



Normal serum IgE levels and eosinophil counts exhibited during *Strongyloides stercoralis* infection



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ARTICLE INFO

Article history:

Received 25 August 2015

Received in revised form 8 August 2016

Accepted 10 October 2016

Available online 12 October 2016

Keywords:

Strongyloides stercoralis

Symptom

Serum IgE levels

HTLV-1

Female

Elderly

ABSTRACT

Infections with parasites, such as *Strongyloides stercoralis*, typically cause elevated levels of serum immunoglobulin E (IgE) and eosinophils; however, co-infection with human T cell lymphotropic virus type 1 (HTLV-1) can cause lower levels of serum IgE during *S. stercoralis* infection. We conducted this study to determine whether serum IgE levels and eosinophil counts could also be related to other patient characteristics or symptoms. Between 1991 and 2014, we measured and compared the symptoms of 237 patients and evaluated serum IgE levels and eosinophil counts of 199 patients who were infected with *S. stercoralis* at the Ryukyu University Hospital and the Nishizaki Hospital. Medical records were reviewed and blood samples were taken before treatment with the anthelmintic, ivermectin, 2 weeks following the first dosage, and 2 weeks following the second dosage. Commonly reported symptoms included abdominal pain, diarrhea, and general fatigue. Serum IgE levels were found to be normal in patients co-infected with HTLV-1. Additionally, females and patients younger than 70 years old exhibited normal serum IgE levels when infected with *S. stercoralis*. No factor included in our analysis was found to affect eosinophil counts. Serum IgE levels can remain within the normal range for some patients infected with *S. stercoralis*. Therefore, physicians should not eliminate *S. stercoralis* infection from the differential diagnosis solely according to findings of normal or low IgE levels.

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1. Introduction

Strongyloides stercoralis is an intestinal nematode and parasite that affects humans and is widely distributed in tropical and subtropical regions. Japan's Okinawa Prefecture is located in a subtropical region and, therefore, considered an endemic area for this parasite. In a previous study conducted in Okinawa, we found that the prevalence of *S. stercoralis* infection was 6.3% among a cohort predominantly composed of patients older than 50 years of age (95%) [1–3]. Tanaka et al. reported that the prevalence of *S. stercoralis* infection was 5.2% in Okinawa [4]. *S. stercoralis* intestinal infection primarily causes gastrointestinal symptoms. However, one report showed that *S. stercoralis* infection can also cause rash, cough, and sore throat shortly after infection [5]. Asymptomatic patients with *S. stercoralis* infection have been diagnosed by medical checkup or a screening test when they are hospitalized in Okinawa. Additionally, 20–30% of patients with mild disease have been reported to experience joint pain, low back pain, abdominal pain, and numbness

[6], while diarrhea, fever, cough, dyspnea, and constipation are considered symptoms of severe *S. stercoralis* infection [7].

Human T cell lymphotropic virus type 1 (HTLV-1) is an oncogenic retrovirus associated with adult T cell leukemia [8,9]. HTLV-1 has worldwide distribution, but is commonly found throughout southwestern Japan, the Caribbean, and some areas of Africa and Latin America [10]. Previous reports have established that there is a close relationship between *S. stercoralis* and HTLV-1 infections [11–13].

Generally, serum IgE levels and eosinophil counts are anticipated to be elevated in patients with an active parasitic infection (>170 IU/ml and >500 cells/μl, respectively). However, serum IgE levels and eosinophil counts have been reported at normal levels, rather than elevated, in patients co-infected with *S. stercoralis* and HTLV-1 [14–16]. Furthermore, a previous study reported that serum IgE levels were low in patients with severe *S. stercoralis* or HTLV-1 co-infection [17]. To our knowledge, previous studies have not investigated whether factors other than HTLV-1 infection affect serum IgE levels and eosinophil counts in patients infected with *S. stercoralis*.

In this study, we closely examine symptomatic and asymptomatic patients infected with *S. stercoralis*, including their characteristics and blood test results (i.e., serum IgE levels and eosinophil counts). Statistical analyses were conducted to identify which factors, if any, affect

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Table 1
Baseline characteristics.

