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REVIEW ARTICLE

Infection

Intestinal parasites in hemodialysis patients from developing countries: A systematic review and meta-analysis

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Abstract

Intestinal parasitic infection (IPI) is the main cause of gastrointestinal complications in hemodialysis patients due to their impaired immune systems. We conducted a systematic review and meta-analysis to evaluate the prevalence and odds ratio (OR) of IPIs in this population. Relevant eligible studies were identified by searching the PubMed, Science Direct, Scopus, Web of Science, and Google scholar databases up to January 30, 2019. A random-effects meta-analysis model was used to estimate the pooled prevalence, OR, and 95% confidence intervals (CI). Twenty-two studies, from Turkey, Iran, Brazil, Egypt, Saudi Arabia, Pakistan, and Malaysia met eligibility criteria for analysis, and included 11 using a case–control design (980 patients and 893 controls) and 11 studies using a cross-sectional design (a total of 1455 participants). Cross-sectional studies suggested that the pooled prevalence of IPIs in hemodialysis patients was 24% (95% CI, 14–36%; 307/1455). In studies using a case–control design, the pooled prevalence of IPIs in hemodialysis patients (30%, 330/980) was found to be significantly higher than controls (10%, 115/893) (OR, 3.40; 95%CI, 2.37–4.87). With respect to the parasites, *Cryptosporidium* spp. (OR, 4.49; 95%CI, 2.64–7.64) and *Blastocystis* sp. (OR, 4.03; 95%CI, 1.20–13.51) were significantly higher in hemodialysis patients compared to the controls. The current study revealed a high prevalence of IPIs in hemodialysis patients from countries in which the baseline prevalence of parasitic infection is high. We recommend that periodic screenings for IPIs in such countries should be incorporated into the routine clinical care of hemodialysis patients.

Keywords: Intestinal parasitic infections, Prevalence, Hemodialysis, Systematic review

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INTRODUCTION

Patients with chronic kidney disease (CKD) or end stage renal disease (ESRD) have a weakened immune system, due to elevated levels of uremic toxins, which can lead to dysfunction of polymorphonuclear leukocytes.[1] This weakened immune system in CKD patients increases the susceptibility to various infections, and infections by bacteria, viruses, fungi, and parasites are the second most

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common cause of death among patients with ESRD undergoing hemodialysis.[2,3]

Globally, intestinal parasitic infections (IPIs) are among the most important causes of morbidity and mortality, particularly in low and middle income countries.[4–6] According to World Health Organization (WHO) reports, over 1 billion people are affected by IPIs throughout the world, and many of them suffer from symptoms and complications.[7,8] Opportunistic intestinal parasites such as *Cryptosporidium* spp., *Microsporidia*, *Isospora belli*, and *Strongyloides stercoralis* are among the most important causative agents of severe diarrhea in immunocompromised individuals, especially in patients undergoing hemodialysis.[9–11] Therefore, accurate and timely diagnosis as well as treatment of these infections is essential to improve patient health and quality of life. Herein, we performed a systematic review using a meta-analysis approach focusing on the odds ratio (OR) of IPIs in hemodialysis patients.

MATERIALS AND METHODS

Search strategy

We followed the "Preferred Reporting Items for Systematic Reviews and Meta-analyses" (PRISMA) guidelines for the design, analysis, and interpretation of our study.[12] To evaluate the prevalence of IPIs in the hemodialysis patients, a comprehensive literature search was performed in five international databases, including PubMed, Science Direct, Scopus, Web of Science, and Google Scholar (from their inception until January 30, 2019). The search process used the following keywords based on medical subject heading (MeSH) terms: "parasite," "intestinal parasites," "hemodialysis patients," "renal failure," "dialysis," "kidney disease," "prevalence," and "epidemiology," alone or in combination with "OR" and/or "AND" in English language.

