disease. The first patients presented with acute myocarditis

presenting with chest pains accompanied by elevated troponin levels, ECG abnormalities and negative CMR findings. The second patients did not present with any cardiac signs but the diagnosis of myocarditis relied on elevated troponin levels and ECG repolarization abnormalities [79]. Both patients were non-immune travellers presenting with hypersensitivity symptoms and eosinophilia characteristics of acute schistosomiasis [79].

Diagnosis: Diagnosis of schistosomiasis rests on demonstration of parasite infection accompanied by evidence myocardial dysfunction. Detection of *Schistosoma* parasite rests on parasitological, serological or molecular diagnostic methods. The gold standard diagnostic tool is detection and demonstration of eggs in stool or urine [93,94]. Tissue biopsy specimen of bladder and rectal mucosa is useful if eggs are undetected in stool or urine [95]. Serological assays are also useful in diagnosing infection by assessing blood serum and cerebrospinal fluid (CSF) to detect antibodies that remain positive for a long time after the resolution of primary infection [96,97]. Eosinophil count and molecular detection of schistosomal DNA by PCR in sera of infected patients may support infection by *Schistosoma* [98,99]. However, these diagnostic methods cannot assess the severity of the disease and resulting complications as well as clinical signs and symptoms are non-specific and non-reliable in assessing disease severity [100]. Recommended diagnosis for suspected myocardial involvement in schistosomiasis include routine screening with ECG, troponin assays and non-invasive imaging. Signs of myocardial dysfunction may include elevated levels of eosinophil, and serum troponin or creatine kinase-MB. ECG may show non-specific repolarization disorders: anomalies in T-wave and S-T segment, and PR prolongation [79,101]. Echocardiography results may show segmentary hypokinesia (apical and anterior medium third). Doppler echocardiography may be useful in assessing right ventricular end-diastolic area, the peak systolic tricuspid annular tissue velocity (S') right ventricular index of myocardial performance, and right atrial area [80]. Finally, CMR imaging may be normal or may show discrete delayed myocardial perfusion of the septum with subendocardial enhancement compatible with endocardial fibrosis [79].

Treatment: The traditional medical treatment for schistosomiasis is praziquantel, a pyrazinoisoquinoline derivative that is enterally well-absorbed, metabolized by the liver and its inactive metabolites excreted primarily in the urine. Oxamniquine is an alternative anthelmintic drug effective for only *S. mansoni*. Praziquantel (or oxamniquine) causes adult worms to detach from the vascular wall of the host and ultimately their death resulting in a cure rate of up to 90%. If the initial dose does no cure the patients, it significantly reduces the parasite and egg burden, and a second treatment is usually successful in eradication the parasite [78]. There is evidence that praziquantel may also suppress schistosomal egg granulomas within the lungs, reducing inflammatory cell and fibroblast numbers [102]. However, praziquantel has a short half-life rendering it a poor choice for chemoprophylaxis, in which case, artemether, an antiparasitic drug (a common antimalarial medication), is a better choice [84]. Whether anthelmintic therapy is effective in curing myocardial dysfunction and conduction abnormalities has not been sufficiently demonstrated. However, in schistosomiasis patients with myocardial involvement, adjunctive corticosteroids and antihypertensive drugs (Acebutolol or Ramipril) may be useful to treat acute myocarditis associated with symptom resolution [79].

Toxocara (Visceral larva migrans)

Visceral larva migrans (VLM) is an uncommon infection by zoonotic helminths that migrate aimlessly throughout the human body because they are in an aberrant host. A variety of worms can be the aetiologic agent for VLH but the most common cause is infection by *Toxocara canis* (the dog ascarid) and less commonly by *Toxocara cati* (the cat ascarid) or *Baylisascaris procyonis* (raccoon ascarid) often in temperate and tropical climate [103-107]. All feline and canine species can carry *Toxocara*. Humans are not the definitive host in which the hatched larvae cannot mature into adults but migrate throughout the visceral organs causing acute eosinophilic syndrome. VLM has a worldwide distribution and more prevalent in children under 12 years of age (often with a history of pica) living in crowded dwelling acquiring infection by ingesting embryonated eggs in contaminated soil or sandbox contents [108-110]. When infected eggs of *T. canis* from contaminated soil or meat reach the GI tract, they enter the portal system and reach the liver. Some larvae then migrate from the liver to thoracic organs (lung and heart) through the systemic circulation [103,105]. Although specific cases of VLM-associated CM have not been described, eosinophilic MC has been observed in 10% to 15% of the cases of VLM often accompanied by increasing levels of circulating eosinophils [108]. Case reports [103-105,110] and animal models [106] have also reported cases of MC in VLM patients mostly in children.

