ORIGINAL ARTICLES

Seroprevalence of Strongyloides infection among steroid recipients in a tertiary care centre in North India

Running title: Seroprevalence of Strongyloides infection

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SUMMARY

Background: *Strongyloides stercoralis (S. stercoralis)*, a unique parasite, can cause mortal disease even years after the exposure. Iatrogenic use of steroids can complicate asymptomatic infections to a life-threatening hyperinfection and/or disseminated infection. Data regarding seroprevalence of strongyloidiasis remains scarce and this knowledge gap needs due attention in many endemic countries including India.

Aim: The present study is aimed at assessing the seroprevalence of Strongyloides infection and the need for routine screening among individuals receiving steroid therapy.

Methodology: Eighty patients receiving steroid therapy and thirty healthy volunteers who had not received any immunosuppressive drugs and/or anthelminthic therapy in last six months were enrolled as cases and controls respectively and they were screened by Strongyloides IgG ELISA.
Results: Among the 80 patients on steroids, the mean cumulative prednisolone equivalent dose received was 8.2 g (± 11.2g) for a mean duration of 184 days, 16 patients (20%, 95% CI 11.9-30) had a positive Strongyloides IgG serology. Only 4 controls (4/30, 13.3%, CI 3.8-30.7) tested positive (p=0.4).
Conclusions: Our study demonstrated a Strongyloides seroprevalence of 20% in the study population emphasizing the need for screening for Strongyloides infection prior to immunosuppressive therapy in order to prevent hyperinfection or possible dissemination.

INTRODUCTION

Strongyloidiasis is an intestinal parasitic disease caused by *Strongyloides stercoralis* and 50% of patients are asymptomatic which leads to an underestimated figure of its prevalence. Other species including *Strongyloides fuelleborni (fülleborni) subsp. fuelleborni and S. fuelleborni subsp. kellyi* are rarely the causative agents of strongyloidiasis in humans. This disease is most commonly seen in the tropics and subtropics and in people infected with Human T-Lymphotropic Virus-1 (HTLV-1), patients on corticosteroid or other immunosuppressive therapy, transplant recipients or those with malnutrition. It has been estimated that at least 600 million individual may be infected with this parasite worldwide [1]. According to the prevalence, the burden of Strongyloides can be classified as: sporadic (< 1%), endemic (1-5%) and hyperendemic (>5%) [2]. In a systematic review conducted among migrants hailing from endemic countries, pooled Strongyloides prevalence was 12.2%, with highest seroprevalence reported amongst those migrating from East Asia and Pacific (17.3%), sub-Saharan Africa (14.6%) and Latin America and the Caribbean (11.4%) regions. This study however projected insufficient data representing South-East Asia [3]. In contrast, another recent review estimated the global prevalence to be 8.1% with South East Asia bearing the highest prevalence (12.1%), followed by the African Region (10.3%) and Western Pacific Region (7.13%) (1). Yet, epidemiological information on strongyloidiasis is relatively scarce due to variability in disease distribution across countries and suboptimal diagnostic yield [4].

Strongyloides species has a complex life-cycle producing both parasitic and free-living form. First stage larva excreted from the infected host can develop by two possible methods, the homogonic (direct) development of filariform larva, the infective stage and heterogonic (indirect) development to free-living adults which reproduce sexually to release eggs. These eggs (oval, thin shelled, measuring 50-58 μm long by 30-34 μm wide) hatch into rhabditiform larvae (measuring up to 380 μm long and 20 μm wide) which then turn into infective filariform larvae (measuring up to 630 μm long and 16 μm wide) [5]. Filariform larvae enter the host through the percutaneous route, find their way circulating through pulmonary vasculature, entering airways to be swallowed and reach their destination in the intestine. By this time, it develops into mature adult worms which remain burrowed in the intestinal lumen. The adult female worm lays embryonated eggs which hatch within the intestinal lumen releasing rhabditiform larvae in the feces.