Inclusion criteria

Articles were included in the meta-analysis if they met each of the following 6 criteria: (1) peer-reviewed original research paper or short report (only those short reports that estimated the prevalence of IPIs in hemodialysis patients, but not case reports); (2) case–control or cross-sectional study; (3) full text or abstract in English; (4) published online up to January 30, 2019; (5) information provided total sample size and total prevalence rates for IPIs in case–control and cross-sectional studies; and (6) survey of at least one type of intestinal parasite using standard parasitological methods.

Exclusion criteria

The exclusion criteria were as follows: (1) review articles, systematic reviews, editorials, letters, and case reports; (2) articles in languages other than English; and (3) those with confusing/unclear analysis were dismissed.

Study selection and data extraction

The final eligibility and inclusion criteria for the downloaded full texts were appraised by two trained researchers (A.T. and M.F.). The selected papers were scrutinized and discrepancies between the reviewers were resolved by discussion and consensus with a third reviewer (A. R). Afterward, an author (M.N.) extracted the necessary data, and others (A.T. and M.F.) rechecked them. Additionally, the references of the eligible papers were carefully hand-checked to find relevant articles that were not retrieved during the primary database search. Eventually, the following characteristics of each relevant article were extracted and recorded using Excel software (Microsoft, Redmond, WA, USA): first author, country, year of publication, sample size, diagnostic method, study design, age range or mean age, number of infected people in cross-sectional studies, the number of patients and healthy people in case–control studies, and the type of parasites detected in each study.

Data synthesis and statistical analysis

Statistical analyses were conducted using the R software, version 3.5.1, package for meta-analysis.[13] The prevalence of IPIs in hemodialysis patients was assessed by generating odds ratios (OR) and 95% confidence intervals (CI) using a random effect model. ORs and 95% CIs were calculated for each study using a two-by-two table in case–control studies. Heterogeneity between studies was assessed using I^2 methods. I^2 values of 25%, 50%, and 75% were considered as being of low, moderate, and high heterogeneity, respectively. In order to investigate the possibility of publication bias, Egger's plot was employed. A P value of less than 0.05 was considered statistically significant.[14] Results are presented as forest plots, with differences in prevalence rates of IPIs in hemodialysis patients and controls illustrated by a mean OR with 95% CI.

RESULTS

Study characteristics

As shown in Figure 1, we found a total of 1863 papers according to the initial search parameters in the 5 databases. After excluding duplicates, 22 articles met all eligibility criteria, and these were the basis of the systematic review and meta-analysis.[11,15–35] Of these, 11 studies had a case–control design and the remaining 11 had a cross-sectional study design. The main characteristics of the included studies are presented in Tables 1 and 2. In studies with a case–control design, the total sample sizes of the cases and controls were 980 and 893, respectively. Case–control studies were conducted in five different countries (3 in Turkey, 3 in Iran, 2 in Brazil, 2 in Egypt, and 1 in Saudi Arabia). The cross-sectional studies reported data on a total of 1455 patients, and were conducted in 6 different countries (5 in Iran, 2 in Brazil, 1 in Pakistan, 1 in Egypt, 1 in Turkey, and 1 in Malaysia).

The overall prevalence of IPIs in hemodialysis patients

Based on the random-effects model, the pooled prevalence of IPIs in hemodialysis patients was estimated to be 27% (95%CI, 19–36%; 637/2435). A substantially high heterogeneity was observed between different studies (I^2 = 95%; τ^2 = 0.0485; $P < 0.01$). Figure 2 depicts the results in forest plot format.