Pathophysiology: Eosinophilic MC or CM in VLM patients is an uncommon complication but potentially fatal. Pathophysiologically, it may be the consequence of direct larval invasion of the myocardium, hypertensive reaction to the *Toxocara* parasites and/or inflammation repair following invasion [103,106]. Murine model of VLM shows that migrating *T. canis* produces direct myocardial damage. Myocardial invasion by *T. canis* elicits a granulomatous reaction rich in eosinophils accompanied by myocyte destruction in the regions of invasion. Cardiomyocyte destruction results from the damage caused by the migrating larvae or the inflammation repair that follows. Several early studies [111-113] have demonstrated evidence of pathologic lesions in the heart they attribute to large numbers of circulating eosinophils. Cookston et al. [106] investigation of a murine model of eosinophilic MC attributes myocardial damage to the consequence of inflammation incurred secondary to the txocaral infection due to a large number of eosinophils infiltrating the heart. The study also suggested myocardial damage to blood vessels obstruction by migrating larvae or possibly the larvae themselves but the observed few larvae and the substantial amount of myocardia damage relative to the numbers of larvae do not support these suggestions. Kim et al. [103] suggest a triphasic development of eosinophilic MC due to *T. canis*: (i) acute necrotizing phase resulting from to the infiltration and extra cellular deposition of eosinophil, and consequently interleukin 5 mediated injury lasting for two to three weeks. (ii) Thrombotic phase characterized by layered thrombus along damaged endocardium due to an activation of tissue factor by eosinophils. (iii) Endomyocardial fibrosis phase characterized by myocardial fibrosis. The second stage corresponds to Loffler's endomyocarditis while the third stage to restrictive CM.

Clinical features: Generally, the clinical presentation of VLM varies with the number of larvae and the organs infected. The infections occur most commonly in children younger than twelve years frequently after the ingestion of contaminated soil. Disease manifestation may vary and often range from asymptomatic to fulminant disease and death although it is increasingly appreciated that most infections are asymptomatic [103,104]. Eosinophilic MC and CM due to VLM infection can present both as acute or chronic condition [114]. In acute presentation, patients may exhibit a rapid decline in cardiac course, has a poor prognosis culminating into death within weeks of illness onset while in chronic presentation, patients usually present with congestive HF responsive to glucocorticoid therapy and cytotoxic agents. Chronic MC often manifests in the setting of systemic disease leading to

eosinophilia [115]. VLM-associated MC has a wide array of clinical manifestation. A common complaint is chest discomfort and pain [116]. Patients may have a history of infection a few weeks or months prior to abrupt onset of chest pain and fatigue [115,117]. Common cardiovascular manifestation include signs and symptoms of congestive CM – low cardiac output, cool extremities, peripheral cyanosis, low pulse volume, elevated jugular pressure, tricuspid regurgitation and massively enlarged heart. Patients may also exhibit conduction delays, ST-T segment abnormalities and S3 or S4 gallop rhythm [118,119].

Diagnosis: Diagnosis of VLM-associated rests on determination of parasite infection and evidence of myocardial dysfunction. Pathological examination of various organ specimens can confirm the diagnosis of human toxocaral infection. However, since such direct parasitologic assessment is not in widespread use, serologic methods are the mainstay for diagnosis [103]. Finding larvae in the affected tissue by histological examination confirms diagnosis of toxocariasis. ELISA with Toxocara secretory antigen is the most commonly utilized diagnostic serologic test. However, interpretation of serologic findings should consider that the numerous seropositive individuals detected through screening of large populations in epidemiological surveys probably represent past rather than recent infection. Thus, a single seropositive finding has limited pathological significance in the diagnosis of toxocara infection [103,105,107,108]. To improve the diagnostic value of immunologic test, a blood eosinophil count is necessary, and if possible, the determination of serum total immunoglobulin E [120]. A positive finding of both peripheral eosinophilia and serologic test result is indicative of active toxocariasis [121].

Diagnosis of myocardial dysfunction in the settings of persistent VLM infection has a wide array of clinical manifestations and lacks an established diagnostic criterion. However, ECG tests may reveal rhythm and electrical abnormalities such as sinus rhythm, ST segment and T-wave abnormalities. Patients presenting with signs of infarction may show ST segment elevation or depression and Q waves. The presence of Q-wave of left bundle branch block (LBBB) suggests an ominous prognosis [122]. On echocardiography, features of toxocaral MC include dilated, restrictive, hypertrophic and ischemic CM. increased sphericity and LV volume manifests in acute CM. Increased sphericity and LV volume manifests in acute active MC and can be useful in detecting RV involvement, pericardial effusion and LV thrombus [122,123]. Other non-invasive procedures that can support diagnosis include cardiac biomarkers such as troponin T and I, and CMR imaging. Massively enlarged heart, oedema and pericardia effusion are common findings. However, CMR imaging cannot be relied entirely for a diagnosis because it lacks details of myocardial inflammation such as degree and type, and thus, it is logical to perform endomyocardial biopsy after CMR imaging [114].