Autoinfection has been classically described in strongyloidiasis where the adult female worm through a process of parthenogenesis lays a large number of eggs which hatch within the lumen. In conducive settings, the rhabditiform larvae mature into filariform larvae within the intestinal lumen, penetrate the gut mucosa and disseminate to various organs, or puncture the skin of the perianal region to re-enter the circulation of the same host, thereby causing hyperinfection or maintaining the chronic carrier state that can last up to decades.

Immuno-compromised hosts, particularly steroid recipients, may have an accelerated auto infective cycle leading to Strongyloides hyperinfection or dissemination which can prove fatal unless intervened timely. Corticosteroids can potentiate subclinical state of infection such as strongyloidiasis by impairing both innate and adaptive immune responses. Evidence shows that steroid therapy even in moderate doses, can trigger off a fatal flare of strongyloidiasis; and hyperinfection syndrome has been described regardless of dose, duration and route of administration of corticosteroids [6-9]. Treatment with steroids induces an increase in fertility of adult female *S. stercoralis* resulting in an increase in production of eggs and facilitates larval dissemination in the infected host [10]. Steroid treatment acutely suppresses eosinophilia and T-helper 2 cell (Th2 response) activation Th2 responses are essential for protection against hyperinfection [11]. Further, expansion of Th2/ Th9 cells lead to concomitant contraction of Th1 and Th17 cells [12]. It is therefore imperative to identify and treat the condition before any immunosuppressive strategy is employed.

Diagnosis of Strongyloides infection is fraught with difficulties of low sensitivity by conventional stool microscopy even with multiple stool samples. Different methods have been described to increase the detection rate of stool examination. These include formalin-ethyl acetate concentration, agar-culture plate method, Baermann method based on the ability of larvae to convert to free-living stage and Harada-Mori filter paper method based on water tropism of the larvae. Stool specimen processed by a modified Harada Mori technique or Petri-dish method were studied and the sensitivity of microscopy using a single stool sample was found to vary between 20% to 50% [13]. To somewhat circumvent these challenges, Enzyme-linked immunosorbent assay (ELISA) for the detection of circulating anti-Strongyloides serum antibodies, with a reported sensitivity up to 95% despite some of its limitations, is being increasingly used in conjunction with stool studies [14]. Genta et. al. found Strongyloides IgG ELISA to be 88% sensitive, 99% specific, with positive and negative predictive values of 97% and 95% respectively [15].

India is considered hyperendemic for strongyloidiasis, however, data from India regarding Strongyloides seroprevalence remains scarce. A systematic review including nine hospital based and five community-based studies from India reported an infection rate of 11.2% and 6.6% respectively [4]. A community-based study from the North Eastern part of India (Assam State) demonstrated positivity of 8.5% (17 of 198) [16]. Most of the studies available from this part of the sub-continent were based on stool examination using various techniques. Serodiagnostic studies on strongyloidiasis in India have been limited, in fact only one as per our knowledge [17]. For screening as well as for early diagnosis, serological testing is arguably the suitable approach. In this context, the present study was carried out to estimate the seroprevalence of Strongyloides among steroid recipients and to compare it with that of a healthy control group.

PATIENTS AND METHODS

Study design and setting

This cross-sectional study was conducted at the All India Institute of Medical Sciences, New Delhi, India which is a tertiary care hospital located within coordinates 28.5672° N, 77.2100° E. Between April and December 2019, patients attending outpatient clinics under departments of Medicine and Dermatology, as well as in-patients admitted in the Departments of Medicine and

Dermatology were screened for eligibility and subsequent enrollment. Ethical clearance for this study was obtained from the Institutional Ethics Committee (IEC) prior to initiation of the study.

Sample size calculation

Considering the prevalence rate (p) of 8.5% as per Indian reports, Confidence interval (CI) at 95% (*i.e.* z=1.96) and error margin(e) of 5%, using the formula sample size (N) = $z^2p(1-p)/e^2$ a sample size of 120 was deduced.

In this study the focus was on the study population receiving steroids in hospital setting. A pilot study including eighty (n=80) patients who were receiving steroid treatment for various illnesses and thirty (n=30) healthy controls were included [Financial constrains for availability of test kits also limited a larger pilot study].