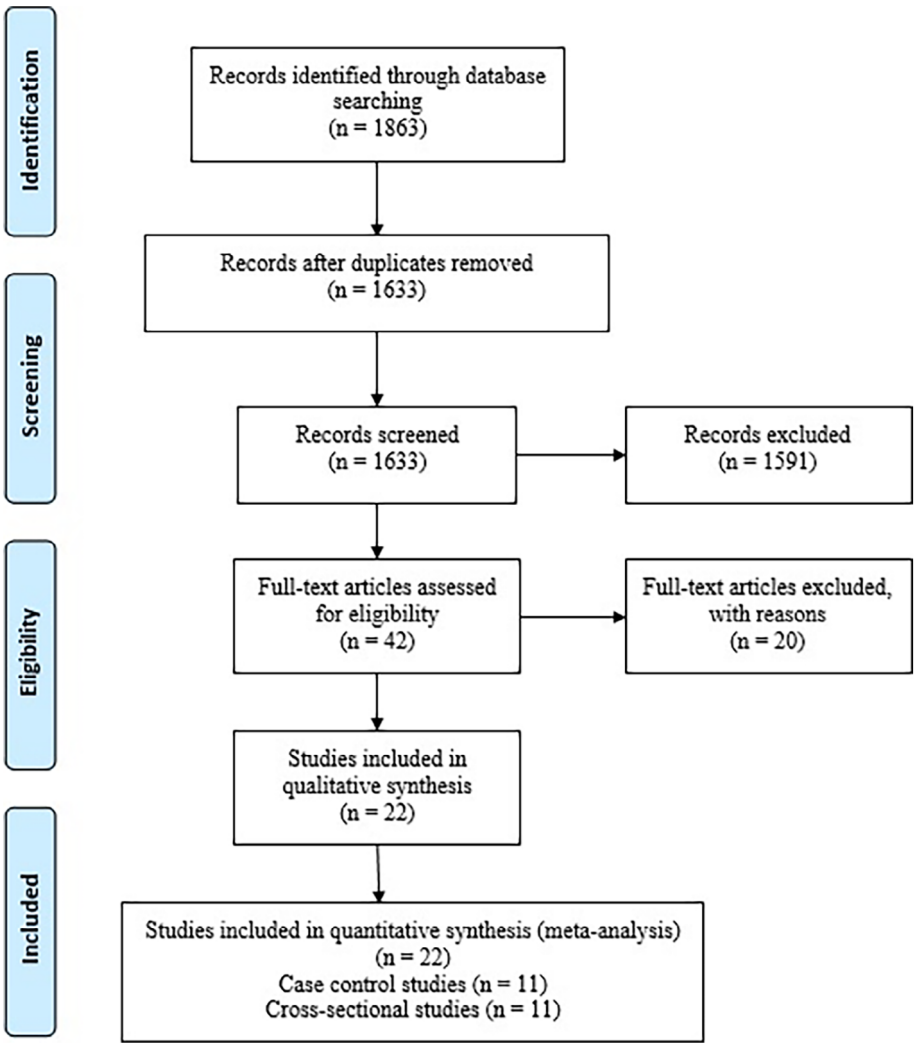

Figure 1 Flow diagram of the study design process. [Color figure can be viewed at wileyonlinelibrary.com]

Table 1 Summary of studies with case–control design investigating the prevalence of IPIs in hemodialysis patients and control subjects

						Hemodialysis patients		Control subjects	
First author	Publication year	Country	Type of parasite	Methods	Age (range or mean ± SD)	No. samples	No. positive	No. samples	No. positive
Chieffi et al.	1998	Brazil	*Cryptosporidium*	Formalin-ether, Modified Ziehl-Neelsen staining	NR	32	8	27	4
Ali et al.	2000	Egypt	Opportunistic protozoa	Formalin-ether, Ziehl-Neelsen staining, Giemsa staining	NR	120	40	40	2
Yücel et al.	2000	Turkey	*Cryptosporidium* & IPIs	Kinyoun staining	14–67	41	12	40	7
Turkcapar et al.	2002	Turkey	*Cryptosporidium*	Modified acid-fast staining	NR	74	15	50	0
Seyrafian et al.	2006	Iran	*Cryptosporidium*	Modified acid-fast staining	<20-≥60 or 45.8 ± 16.9	104	12	140	5
Hazrati Tappeh et al.	2006	Iran	*Cryptosporidium*	Formalin-ether, modified acid-fast staining	50	103	4	60	0
Kulik et al.	2008	Brazil	*Blastocystis* & IPIs	Modified Kinyoun acid-fast staining	21–82	86	33	146	36
Karadag et al.	2013	Turkey	IPIs	Formalin-ether, modified trichrome staining, acid fast, and Calcofluor staining	NR	142	62	150	19
Fallah omrani et al.	2015	Iran	IPIs	Formalin-ether, Ziehl-Neelsen	20-≥65 or 51.6 ± 16.4	78	24	140	15
Hawash et al.	2015	Saudi Arabia	Intestinal protozoa	Formalin-ether, Ziehl-Neelsen	Male:54.4 ± 12.8/ Female:51.9 ± 14.3	50	21	50	14
El-Kady et al.	2018	Egypt	*Cryptosporidium* & other protozoa	Formalin-ether, cold modified acid-fast staining	38–73	150	99	50	13