Treatment: Many patients with VLM recover without therapy and no single agent has proved to be particularly effective. However, in the setting of severe cardiac disease, treatment with benzimidazole anthelmintic drugs (albendazole, mebendazole, or thiabendazole) is advisable to eliminate or reduce parasite load [104]. The mechanism of its anthelmintic action is inhibition of tubulin polymerization and microtubule-dependent glucose uptake inhibition [103-105]. The Myocarditis Treatment Trial found no statistical advantage of corticosteroid treatment in biopsy-proven MC by Dallas Criteria [105] although in eosinophilic heart disease might be a subset with greater responsiveness. Corticosteroid therapy in the early stage may have a favourable effect if early diagnosis by endomyocardial biopsy has been made. Clinical vigilance on the use of albendazole must remain high

because of reported incidence of advance effects (23% of the cases) especially on liver damage (16% of the cases) [103,104]. For the control of aggravated eosinophilia and inflammatory reaction, adjunctive therapy of corticosteroids (mainly prednisolone) may be considered [103-105].

Ascaris (**Ascariasis**)

Ascariasis is the most frequent helminthic disease in the world with an estimated worldwide prevalence of 804 million cases [124]. It is caused by *Ascaris lumbricoides*, the largest of the common nematodal worms that infect humans, which can reach a length of up to 45 cm with a diameter of 5 mm [125]. It is a chronic intestinal soil-transmitted nematode endemic in developing countries and residing within the lumen of the human intestine as an adult parasite. Ascariasis is prevalent in tropical and sub-tropical countries and it is frequently documented in Sub-Saharan Africa, Latin America, Chins and East Asia. The roundworm infects humans via the faecal-oral route. Another transmission pathway in humans is the consumption of fruits, vegetables, or anything the sticky eggs attach to after release into the environment from faecal matter. Eggs released by the adult females and the host shed them in faeces. Unfertilized eggs are not infective while fertilized eggs become embryonated and infective after 18 days to several weeks in soil depending on the prevailing conditions [126].

Pathophysiology: The exact pathophysiology of Ascariasis is not well defined although it is believed Ascaris infection causes CM through immune-mediated reaction to migrating larvae similar to VLM disease and nutrient depletion and/or obstruction due to physical presence of adult worms in the GI [127]. Upon ingestion of an embryonated egg, a larvae hatch, penetrates the duodenum wall and enter the blood stream. The larvae migrate to the liver and heart and enters pulmonary circulation to break free in the alveoli. After three weeks the larvae from the respiratory system, coughed and swallowed, and return to the small intestine, where they mature into an adult male or female worm. Fertilization occurs and the female produces as many as 200,000 eggs per day for 12-18 months [126]. Infections by Ascaris are unique since adult worms not multiple inside the host rather are the result of independent infections from repeated exposure particularly in endemic areas [125]. In the course of *ascariasis,* the reactive eosinophilia is often present. Cardiac disease is a major cause of death in the setting of sustained eosinophilia, whether reactive or clonal. In ascariasis, myocarditis is a rare complication although potentially fatal. Cardiac disease does not correlate with serum eosinophilia but in the heart, eosinophilic infiltration may produce MC, intramural thrombus formation, constrictive pericarditis and fibroblastic endocarditis [125].

Clinical features: *Ascaris* infection is often asymptomatic and may occur alongside other parasitic diseases including malaria, amebiasis, echinococcosis, and Chagas disease, as well as bacterial infections [126]. Although asymptomatic, patients with ascariasis may exhibit long-term manifestation of growth, retardation and malnutrition. If symptomatic, early symptoms during initial lung infection may include cough, dyspnoea, wheezing, urticaria, haemoptysis, and chest pain [127]. Other symptoms may include abdominal pain, bloating, nausea, vomiting, anorexia, intermittent diarrhoea and common clinical manifestations of intestinal infection. If the number of Ascaris larvae are significant, pneumonitis and eosinophilia can be seen (or Loeffler syndrome) as well as symptoms such as symptoms include wheezing, dyspnoea, cough, haemoptysis, and fever [126,127]. Signs and symptoms of cardiac involvement may include leucocytosis with marked elevated peripheral blood eosinophils, upper extremities

oedema or hyperechogenic thrombus with observed minimum blood flow in the vein [125,128].

Diagnosis: Individual diagnosis of ascariasis depends on a thorough investigation including travel history or origin from endemic countries (when presenting in non-endemic areas), and clinical and laboratory examination including serological, molecular and imaging-based diagnostics [126]. In recent findings, ascariasis should be suspected in patients with relevant symptoms even without traveling to endemic areas [129]. Definitive diagnosis of ascariasis with myocardial involvement rests on evidence of parasite and of cardiac dysfunction. Stool examination for ova and parasite often detects tri-layered eggs in person with ascariasis. However, stool examination may be negative for ova for up to 40 days after infection due to the time needed for migration and maturation of the worm in the human host. Serological tests are not clinical useful for ascariasis. Microscopic wet preparations of sputum during pulmonary migration may detect *Ascaris* larvae [125]. On ECG, abnormalities may mimic acute ST elevation MI and echocardiography may reveal global hypokinesia of the LV [128]. In a case report of a patient with ascariasis MC, blood tests may reveal leucytosis with high absolute eosinophil granulocytes, C-reactive protein and Troponin I level as well as antinuclear antibodies. ECG findings are non-specific revealing regular rhythm and negative T-waves. Echocardiography shows hyperechogenic thrombus in the heart apex, diastolic enlargement with intensified contractility, clamping of apical segments and dynamic gradient, and pericardial thickening and minimal pericardial liquid [125].