Sampling

Patients above sixteen years of age (>16 years), visiting the outpatient department and/or admitted under the departments of Medicine or Dermatology were screened for eligibility. Those receiving systemic corticosteroids at a minimum dose of 10 mg/day of methyl prednisolone or an equivalent dose of other corticosteroids for a minimum duration of 2 weeks were included in the steroid recipient arm (n=80). Thirty healthy volunteers who had never received any immunosuppressive agent and/or anthelmintic therapy in last 6 months were included as controls (n=30). Patient screening conducted for the study has been depicted in Figure 1.

After obtaining a written informed consent, an interview was conducted and necessary examination was carried out. Data collection included clinic-demographic data, details regarding prior illness, details of steroid use such as dose and duration, and use of any other immunosuppressant drug. Physical examination was performed to look for any suggestive dermatological lesion. Biochemical investigations such as hemoglobin levels and eosinophil count were recorded. After obtaining patients' consent, approximately 2-3 mL of blood sample were collected by venipuncture in a plain vacutainer. Serum obtained on centrifuging these samples were tested for Strongyloides IgG ELISA. All patients were advised to submit freshly collected stool specimen on three consecutive days to screen for Strongyloides infection.

The serum samples of the study subjects were tested for the presence of Anti-Strongyloides IgG antibodies using a commercial ELISA kit (Bordier Affinity Products SA, Switzerland). This kit uses the *Strongyloides ratti* antigen with sensitivity and specificity of 83% and 97.2% respectively [18]. The assays were performed as per the manufacturer's instructions.

Statistical analysis

Data was collected in a predesigned proforma**.** Categorical variables were summarized as absolute numbers or frequency (percentage) and analyzed using χ^2 or Fisher's exact test. Continuous variables were summarized as mean and standard deviation (SD) or median and range (when SD was >50% of mean) and analyzed using appropriate test. Two-tailed Fisher's exact tests were used to define associations between patient factors and positive *Strongyloides* laboratory results. A value of P <0.05 was considered significant. The SPSS software for Windows (version 19.0; SPSS Inc., Chicago, IL) was used for statistical analyses.

RESULTS

A total of 80 patients receiving steroids (41males, 39 females) and 30 healthy controls (18 males, 12 females) were recruited in the year 2019 at AIIMS, New Delhi. The mean age of participants in the steroid group was 37.6 ± 14.2 years, and that in the control group was 45 ± 23 years. Patients included in the study were residents of New Delhi (40%) or other neighboring states namely Uttar Pradesh, Haryana or Bihar.

Among the 80 patients on steroids, 59 (73.7%) received prednisolone, 20 (25%) patients received dexamethasone and one patient received methyl-prednisolone 1 (1.25%). The mean cumulative prednisolone equivalent dose received was 8.2 g (± 11.2 g) for a mean duration of 184 days. Among these, 12 patients had received a high dose pulse steroid therapy in addition to maintenance therapy. Additionally, 12 patients received azathioprine and 8 patients received cyclophosphamide, of which 4 patients were on a combination of two immunosuppressants. rituximab, tocilizumab and mycophenolate mofetil were prescribed to one patient each, in addition to steroids. Various clinical conditions for which steroid therapy was prescribed, have been listed in Table 1.

All patients enrolled in our study were screened for symptoms suggestive of Strongyloides infection. None of the controls reported any symptoms. Among steroid recipients, gastrointestinal symptoms were observed in 13 (16.25%, 13/80) patients (Figure 2).

Diarrhoea and abdominal pain were reported by 13.75% and 8.75% respectively. Majority of patients reported other symptoms such as fever, weight loss and abdominal bloating which was attributed to the pre-existing underlying illness after individual case assessment and seemed unlikely to be related to strongyloidiasis. One patient with Idiopathic Thrombocytopenic Purpura

(ITP) on long term oral steroids presented with Strongyloides hyperinfection, with multiple episodes of watery diarrhoea and hypovolemic shock. Rhabditiform larvae were demonstrated on stool and sputum microscopy. He received oral ivermectin therapy for 8 days after which parasite clearance in the stool was documented.