Table 2 Summary of studies with cross-sectional design investigating the prevalence of IPIs in hemodialysis patients

First author	Publication year	Country	Type of parasite	Methods	Age (range or mean ± SD)	Hemodialysis patients	
						No. samples	No. positive
Baqai et al.	2005	Pakistan	*Cryptosporidium*	Kinyoun acid-fast staining	30–49	20	7
Baiomy et al.	2010	Egypt	Opportunistic parasites	Ziehl-Neelsen staining, Agar plate	NR	30	6
Ferreira-Filho et al.	2011	Brazil	*E.histolytica/dispar*&IPIs	Hoffman method	52.1 ± 4.6	110	28
Emami Naiini et al.	2011	Iran	IPIs	Formalin-ether, modification of Sheater's sugar flotation, Modified Ziehl-Neelsen staining, Harada-Mori tube method	≤20->65	330	79
Seyrafian et al.	2011	Iran	IPIs	Formalin-ether, trichrome staining	54 ± 17	155	45
Gil et al.	2013	Brazil	IPIs	Formalin-ether	52.8 ± 14.8	110	57
Barazesh et al.	2015	Iran	IPIs	Formalin-ether	≤30->71	88	25
Cengiz et al.	2017	Turkey	*Cryptosporidium*	Modified acid fast staining	51.24 ± 15.25	96	7
Rasti et al.	2017	Iran	IPIs	Formalin-ether, Ziehl-Neelsen staining, Agar plate	<20-≥60	135	16
Mohaghegh et al.	2017	Iran	*Cryptosporidium*	Formalin-ether, modified Ziehl-Neelsen staining	≤20-≥65	330	10
Hassan et al.	2018	Malaysia	Microsporidia	Formalin-ether, Gram-Chromotrope Kinyoun staining	<18-≥18	51	27

Prevalence/odd ratio of IPIs based on the type of study

In studies with a case–control design, the pooled prevalences of IPIs were estimated to be 30% (330/980) and 10% (115/893) in hemodialysis patients and healthy controls, respectively. In cross-sectional studies, the pooled prevalence of IPIs in hemodialysis patients was estimated as 24% (95%CI, 14–36%; 307/1455; I^2 = 95%; τ^2 = 0.0420; P < 0.01) (Supporting Information Figure S1A,B).

As shown in Figure 3, we found that the overall pooled odds ratio (OR) of IPIs was significantly higher in hemodialysis patients compared to healthy controls (OR, 3.40; 95%CI, 2.37–4.87). A moderate heterogeneity (I^2 = 37%; τ^2 = 0.1220; P = 0.11) was observed between studies.

Prevalence/odd ratio of IPIs based on the type of parasites in case–control studies

Based on the types of parasites identified in the case–control studies, the estimation of the pooled prevalences of *Cryptosporidium* spp., *Giardia lamblia*, *Entamoeba histolytica/dispar*, and *Blastocystis* sp. were 13% (95%CI, 7–22%), 4% (95%CI, 1–10%), 3% (95%CI, 0–10%), and 6% (95%CI, 0–21%), respectively, in hemodialysis patients, and 2% (95%CI, 0–4%), 4% (95%CI, 1–7%), 2% (95%CI, 0–6%), and 1% (95% CI, 0–4%) in healthy controls (Supplementary Figure 2, 3A, and 3B).