Characteristics	First cohort (n = 237)	Second cohort (n = 199)	p values
Age (years), mean $\pm$ SD	63.47 $\pm$ 0.68	62.39 $\pm$ 11.0	0.92 ^a
Male, % (n)	66.6 (158)	66.8 (133)	0.97 ^b
HTLV-1 positive, % (n)	40.9 (95/232)	40.7 (81)	0.96 ^b
Normal IgE levels, % (n)	43.0 (86/200)	40.0 (79)	0.50 ^b
Serum IgE levels (IU/ml), mean $\pm$ SD	869.6 $\pm$ 1721.9	889.5 $\pm$ 1726.4	0.91 ^c
Normal eosinophils, % (n)	66.7 (150/225)	65.3 (130)	0.77 ^b
Eosinophils (cells/ μ L), mean $\pm$ SD	491.1 $\pm$ 496.7	503.4 $\pm$ 510.4	0.80 ^c

^a Statistical analysis using the Mann–Whitney *U* test.^b Statistical analysis using the chi-square test.^c Statistical analysis using the *t*-test.

serum IgE levels and eosinophil counts in such patients. We also report the symptoms most frequently encountered in patients infected with *S. stercoralis* within our cohort.

2. Materials and methods

2.1. Study population

This study was reviewed and approved by the ethics review board of the Ryukyus University (approval number: 557). Informed consent was waived. Between January 1991 and December 2014, 717 patients were treated for *S. stercoralis* infection at either the Ryukyu University Hospital or the Nishizaki Hospital in Okinawa. All 717 patients were diagnosed, treated, and had confirmed elimination of *S. stercoralis* using the agar plate culture method [18]. All patients were treated with the anthelmintic ivermectin. A single dose of ivermectin (approximately 200 μ g/kg) was administered at the time of confirmed *S. stercoralis* infection, and the same dose was readministered 2 weeks later according to treatment guidelines. This investigation was completed using two separate cohorts. The first cohort (n = 237) was investigated for symptoms. The second cohort (n = 199) was investigated for serum IgE levels and eosinophil counts. Patients (n = 480) that did not complete the entire series of interviews were excluded. A subset of patients from the first cohort (n = 38) were excluded because of a lack of complete blood testing.

Table 2
Symptom survey results (n = 237).

Symptoms	Symptom prevalence, % (n)	Symptom scores, mean $\pm$ SD			p value
		D ₀	D ₁₄	D ₂₈	
Abdominal pain	20.7 (49)	0.22 $\pm$ 0.46	0.11 $\pm$ 0.32	0.08 $\pm$ 0.29	<0.01
Diarrhea	11.8 (28)	0.13 $\pm$ 0.36	0.05 $\pm$ 0.23	0.04 $\pm$ 0.20	<0.01
General fatigue	11.0 (26)	0.11 $\pm$ 0.31	0.05 $\pm$ 0.22	0.04 $\pm$ 0.19	<0.01
Appetite loss	5.1 (12)	0.05 $\pm$ 0.25	0.03 $\pm$ 0.16	0.02 $\pm$ 0.13	0.06
Constipation	19.4 (46)	0.20 $\pm$ 0.41	0.15 $\pm$ 0.37	0.12 $\pm$ 0.34	0.06
Pruritus	11.8 (28)	0.12 $\pm$ 0.34	0.10 $\pm$ 0.33	0.06 $\pm$ 0.27	0.07
Nausea	3.8 (9)	0.03 $\pm$ 0.18	0.01 $\pm$ 0.11	0.01 $\pm$ 0.09	0.09
Heart burn	5.9 (14)	0.06 $\pm$ 0.26	0.04 $\pm$ 0.19	0.03 $\pm$ 0.16	0.13
Vertigo	4.6 (11)	0.05 $\pm$ 0.22	0.03 $\pm$ 0.17	0.02 $\pm$ 0.14	0.19
Rash	9.7 (23)	0.10 $\pm$ 0.32	0.08 $\pm$ 0.28	0.06 $\pm$ 0.24	0.26
Vomiting	1.9 (4)	0.02 $\pm$ 0.13	0.01 $\pm$ 0.09	0.00 $\pm$ 0.07	0.27
Nephelopsia	12.2 (29)	0.12 $\pm$ 0.33	0.11 $\pm$ 0.31	0.08 $\pm$ 0.28	0.27
Headache	5.9 (14)	0.06 $\pm$ 0.24	0.04 $\pm$ 0.20	0.04 $\pm$ 0.17	0.29
Numbness	8.0 (19)	0.08 $\pm$ 0.27	0.06 $\pm$ 0.24	0.05 $\pm$ 0.22	0.42
Cough	8.4 (20)	0.08 $\pm$ 0.28	0.07 $\pm$ 0.25	0.06 $\pm$ 0.24	0.55
Fever	2.1 (5)	0.03 $\pm$ 0.18	0.01 $\pm$ 0.15	0.02 $\pm$ 0.16	0.69
Arthralgia, lumbago	21.1 (50)	0.22 $\pm$ 0.44	0.21 $\pm$ 0.43	0.19 $\pm$ 0.43	0.81
Muscle pain	1.3 (3)	0.02 $\pm$ 0.16	0.02 $\pm$ 0.16	0.02 $\pm$ 0.17	0.95
Frequent urination	6.8 (16)	0.07 $\pm$ 0.25	0.07 $\pm$ 0.25	0.07 $\pm$ 0.25	1.00