Among the total one hundred and ten (n=110) participants included in the study, 38 patients had submitted stool samples which were processed using formol-ether concentration technique. Strongyloides IgG ELISA was performed on a single serum sample obtained from all participants. Among 80 steroid recipients, 16 (20%, 95% CI 11.9-30) were positive for Strongyloides IgG serology, while 4 out of 30 controls (13.3%, 95% CI 3.8-30.7, p=0.4) tested positive. Among the 16 steroid recipients with positive Strongyloides serology, gastrointestinal symptoms were seen in 2 (12.5 %) patients. Surprisingly eosinophilia (>500 cells/cu. mm.) was encountered in 4 patients, all four were steroid recipients, of which only one patient had Strongyloides IgG antibodies. Only one patient among the 16 with positive Strongyloides serology had eosinophilia. Influence of various other factors on Strongyloides seropositivity has been outlined in Table 2.

DISCUSSION

S. stercoralis due to its unique ability to auto-infect, can cause life-long infection with most patients remaining unaware of their infection. Risk of potentially fatal complications makes it imperative for the clinicians to search and treat the infection even in those asymptomatic, especially in patients receiving steroids or other immunosuppressive therapy.

The risk factors for acquiring the disease have been elucidated by multiple previous publications. In India, factors like poor sanitation and the practice of walking barefoot increases the risk of acquiring the infection. A cross sectional study from South India reported higher incidence of strongyloidiasis (diagnosed by stool microscopy) among patients receiving steroids and in HIV-positive individuals with low CD4 count [19]. This can be explained as steroid hormones have been proposed to serve as endogenous ligands of the *S. stercoralis* nuclear hormone receptor DAF-12, which regulates the reproductive process of nematodes [20].

Screening using serology for Strongyloides is being adopted in the context of hematopoetic stem cell transplantation as well as solid organ transplantation. In a USA based study involving 1689 renal transplant candidates, 168 (9.9%) were seropositive when screened prior to transplantation

and 6.8% subsequently seroconverted on serial screening [21]. While the Infectious Diseases Society of America, the American Society of Transplantation, the Centers for Disease Control and Prevention, and the American Society of Blood and Marrow Transplantation recommend screening for Strongyloides IgG by ELISA in patients from endemic regions, with gastrointestinal symptoms or those with eosinophilia prior to transplantation, no such clear guidelines exist with regard to steroid therapy [22, 23].

Diagnosis of strongyloidiasis is limited by low sensitivity of stool microscopy. Therefore, there is growing interest in serodiagnosis, although there have been no large-scale studies reporting the seroprevalence from India. In our study, of the 110 total samples, 20 (18.18%, 95% CI 11.47-26.67) tested Strongyloides ELISA positive. This is in agreement with recent estimates from other studies. In a serology study conducted in Malaysia, asymptomatic people of Indian or Myanmar nationality had significantly higher seropositivity rates as compared with other countries [24]. A study performed in hemophilia patients from India showed 20.4% seropositivity (33 of 161 serum samples), with highest seroprevalence seen among patients from North India (9 of 33 seropositive samples) [17].

Advantages of serology testing is that ELISA may be positive despite repeated stool examinations being negative. However, it can be false negative in immunocompromised hosts and false positive in patients with filariasis or ascariasis. Antibodies can persist even after treatment; therefore, a single test cannot distinguish between past and current infection [25].