Treatment: Medical treatment using antihelminthic is the first-line of treatment for ascariasis with myocardial involvement. Ascariasis patients who have other concomitant helminthic infections should first undergo treatment for *Ascaris* to avoid the risk of complications. However, during active pulmonary infection, medical therapy may be contraindicated because dying larvae poses a higher risk for significant pneumonitis, and in this case, amelioration of pulmonary symptoms may require inhaled bronchodilator therapy or corticosteroids if necessary. The primary antihelminthic medication is oral albendazole in stable patients older than 12 months [124]. An alternative therapy is mebendazole but not recommended during pregnancy, instead, pyrantel pamoate is the drug of choice during pregnancy. In an Indonesian study, albendazole had better sterilization of Ascaris eggs compared to mebendazole but equivalent cure rates and egg reduction rates [130]. In two case reports of ascariasis MC treatment with albendazole [125] and a dual therapy of albendazole and prednisolone [128] lead to a dramatic reduction of eosinophilic granulocyte count and normalization of peripheral blood count, which correlated with significant improvement in LV function and clinical syndromes.

Other helminthic parasites: Other less common helminthic parasites with the potential to cause myocardial infection and CM are Heterophyes, Paragonimiasis, Filariae and Strongyloidiasis.

Heterophyes (Heterophyiasis)

Heterophyes species belong to intestinal trematode of the family Heterophyidae and are the smallest digeneans infecting humans. They commonly inhabit the mid-region of the small intestine and are the aetiologic agent of heterophyiasis. Human infection by *H. heterophyes* is prevalent in Asia, Egypt, and Hawaii [131,132]. Transmission of *H. heterophyes* occurs via marine lagoons and saline inland waters, where euryhaline intermediate hosts are abundant. The human host passes *H. heterophyes* eggs containing fully developed miracadia in faeces and hatch when ingested by a suitable molluskan (the first

intermediate host: freshwater or brackish water snail). The miracadia hatches penetrates the snail intestines, give rise to cercariae that escape to the environment, penetrate the musculature of a number of fishes (second intermediate host: mostly mullet in Egypt). Human infection results from the consumption of raw or improperly cooked mullet fish [132]. Common extra-intestinal infection include kidney, liver, spleen, lymph nodes, lungs, heart and blood vessels with possibility of parasitic migration to liver through bile ducts or lymph nodes and blood to other organs. Cardiac involvement in Heterophyiasis is rare. In the heart, Zenker's necrosis and mononuclear cells infiltration could be the result of secretory and/or excretory toxic products of the parasites or due to erratic parasitism in the heart [133]. Vasculitis may be the result of direct parasitic irritation to cause endothelial damage or indirectly via the action of various parasitic toxic products on the vessel walls causing injury. Congestion, haemorrhage and oedema in various organs can be due to vasculitis because of the involvement of intima and endothelial lining of blood vessels rendering them leaky or permitting the escape of plasma, lymph and erythrocytes with subsequent oedema and haemorrhages [131].

Paragonimus (Paragonimiasis): *Paragonimus* are trematodal parasites that cause paragonimiasis, a parasitic disease that strikes carnivores resulting in a subacute to chronic inflammatory disease of the lung. Four *paragonimus* species are pathogenic to humans (*P. westermani, P. kellicotti, P. ohirai* and *P. iloktsuenensis*). The rate of infection of paragonimiasis decreased in many endemic countries after the 1970s although the rates have persisted in South Korea in which the major source of infection has been the soybean-sauced fresh water crabs ("Kejang") [134]. Since "Kejang" is sold more in large cities than in rural areas, there is need for clinicians to include paragonimiasis as a possible diagnosis when the patient's chest radiograph shows pulmonary infiltration and peripheral blood eosinophilia even in metropolitan cities [134,135]. Cardiac involvement is rare but associated with a poor prognosis. The major symptoms of paragonimiasis are cough, haemoptysis and dyspnoea, which may overlap with symptoms of tuberculosis and other pulmonary disorders. Pathophysiology may be due to direct parasite effect or inflammatory reaction of immune response to parasitic invasion. Clinical presentation may vary based on differences in the numbers of infecting worms, duration from the onset of the disease to clinical findings or autopsy and susceptibility of the individual to the worms [136]. Chest radiograph reveals pleural effusion and abdominal sonography reveals low-echoic lesion with inflammation of the surrounding fat in the psoas muscle, possible the effect of adult flukes present in loosely formed cysts in the psoas muscles [134]. Diagnosis of paragonimiasis is established by the detection of characteristics eggs in the faeces, sputum or pleural fluids as well as serological tests using specific IgG antibody to detect IgG antibody in the serum by ELISA [137]. Studies on electrical or conduction abnormalities and cardiac dysfunction specific to paragonimiasis are missing but might be warranted in endemic areas such as South Korea.