One-way ANOVA was used to compare the scores of symptoms before and after treatment. D₀: before treatment, D₁₄: 2 weeks following the first dosage, and D₂₈: 2 weeks following the second dosage.

2.2. Patient interviews

Patients were interviewed about various symptoms, including presence of abdominal pain, diarrhea, pruritus, general fatigue, appetite loss, nausea, constipation, vertigo, heart burn, vomiting, rash, headache, cough, numbness, blurred vision, muscle pain, arthralgia, lumbago, frequent urination, and fever. Patient experience for each variable was graded using an ordinal Likert-type scale: 0 = no symptoms; 1 = mild, symptoms are easily tolerated; 2 = moderate, symptoms are sufficient to cause interference with normal activities; or 3 = severe, symptoms prohibit the performance of normal activities. Patient interviews were conducted before treatment (D₀), 2 weeks following the first dosage (D₁₄), and 2 weeks following the second dosage (D₂₈).

2.3. Blood testing

Blood samples were tested for serum IgE levels and eosinophil counts before treatment and after each administration of ivermectin. In our analysis, we defined serum IgE levels > 170 IU/ml and peripheral eosinophil counts $\geq$ 500 cells/ μ L as elevated.

2.4. Statistical analyses

One-way ANOVA was used to compare the scores of symptoms before and after treatment. Spearman's non-parametric correlation coefficient, ρ , was used to investigate the correlation between serum IgE levels or eosinophil counts and age, because age was not normally distributed. Patient age was changed from a continuous scale to a binary category (<70 years old or $\geq$ 70 years old). A multiple logistic regression model yielding odds ratios (ORs) and 95% confidence intervals (CIs) was used to identify factors that were significantly associated with serum IgE levels or eosinophil counts. ANOVA analysis was used to analyze the difference in serum IgE levels and eosinophil counts among groups. Cohorts were divided by sex, age (<70 years old or $\geq$ 70 years old), and HTLV-1 status.

All statistical analyses were conducted using the SPSS (version 21.0) software package, and *p*-values reported were two-sided.