In our study, 16 of 80 patients (20%, 95% CI 11.9-30) on steroids, with no prior symptoms or treatment for Strongyloides infection tested Ig G ELISA positive, but no statistically significant difference was observed between the steroid group and controls, possibly owing to a smaller sample size. One patient receiving steroids for Idiopathic Thrombocytopenic Purpura presented with hyperinfection. A relatively high number of steroid recipients may have been exposed, and may still harbour the parasite and steroid therapy could potentially complicate it to a hyperinfection. A study conducted in Thailand including 135 patients noted a seroprevalence rate of 5.4% by IgG ELISA (sensitivity 42.9%, specificity 96.3%) and 6.7% by the gold standard agar plate culture technique (sensitivity 75%, specificity 100%). Similarly to our study, the authors did not find a statistically significant difference in prevalence between patients on steroid therapy and others. Among eight Strongyloides positive patients, three patients presented with hyperinfection syndrome, two of these three patients had received steroids and the third patient

had acute myeloid leukemia. Similar to our results, the authors concluded that an association between Strongyloides positivity and eosinophilia could not be drawn [26]. Hence, routine screening for Strongyloides infections by stool microscopy, culture and serological assays should be incorporated as an essential component in patient management prior to initiation of steroids.

It is noteworthy that patients with hyperinfection may have low titres of Strongyloides specific antibodies with low or normal eosinophil count [26, 27]. A systematic review studying the correlation between strongyloidiasis and eosinophilia reported sensitivity and PPV for the diagnosis of recent infection to be 0%; the specificity and NPV were 95% and 99%, respectively [28].

The drug of choice for strongyloidiasis is ivermectin which mediates parasite killing through glutamate activated chloride channels. The recommended therapy schedule is ivermectin 200 μg/kg per day (or double dose) for 2 days, repeated during the second and fourth week [29]. In case of hyperinfection, daily doses are continued until parasite clearance has been demonstrated. Several studies have demonstrated better results with ivermectin as compared to albendazole and thiabendazole, making it the drug of choice for strongyloidiasis [29]. Although a recent randomized controlled trial showed that a multiple dose regimen of ivermectin offered no advantage in efficacy over single dose, the applicability of this in the immunocompromised cohort is questionable owing to severe complications in these patients [30]. While serological testing may have economical and technical limitations, few studies assessing cost effectiveness of screening showed presumptive therapy was the most cost-effective strategy [31]. It is prudent to also keep in mind principles of antimicrobial stewardship at the same time and implement screening practices when available and accessible.

There were few limitations to our study. This study could manage to include a small sample size of 110 patients. The steroid recipient group constituted a heterogenous population with varied underlying co-morbid conditions, and this may lead to some bias. However, the overall objective to identify the at-risk group could be addressed. In the immunosuppressed cohort, screening of stool samples by either agar plate cultures or Baermann technique is recommended along with serological screening [32]. Adequate numbers of stool specimen could not be obtained due to non-compliance of patients even after adequate counseling. Positive serology cannot distinguish between current and past infection, and serology may give false negative results in immunocompromised patients. However, for patients who currently reside, or have lived in areas

where strongyloidiasis is endemic, it is appropriate to conduct serological studies for early diagnosis. An important drawback in this context would be false positivity of Strongyloides serology with other nematodes such as *Ascaris lumbricoides*, which may co-exist in these regions. Therefore, use of recombinant antigen in place of crude antigen would prove useful especially in such endemic areas, for screening of strongyloidiasis.

CONCLUSION

Our study reports a 20% seroprevalence in patients on steroids, who had no prior symptoms or therapy for Strongyloides infection. This underscores the need to be aware of this neglected tropical disease to timely screen and treat the infection. Further studies are required to evaluate the need for routine screening for Strongyloides infection by serological assays and/or stool microscopy, preferably prior to initiation of immunosuppressive therapy.

CONFLICT OF INTEREST

None

FUNDING

None

AUTHORS CONTRIBUTIONS

PK and MS conceived the study; AR and PK designed the study protocol; AR and KJ carried out the clinical assessment; RB, NV and BRM carried out the immunoassays and stool processing, AR, PK, KJ and MS performed analysis and interpretation of the data. AR, KJ and PK drafted the manuscript; MS, NV, KS, NKV, BRM and NW critically revised the manuscript for intellectual content. All authors read and approved the final manuscript. MS and NW are guarantors of the paper.