Strongyloides (Strongyloidiasis)

Strongyloidiasis is a human infection caused by parasitic nematode *Strongyloides*. The most common and clinically relevant pathogenic species in humans is *S. stercoralis* and less commonly *S. fuelleborni* that is found sporadically in Africa and Papua New Guinea. Distinctive features of *Strongyloides* is the ability to persist and replicate within a host for decades while producing minimal or no symptoms (immunocompetent individuals) and the potential to cause life threatening infection (disseminated infection) in immunocompromised host [138,139]. Human infection by *Strongyloides* occurs via penetration of the skin or

mucous membranes by infective flariform larvae from autoinfection or faecal-oral route. The larvae migrate into pulmonary circulation via the lymphatic system or venuoles, and are swallowed to reach the GI system where they mature into adult females. Disseminated infection involves extra-intestinal organs mostly the CNS, liver, lungs or heart.

Cardiac involvement in Strongyloidiasis is not that common. Pathologically, it is characterized by restrictive CM resulting from toxic damage produced by activated eosinophils and endomyocardial fibrosis with obliteration of the RV and LV [140-142]. Clinical manifestation of Strongyloidiasis vary based on the acuity of the infection and the underlying host response. As many as 50% of the patients may remain asymptomatic while some patients may develop severe symptoms and even death. Cardiac involvement may manifest as restrictive CM due to toxic damage by activated eosinophils [142]. Case reports reveal that Patients with cardiac develop may exhibit atypical chest pain and exertional dyspnoea. Transthoracic echocardiogram may reveal apical masses in the LV and the RV, and thickened posterior mitral valve leaflet and CMR can be useful to confirm the presence of a LV apical mass with diffuse subendocardial delayed enhancement consistent with endocardial fibrosis [142]. CMR may reveal hyper-signal sub-endocardium in favour of endomyocardial fibrosis.

Dirofilaria Immitis (Zoonotic Filariasis)

Human infections with Filariae infecting animals referred to as zoonotic Filariasis occur worldwide. Although various species of Filariae can cause common infections in birds, reptiles and amphibians, only Filariae, which are natural parasites of mammals, can cause zoonotic infections in humans [143]. *Dirofilaria immitis*, an aetiologic agent for zoonotic filariasi, a common parasitic infection in dogs and other canids, is prevalent in many areas around the world, and can occasionally infect humans. In the dog, filariasis undergoes early development in the subcutaneous tissues for three months before migrating to the right side of the heart. Transmitted by a mosquito vector, the adult worms live in vascular beds and can potentially induce MC [143,144]. Adult *D. immitis* worms also occur on the heart and major blood vessels of humans at autopsy [145] although the usual findings for immature worms is located in partially or completely occluded small pulmonary arteries, where the occlusion produces a distal pneumonitis followed by granuloma formation leading to a well circumscribed coin lesion

containing the parasite [143,146]. These lesions are common in asymptomatic individuals undergoing routine chest examinations. Echocardiography or angiography are unable to identify the parasite during premortem evaluation. However, the occurrence of severe and occasionally fatal myocardial development prevalent in dogs and other canids has not been described for humans [144].

Meta-analysis of diagnosis/management

Helminthic parasites are among the most prevalent infectious agents in the world but also they feature prominently among the group of neglected tropical diseases. These diseases affect the most resource-constrained countries and tropical regions of the world characterized by sub-standard housing, crowded living conditions, inadequate hygiene, sanitation and unsafe water supplies, and abundance of insects but diagnosed cases are emerging even in resource-rich countries due to increased international human migration [1]. Although mortality associated with helminthic cardiac infection is low, morbidity and public health burden are significantly high [3,5]. Thus, the present systematic review and meta-analysis evaluates published evidence on diagnostic methods and findings on helminthic CM, as well as determine risk factors, and treatment strategies in patients with helminthic infection associated CM.

An online search was performed on PubMed, EMBASE and Cochrane from inception to May 2019. To improve the search for studies whose title did not mention helminthic CM, a full text search in Google Scholar was performed and the first 100 relevant-ranked articles considered for inclusion. There were no restrictions on publication period or language. The references of included studies and review articles were manually screened for additional studies overlooked by the online search. The search criteria included patients diagnosed with helminthic infection and cardiac involvement, used serological, microscopic, ECG, cardiac biomarkers or non-invasive methods for diagnosis, and treated with medication for helminthic infection and/or heart failure. Case reports, conference papers and review articles were excluded from the meta-analysis. In total, seven studies enrolling patients diagnosed with helminthic diseases and cardiac dysfunction were included in the present systematic review and meta-analysis (Table 1).