Subgroup analysis considering the causative parasite revealed a significantly higher prevalence of *Cryptosporidium* spp. (OR, 4.49; 95%CI, 2.64–7.64; I^2 = 0%; τ^2 = 0.0419; P = 0.55) and *Blastocystis* sp. (OR, 4.03; 95%CI, 1.20–13.51; I^2 = 46%; τ^2 = 0.6972; P = 0.12) in hemodialysis patients compared to healthy controls (Supporting Information Figure S4A,B). On the other hand, the prevalences of pathogenic protozoa, nonpathogenic protozoa, and helminths were calculated to be 18% (95%CI, 6–35%), 5% (95%CI, 0–15%), and 0% (95%CI, 0–2%) respectively, among hemodialysis patients, and 5% (95%CI, 1–11%), 1% (95%CI, 0–3%), and 0% (95%CI, 0–1%) among controls (Supporting Information Figure S5A,B and 6). Prevalence estimates of pathogenic protozoa (OR, 3.33; 95%CI, 2.09–5.30; I^2 = 1%; τ^2 = 0.0867; P = 0.42) and nonpathogenic protozoa (OR, 3.34; 95%CI, 1.21–9.25; I^2 = 51%; τ^2 = 0.9601; P = 0.04) showed significantly higher prevalences of these organisms in hemodialysis patients in comparison to healthy controls (Supporting Information Figure S7). These data are summarized in Table 3.

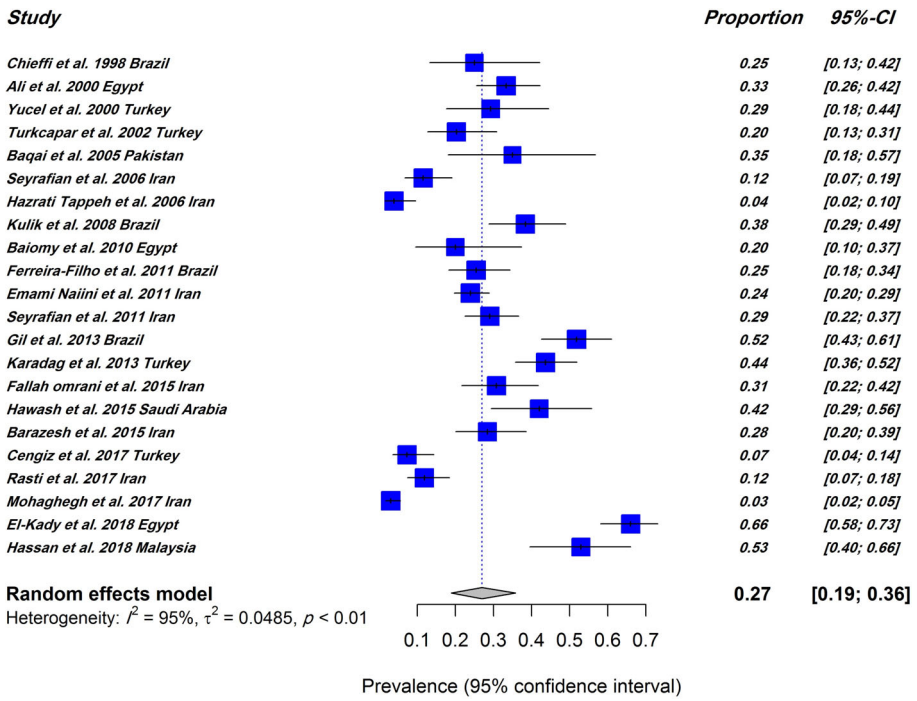

Figure 2 Forest plot of prevalence of intestinal parasitic infections in hemodialysis patients. [Color figure can be viewed at wileyonlinelibrary.com]