ETHICAL APPROVAL

Obtained from AIIMS Institutional Ethics Committee: Ref. No. IECPG-193/27.03.2019

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Table 1 - Underlying clinical conditions of patients warranting steroid therapy (total number of patients=80).

Clinical conditions	**Patients, n (%)**	**Details**
Rheumatologic conditions	27 (33.75)	SLE (12), MCTD (4), Vasculitis (3), Ankylosing spondylitis (2), Adult onset Still's disease (2), Dermatomyositis (2), Systemic sclerosis (2)
Dermatological condition	18 (22.5)	Pemphigus vulgaris (13), DRESS/TEN (2), Pyoderma gangrenosum (1), Hereditary Angioedema (1), Endogenous dermatitis (1)
CNS TB	13 (16.25)	
Hematological conditions	7 (8.75)	AIHA (3), ITP (3), AML (1)
Respiratory conditions	7 (8.75)	NSIP (4), PCP (2), Sarcoidosis (1)
Others	8 (10)	Autoimmune encephalitis (4), Peliosis hepatis (1), Nephritic syndrome (1), Neurocysticercosis (1), Adrenal insufficiency (1),

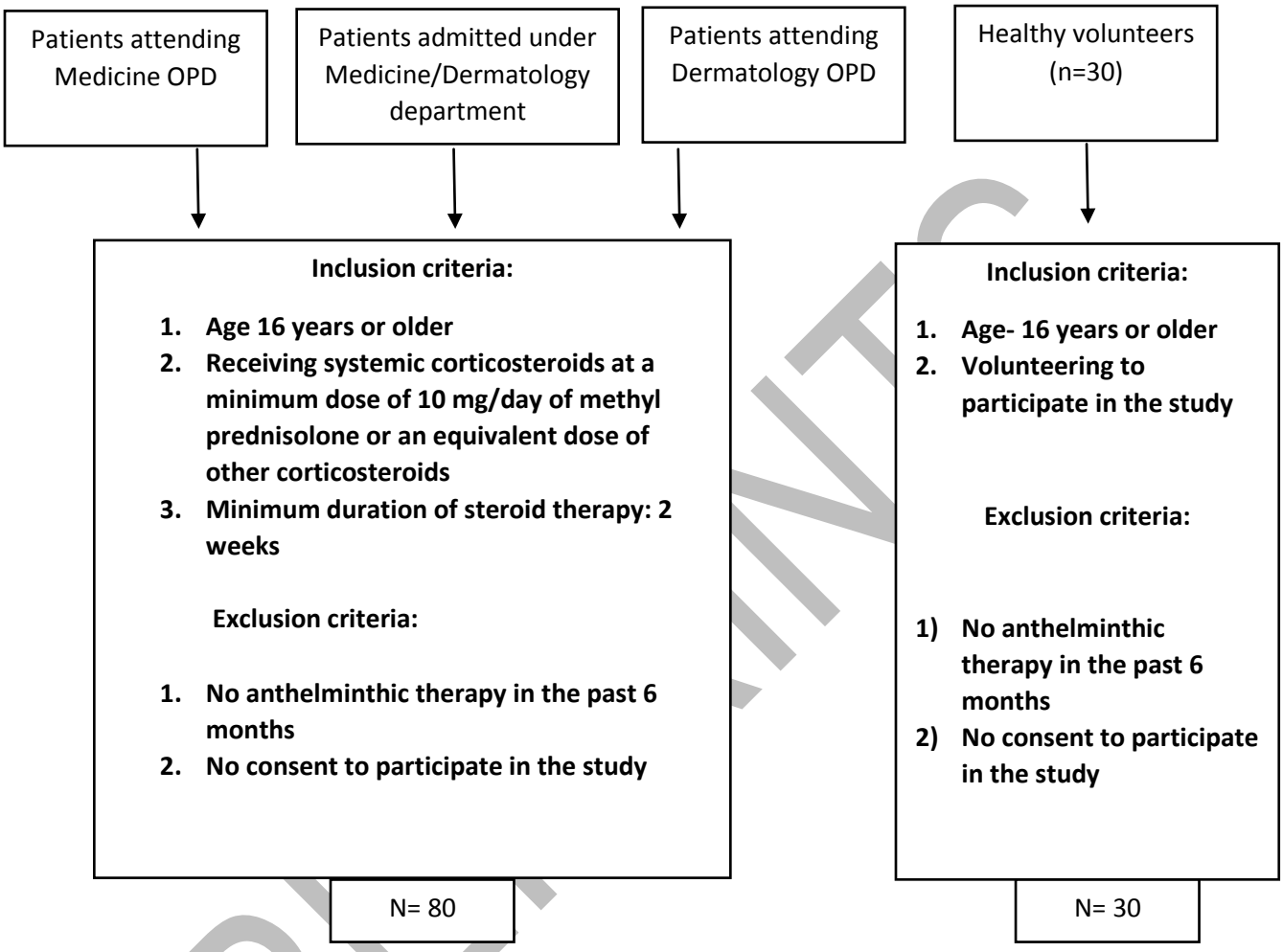
Abbreviations: SLE: Systemic Lupus Erythematosus; MCTD: Mixed connective tissue disorder; DRESS: Drug reaction with eosinophilia and systemic symptoms; TEN: Toxic Epidermal Necrolysis; CNS TB: Central nervous System Tuberculosis; AIHA: Autoimmune hemolytic anemia; ITP: Immune thrombocytopenic purpura; AML: Acute Myeloid Leukemia; NSIP: Nonspecific Interstitial pneumonia; PCP: *Pneumocytis carinii* pneumonia