Table 1. *Summary of study characteristics and findings included in the meta-analysis* (**CT:** Computer Tomography; **ECG:** Electrocardiogram; **Echo:** Echocardiograph; **TEE:** Transesophageal Echocardiography; **TTE:** Transthoracic Echocardiography)

Author (year) [Ref #]	Year	No.	Mean age	Parasite	Diagnostic tests	ECG abnormalities	Summary of findings
Solarz [147]	1947	114	NR	Trichinella	ECG	24	ECG abnormalities is common in patients with Trichinosis (21%; n=24)
Vujisic [148]	1991	16	NR	Trichinella	Echo	15	Echo abnormalities are common in cardiac trichinosis (n=15) compared to normal controls
Siwak [11]	1994	59	6-75	Trichinella	ECG	NR	ECG changes- ventricular repolarization (66%), depolarization disturbances (32%). Persistence pathological ECG records in 6.7% suggesting prolonged inflammatory process of the myocardium
Bouraoui [51]	2005	12	NR	Echinococcus	ECG, Echo, CT, MRI	12	TTE and TEE imaging modality are sufficient to diagnose cardiac hydatid cyst and MRI provides additional information about the extension of Echinococcus disease
Puljiz [23]	2005	154	35.6 (14.64)	Trichinella	ECG	87	ECG abnormalities are common (56% of the patients) but rarely associated with poor prognosis
Neghina [149]	2010	28	38 (3-80)	Trichinella	ECG, Echo	10	ECG changes in 10 patients including T-wave (3), ST depression (2), sinus tachycardia (9) and extrasystoles (4), arrhythmias (2)
Gvozdenovic [150]	2014	53	42.3 (14.5)	Trichinella	ECG, biomarkers	2	ECG abnormalities are uncommon in individuals infected with *Trichinella* (3.7%) but CK elevation is common in 80% of the patients

Results

Study characteristics

The seven studies [11,23,51,147,148-150] included in the present meta-analysis were either retrospective or prospective cohort published between 1947 and 2014. None was a randomized controlled trial. Most of the excluded studies enrolled patients with helminthic infections in general including those without cardiac involvement as well as case reports investigating one, or two, or less than five patients. All the included studies enrolled patients with *Trichinella* parasite infection (or trichiniasis disease) except one study [51] that enrolled patients with echinococcal disease. Although cysticercosis, schistosomiasis and VLM are common helminthic causes of CM (mainly eosinophilic CM), they are mainly documented in case reports and expert review, and thus were excluded. The total number of patients enrolled in the seven studies were 436 with mean age 38.6 years, range 35 to 42 years in three studies [23,149,150]. Common diagnostic tests used for patient selection were serological and microscopic tests for the identification of causative parasite and cardiac biomarkers, ECG, and non-invasive imaging tests (mainly echocardiography and less commonly MRI and CT) for evaluating cardiac function.

Study findings

Pooled data from six studies [23,51,147-150] reveal that ECG abnormalities were common in patients with helminthic infection and myocardial involvement. ECG abnormalities occurred in 150 out of 377 patients, translating into an event rate 44.4% (95% CI: 20.7% to 71.0%) (Figure 1). Data on changes in individual ECG features were few and could not be pooled. However, individual studies reveal that the most frequent ECG changes in trichiniasis patients are ventricular repolarization disturbances (66.1%) and depolarization disturbances (32.2%) and these ECG changes persisted for four months suggesting prolonged inflammatory process within the myocardium [11]. In echinococcosis patients, the common ECG abnormalities included T-wave inversion (67%), ST depression (42%), incomplete right bundle branch block (RBBB) (8%), and atrial fibrillation (8%) [51]. In hospitalized trichiniasis patients, ECG abnormalities include repolarization abnormalities (36%), sinus tachycardia (32%), ventricular extrasystoles (14%), ST-segment depression (7%), low voltage (4%). On echocardiography, 3.6% had concentric cardiac hypertrophy [149]. Solarz et al. [147] ECG study on 114 consecutive cases of trichinosis found abnormalities in ST segment and T-wave (66.6%), prolonged QRS duration (29.2%), low voltage QRS complex (29.2%) and prolonged PR interval (8.2%). In 12 patients with echinococcosis, echocardiography was found to have a high sensibility and specificity, and computed tomography (CT) and MRI confirm findings of echocardiography [51].

Data on the other diagnostic tests such as serology and cardiac biomarkers could not be pooled due to insufficiency. However, findings from individual studies suggest increased eosinophil count ($\geq$ 5%) in 78.6% of the patients, increased leukocytes (> 10,000 cells/mL) in 17.9% and erythrocyte sedimentation rate (ESR) increased > 10 mm/hour in 46.4% of the patients [149]. Gvozdenovic et al. [150] report on 150 trichiniasis patients reveals eosinophilia, elevated C-reactive protein (100%) and creatine kinase (80%) [150]. Treatment for cardiac dysfunction in patients with helminthic infection has not been evaluated. The included studies indicate that a combination of antihelminthic therapy (thiabendazole, mebendazole or diethylcarbamazinum, and corticosteroids leads to resolution of cardiac symptoms and reduction in parasitic burden [149,150]. The efficacy of heart failure medication was not evaluated in these studies.