Prevalence of IPIs based on the type of parasite in cross-sectional studies

Analysis of cross-sectional studies based on the type of parasite estimated the pooled prevalences of *Cryptosporidium* spp., *G. lamblia*, *E. histolytica/dispar*, and *Blastocystis* sp. to be 5% (95%CI, 1–11%), 2% (95%CI, 1–4%), 2% (95%CI, 0–5%), and 26% (95%CI, 17–37%), respectively among hemodialysis patients (Supporting Information Figures S8 and S9). Furthermore, the prevalences of pathogenic protozoa, nonpathogenic protozoa, and helminths were 13% (95%CI, 6–22%), 10% (95%CI, 3–20%), and 1% (95%CI, 0–2%), respectively (Supporting Information Figures S10 and S11). These data are summarized in Table 4.

Publication bias

To identify potential publication bias, we used an Egger's plot. The plot indicated that there was no significant

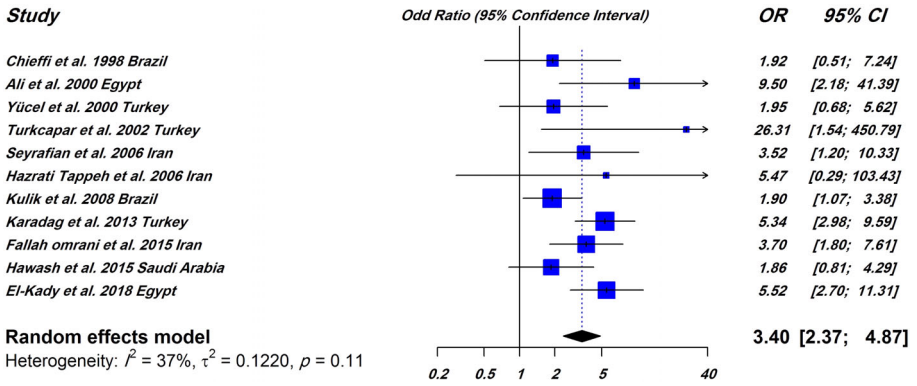

Figure 3 Forest plot of odds ratios for relationship between prevalence of IPIs and hemodialysis patients in case–control studies. [Color figure can be viewed at wileyonlinelibrary.com]

Table 3 Subgroup meta-analysis of the prevalence/OR of IPIs in case–control studies

		Cases		Controls			OR heterogeneity		
Parasites	No. studies	N/infected	Pooled prevalence%	N/infected	Pooled prevalence%	OR (95%CI)	I^2%	τ^2	P
Pathogenic protozoa[a]	9	718/171	18	703/42	5	3.33 (2.09–5.30)	1	0.0867	0.42
Nonpathogenic protozoa[b]	9	718/63	5	703/17	1	3.34 (1.21–9.25)	51	0.9601	0.04
Cryptosporidium spp.	10	838/136	13	743/19	2	4.49 (2.64–7.64)	0	0.0419	0.55
Giardia lamblia	5	405/26	4	426/15	4	1.13 (0.51–2.53)	0	0.0143	0.57
E. histolytica/dispar	5	405/25	3	426/10	2	1.07 (0.50–2.29)	0	0	0.84
Blastocystis sp.	5	405/37	6	426/8	1	4.03 (1.20–13.51)	46	0.6972	0.12
Helminthes	4	255/2	0	376/2	0	—	—	—	—

[a]The pathogenic intestinal protozoa include: *Entamoeba histolytica*, *Giardia*, *Cryptosporidium* spp., *Cyclospora cayetanensis*, *Isospora belli*, Microsporidia, *Dientamoeba fragilis*, and *Balantidium coli*.
[b]The nonpathogenic intestinal protozoa include: *Blastocystis* sp, *Chilomastix mesnili*, *Endolimax nana*, *Entamoeba coli*, *Entamoeba dispar*, *Entamoeba hartmanni*, *Entamoeba polecki*, *Iodamoeba buetschlii*, and *Trichomonas hominis*.

publication bias in both case–control (P = 0.43) and cross-sectional (P = 0.17) designs (Supporting Information Figures S12A,B).