Table 2 - Factors associated with Strongyloides seropositivity (total number of patients=80)

		Strongyloides ELISA		Total (%)	p value
		Positive	**Negative**		
Sex	Male	10	31	41 (51.25)	NS
	Female	6	33	39 (48.75)	
Age	≤40	11	41	52(65)	NS
	>40	5	23	28(35)	
GI symptoms	Present	2	11	13(16.25)	NS
	Absent	14	53	67(83.75)	
Eosinophilia (>500 cells/ cu. mm.)	Present	1	3	4(5)	NS
	Absent	15	61	76(95)	
Steroid therapy (n=110)	Yes	16	64	80	P=0.4
	No	4	26	30	
Stool microscopy*	Positive	0	1**	1	NA
	Negative	9	28	37	
Stool occult blood test*	Positive	4	5	9	P=0.09
	Negative	5	24	29	

*Available for 38 patients
** Patient with ITP, presented with Strongyloides hyperinfection
NS: not significant, NA: not applicable

Figure 1 - A schematic diagram outlining the sampling method.



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420 **Figure 2 -** Symptoms among participants screened.

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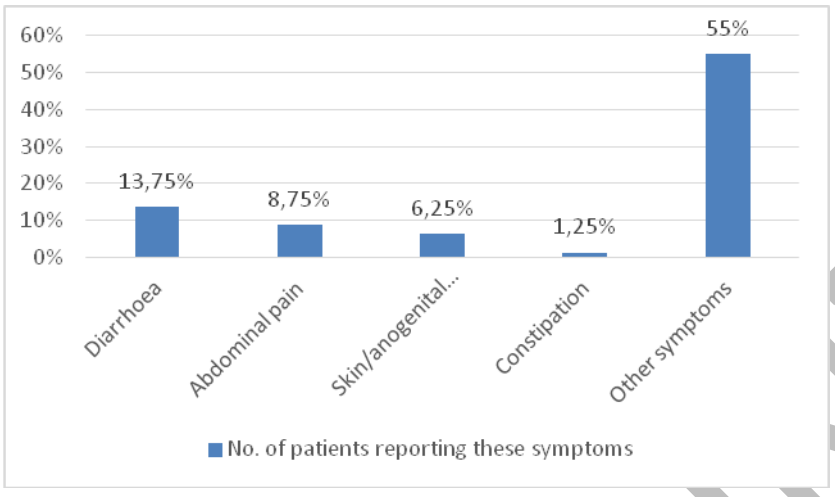

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