Discussion

Some important helminthic infections and diseases – endomyocardial fibrosis, schistosomiasis and hookworm infections – are among the group of neglected tropical diseases. In contrast, these diseases in tropical and sub-tropical areas are an important cause of restrictive CM [151]. As neglected diseases, helminthic cardiac infection are both under-appreciated and under-researched aetiologies of cardiomyopathy as well as other heart diseases. The need for current knowledge of the status of helminthic infection is clinically revenant because of the growing migration, population displacement and travel, which are altering the epidemiology of helminthic infection, with diagnosed cases reported even in resource-rich countries. In addition, efforts to eradicate helminthic infection is problematic because of the lack of effective vaccines, limited pharmacological efficacy, emerging drug resistance and rapid re-infection in endemic areas. Despite the importance of research on helminthic cardiac infection, the search for studies in the present meta-analysis reveals a paucity of studies investigating helminthic CM. Even the available studies, most of them are case reports while others enrol patients with helminthic diseases but with no evidence of cardiac dysfunction. As a result, only seven studies were included in the present meta-analysis.

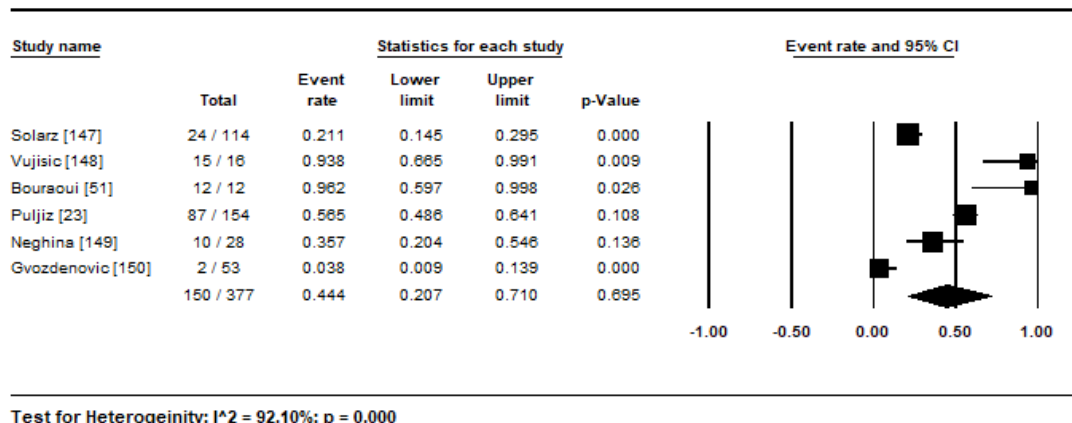**Event Rate and 95% CI for ECG abnormalities in Individuals with Helminthic Infections**

Study name	Total	Event rate	Lower limit	Upper limit	p-Value
Solarz [147]	24 / 114	0.211	0.145	0.295	0.000
Vujisic [148]	15 / 16	0.938	0.665	0.991	0.009
Bouraoui [51]	12 / 12	0.962	0.597	0.998	0.026
Puljiz [23]	87 / 154	0.565	0.486	0.641	0.108
Neghina [149]	10 / 28	0.357	0.204	0.546	0.136
Gvozdenovic [150]	2 / 53	0.038	0.009	0.139	0.000
	150 / 377	0.444	0.207	0.710	0.695

Test for Heterogeinity: I^2 = 92.10%; p = 0.000

Figure 1. Forest plot of event rate of ECG abnormalities in helminthic cardiomyopathy

Clinical evaluation

The finding of the present meta-analysis indicates that ECG abnormalities are common events in individuals with helminthic CM, affecting about 44% of the reviewed cases. Common ECG changes include repolarization abnormalities – T-wave, ST-segment depression, and sinus tachycardia, and less commonly prolonged QRS duration, low voltage QRS complex and prolonged PR interval. However, these ECG abnormalities are non-specific and less useful in the diagnosis of helminthic CM. These finding support expert consensus and reviews on the use of ECG in the diagnosis of infectious MC, where sinus tachycardia with non-specific ST segment and T-wave abnormalities are common [152]. However, the sensitivity of ECG for myocarditis is low (47%) [153]. Although the presence of Q waves or left bundle branch is uncommon, they signify a worse prognosis and higher rates of death or cardiac transplantation [154].