DISCUSSION

IPIs are one of the important causes of diarrhea in hemodialysis patients occurring mostly in lower income and less developed countries.[15,29] Thereby, understanding their epidemiology is crucial in implementing effective control strategies against IPIs in these populations. In this systematic review, we evaluated the prevalence and ORs of IPIs in hemodialysis patients from developing countries.

Our review and meta-analysis revealed that IPIs had an overall prevalence of 27% in hemodialysis patients in developing economies in the Middle East and South America. According to the case–control studies analyzed, the prevalences of IPIs overall were significantly higher in the hemodialysis patients compared to controls (OR, 3.40; 95%CI, 2.37–4.87). Of the 11 articles analyzed that used a case–control design, 7 reported a significantly higher prevalence of IPIs in the hemodialysis patients[15,18,20,29,31,32,35] in comparison to the controls.

Our findings showed that *Cryptosporidium* spp. had a higher prevalence in hemodialysis patients (13%) than in controls (2%), with the prevalence rate in dialysis patients being similar to that reported in other immunocompromised patients; for example, a recent global meta-analysis study performed among HIV-infected persons reported a pooled prevalence of *Cryptosporidium* species as 14%.[36] This parasite is an intracellular opportunistic pathogen that can cause life-threatening infection in immunocompromised subjects.[37]

Our results demonstrated that *Blastocystis* sp. as another parasite with high prevalence rates in hemodialysis patients, which is in line with recent studies conducted in various population groups.[4,38,39] *Blastocystis* is a

Table 4 Subgroup meta-analysis of the prevalence of IPIs in cross-sectional studies

				Heterogeneity		
Parasites	No. studies	N/infected	Pooled prevalence (N/%)	I^2%	τ^2	P
Pathogenic protozoa[a]	10	1300/127	13	94%	0.030	<0.01
Nonpathogenic protozoa[b]	10	1300/156	10	96%	0.052	<0.01
Cryptosporidium spp.	9	1249/65	5	93%	0.024	<0.01
G. lamblia	6	803/21	2	30%	0	0.21
E. histolytica/dispar	6	803/12	2	74%	0	<0.01
Blastocystis sp.	6	803/54	26	90%	0.01	<0.01
Helminthes	3	528/4	1	0	0	0.87

[a]The pathogenic intestinal protozoa include: *Entamoeba histolytica*, *Giardia*, *Cryptosporidium* spp., *Cyclospora cayetanensis*, *Isospora belli*, Microsporidia, *Dientamoeba fragilis*, and *Balantidium coli*.
[b]The nonpathogenic intestinal protozoa include: *Blastocystis* sp, *Chilomastix mesnili*, *Endolimax nana*, *Entamoeba coli*, *Entamoeba dispar*, *Entamoeba hartmanni*, *Entamoeba polecki*, *Iodamoeba buetschlii*, and *Trichomonas hominis*.

molecularly divergent microorganism with 17 subtypes (STs) reported among human and animal hosts.[40,41] Despite the availability of several articles on the distribution pattern of *Blastocystis* and the risk factors for the infection, there is no strong proof signifying the pathogenic nature of this protozoan in human cases.[42] Studies suggested that the organism's role in nonspecific gastrointestinal symptoms such as diarrhea, constipation, abdominal pain, nausea, and vomiting together with extraintestinal manifestations, particularly urticaria.[43] The role of *Blastocystis* in the development of inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS)[44–46] was also reported recently, but there was not good evidence supporting the association of *Blastocystis* with gastrointestinal disorders. Thus *Blastocystis* is still considered as a nonpathogenic parasite.[47,48] Nonetheless, our study pointed out that *Blastocystis* is prevalent in hemodialysis patients, and thus may warrant further study to better understand its potential adverse effects on this population.