In the present study, echocardiography was suggested to have a high sensitivity and specificity in the diagnosis of helminthic CM. However, in the diagnosis of MC, echocardiography has no pathognomonic features for diagnosis; instead, it is a useful test to rule out other causes of CM or heart failure [152]. The loss of RV function is the most powerful predictor of death or the need for cardiac transplantation in patients with biopsy-proven myocardial damage [155]. There was limited data on the value of CMR imaging in evaluating cardiac morphological and functional changes. However, previous studies shows increasing frequency in the use of CMR in the diagnosis of suspected acute MC and it is useful to localize sites for endomyocardial biopsy, regarded as the diagnostic gold standard [156,157]. A combination of CMR modalities – T1- and T2-weghted images provide the best diagnostic sensitivity and specificity although delayed enhancement may diagnose up to 90% of the cases [158].

Besides ECG and imaging tests, serology tests, cardiac biomarkers and eosinophil count may provide additive diagnostic information. In the present findings, marked elevation of cardiac biomarkers such as C-reactive protein and creatine kinase, positive serological tests for parasite presence, and increased eosinophil count may suggest helminthic CM and pointer for additional definitive tests. The present findings are consistent with current understanding that biomarkers of cardiac injury are elevated in patients with myocardial injury especially Troponin I, which has a high diagnostic specificity (89%) but ow sensitivity (34%) in the diagnosis of MC [159]. Clinical and experimental data also suggests that increased serum levels of Troponin I is more common that increased levels of creatinine kinase MB in acute MC and CM [160]. Serological tests, used in the detection of parasite, in combination with imaging biomarkers suggest poor clinical outcomes and increased risk of death [161,162].

Clinical management

Clinical trials of therapy for hearty failure in patients with helminthic CM are clearly lacking. However, a majority of current studies support the use of antihelminthic therapy (thiabendazole, mebendazole, and diethylcarbamazinum) as the first-line treatment for helminthic infection and CM [149,150]. Antihelminthic therapy works by inhibiting tubulin polymerization and microtubule-dependent glucose uptake inhibition [103]. Since helminths have been implicated in the pathogenesis of CM particularly because of its occurrence linked to eosinophilia and hyper-eosinophilia [151], an adjunctive therapy of corticosteroids may useful in the treatment of myocardial inflammatory reaction and/or controlling aggravated eosinophilia [103,104]. Although the Myocarditis Treatment Trial advises corticosteroid treatment in

patients with biopsy-proven myocarditis has no statistical advantage but eosinophilic MC is a subset that responds well to corticosteroids [163]. A dual therapy of antihelminthic and corticosteroid has been associated with reduced parasite load and resolution of symptoms [150]. However, the value of traditional heart failure medication in the treatment of helminthic associated CM has not been evaluated. In helminthic CM patients presenting with arrhythmias, therapy for arrhythmias should be considered [164]. In patients with acute onset of infection and myocardial injury, temporary pacemaker may be required for management of bradycardia or complete heart block and patients with symptomatic or sustained ventricular arrhythmias may require amiodarone and possible implantable cardioverter defibrillator. The use of heart failure medication in the treatment of cardiac dysfunction have not been systematically evaluated [152].

Conclusion

Many diseases due to infection by helminthic parasites remain a part of neglected tropical diseases yet they are among the leading infectious agent in the world, particularly in resource-constrained countries. The thoracic organs most frequently infected are the heart and the lungs. Helminthic parasites can infect the myocardium, pericardium, endocardium or coronary vasculature. Helminthic diseases known to affect the myocardium and result in myocarditis or cardiomyopathy are *trichiniasis, cysticercosis, echinococcosis, schistosomiasis, visceral larvae migrans and ascariasis,* and less commonly *heterophyiasis, paragonimiasis, Strongyloidiasis and zoonotic filariasis.* Pathogenetic mechanisms of helminthic infection includes significant downregulation the host immune response. Myocardial injury may result from direct effect of migrating parasite larvae, eosinophil-enriched inflammatory response resulting in eosinophilic cardiomyopathy or the consequence of a more generalized illness on myocardial structures. A wide variation and non-specificity of clinical signs/symptoms and electrocardiographic abnormalities render them less useful for diagnosing helminthic cardiomyopathy. Depending on the causative parasites, definitive diagnosis rests on a combination of tests – serological tests (indirect hemagglutination test and ELISA), polymerase chain reaction (PCR)-based tests (mainly in epidemiological examinations), microscopy, and non-invasive imaging commonly echocardiography, and less commonly, cardiac magnetic resonance imaging for evaluation of signs of cardiac dysfunction. The first line of treatment of helminthic infection with myocardial involvement is often antihelminthic therapy (albendazole, mebendazole, or thiabendazole) targeting to eliminate or reduce parasite load. Adjunctive corticosteroids may be administered to control aggravated eosinophilia and treat myocardial inflammation. There is a need for further clinical trials to evaluate the efficacy of a dual therapy of antihelminthic and corticosteroid in helminthic cardiomyopathy in reducing parasite load and resolving symptoms as well as clarifying the therapeutic value of heart failure medication in patients diagnosed with helminthic cardiomyopathy.

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