Our analysis of the literature found that the prevalences of *G. lamblia*, *E. histolytica/dispar*, and helminths were no significant higher in hemodialysis patients than in controls. The prevalence of helminthic infections was estimated to be less than 1%. Although the prevalence of helminthic infections was very low among hemodialysis patients,[15,17,18,33] one should not neglect these infections as they can still cause hyperinfections (Medical definition: repeated reinfection with larvae produced by parasitic worms already in the body due to the ability of various parasites to complete the life cycle within a single host) in immunocompromised persons.[30,49,50]

Limitations

Our systematic review and meta-analysis has several limitations as mentioned below: (1) Lack of published information on the prevalence of IPIs in hemodialysis patients from many parts of the world; all the selected studies were from countries with high prevalence of parasitic infections, and thus the data cannot be extrapolated to countries where the risk of parasitic infections is low. Diagnosis of parasitic infection was based on microscopic analysis of the stool. Although patients and controls were screened with the same diagnostic tools.

CONCLUSION

The results of this systematic review and meta-analysis revealed a higher prevalence of IPIs in hemodialysis patients compared to controls, especially of severe *Cryptosporidium* species infection. In endemic regions, providing a suitable personal hygiene and also regular health checkup for IPIs in hemodialysis patients presenting with gastrointestinal symptoms are recommended.

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AUTHOR CONTRIBUTIONS

All authors contributed to the study design. A.T. contributed to all parts of the study. A.R., M.F., and M.N. contributed to study implementation. M.O. collaborated in the analysis and interpretation of data. A.T., V.V., and A.R. collaborated in the manuscript writing and revision. All the authors commented on the drafts of the manuscript and approved the final version of the article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Supplementary Fig 1A Forest plot of prevalence of Intestinal parasitic infections in case–control studies.

Supplementary Figure 1B: Forest plot of prevalence of Intestinal parasitic infections in cross-sectional studies and cases from case–control studies.

Supplementary Figure 2: Forest plot of prevalence of *Cryptosporidium* sp. case–control studies.

Supplementary Figure 3A: Forest plot of prevalence of *Giardia lamblia*, *Entamoeba histolytica/dispar* and *Blastocystis* sp from cases in case–control studies.

Supplementary Figure 3B: Forest plot of prevalence of *Giardia lamblia*, *Entamoeba histolytica/dispar* and *Blastocystis* sp from controls in case–control studies.

Supplementary Figure 4A. Forest plot of odds ratios for relationship between prevalence of *Cryptosporidium* sp. and hemodialysis patients in case–control studies.

Supplementary Figure 4B. Forest plot of odds ratios for relationship between prevalence of *Giardia lamblia*, *Entamoeba histolytica/dispar* and *Blastocystis* sp with hemodialysis patients in case–control studies.

Supplementary Figure 5A: Forest plot of prevalence of pathogenic protozoa and non-pathogenic protozoa from cases in case–control studies.

Supplementary Figure 5B: Forest plot of prevalence of pathogenic protozoa and non-pathogenic protozoa from controls in case–control studies.

Supplementary Figure 6: Forest plot of prevalence of helminths in case–control studies.

Supplementary Figure 7. Forest plot of odds ratios for relationship between prevalence of pathogenic protozoa and non-pathogenic protozoa with hemodialysis patients in case–control studies.

Supplementary Figure 8: Forest plot of prevalence of *Cryptosporidium* sp. in cross-sectional studies.

Supplementary Figure 9: Forest plot of prevalence of *Giardia lamblia*, *Entamoeba histolytica/dispar* and *Blastocystis* sp from cases in cross-sectional studies.

Supplementary Figure 10: Forest plot of prevalence of pathogenic protozoa and non-pathogenic protozoa from controls in cross-sectional studies.

Supplementary Figure 11: Forest plot of prevalence of helminths in cross-sectional studies.

Supplementary Figures 12A and B: Publication bias using Egger's plot. (A) Publication bias in studies with case–control design (B); Publication bias in studies with cross-sectional design.