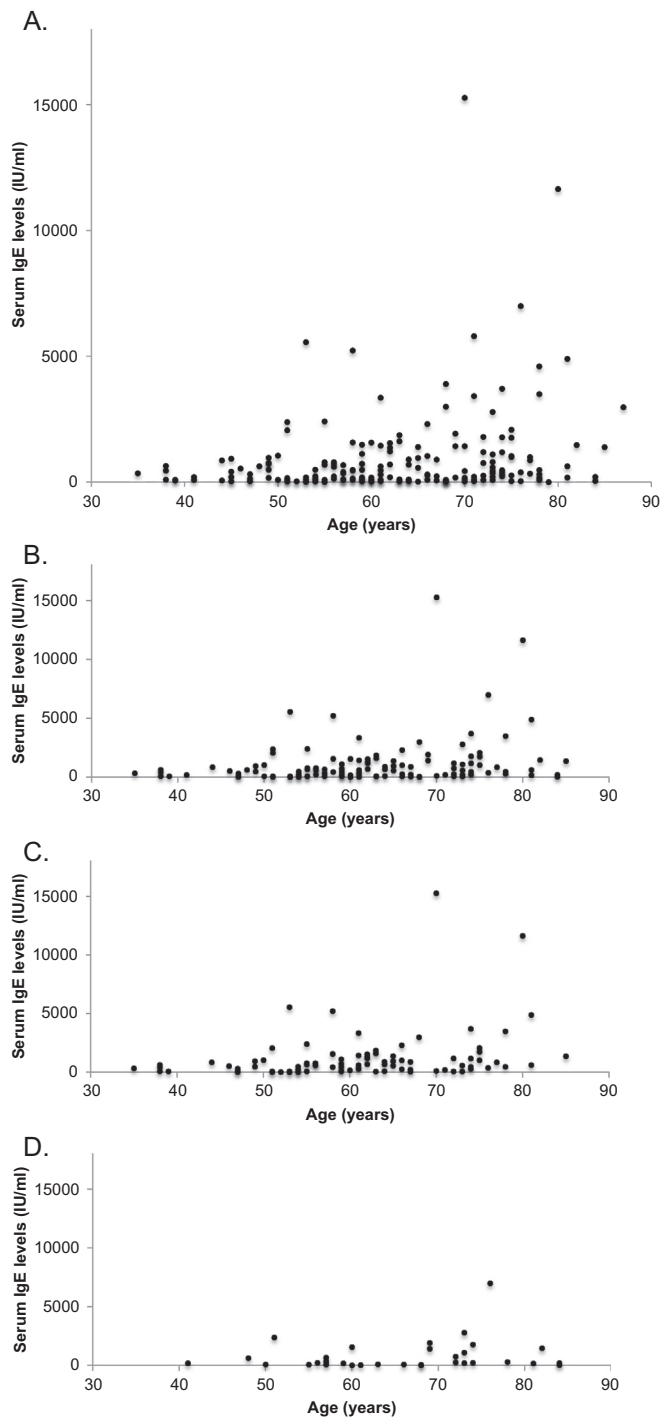


Fig. 1. (A) Correlation between serum IgE levels and age in the second cohort ($\rho = 0.22$, $p < 0.01$, $n = 199$). (B) Correlation between serum IgE levels and age in HTLV-1 negative patients ($\rho = 0.24$, $p < 0.01$, $n = 118$). (C) Correlation between serum IgE levels and age in male patients without HTLV-1 infection ($\rho = 0.32$, $p < 0.01$, $n = 86$). (D) Correlation between serum IgE levels and age in female patients without HTLV-1 infection ($\rho = 0.21$, $p = 0.05$, $n = 32$).

3. Results

3.1. Patient characteristics

The mean age of the first cohort was 63.47 years, approximately 70% was male, and 28.2% was co-infected with HTLV-1. The mean age of the second cohort was 62.39 years, approximately 70% was male, and 40.7%

Table 3

Logistic regression analyses of normal IgE levels in the second cohort ($n = 199$).

Factor		Number	OR	95% CI	p values
Sex	Male	133	0.39	0.19–0.80	<0.05
	Female	66	2.56	1.25–5.23	
Age	<70 years old	138	4.62	2.05–10.40	<0.001
	≥70 years old	61	0.22	0.09–0.49	
HTLV-1	Positive	81	5.12	2.58–10.17	<0.001
	Negative	118	0.2	0.10–0.39	
Eosinophils	High	69	0.36	0.17–0.78	<0.01
	Normal	130	2.75	1.29–5.88	
Symptoms	+	68	1.59	0.78–3.21	0.2
	–	131	0.63	0.31–1.27	

Logistic regression analyses of factors identified as significant using the chi-square test. Serum IgE level (dependent variable) was coded so that 0 = elevated IgE level ($n = 120$) and 1 = normal IgE level ($n = 79$). Model $\chi^2 = 56.7$, $p < 0.01$, pseudo $R^2 = 0.25$, $n = 199$. OR: odds ratio, 95% CI: 95% confidence interval.

was co-infected with HTLV-1. There were no significant differences between the two cohorts (Table 1).

Table 2 shows a comparison of symptom scores on D₀, D₁₄, and D₂₈. The symptom scores for abdominal pain, diarrhea, and general fatigue were all significantly improved after treatment with ivermectin ($p < 0.01$ for all). The scores of other symptoms, although trending toward improvement following ivermectin treatment, were not significantly different.

3.2. Investigation of factors affecting serum IgE levels

Fig. 1 shows the correlation between serum IgE levels and age. A positive direct correlation was observed overall between serum IgE levels and age ($\rho = 0.22$, $p < 0.01$, $n = 199$). A significantly positive correlation was also observed between serum IgE levels and age in HTLV-1 negative patients ($\rho = 0.24$, $p < 0.01$, $n = 118$) and male patients without HTLV-1 infection ($\rho = 0.32$, $p < 0.01$, $n = 86$). A slightly positive correlation was also observed between serum IgE levels and age in female patients without HTLV-1 infection ($\rho = 0.21$, $p = 0.05$, $n = 32$). However, this correlation was not observed in HTLV-1 positive patients ($\rho = 0.18$, $p = 0.10$, $n = 81$). This correlation was confirmed in logistic regression analyses, which showed that patients who were female, younger than 70 years old, had normal eosinophil counts, or were co-infected with HTLV-1 were more likely to present with normal serum IgE levels ($p < 0.01$ for all) (Table 3).

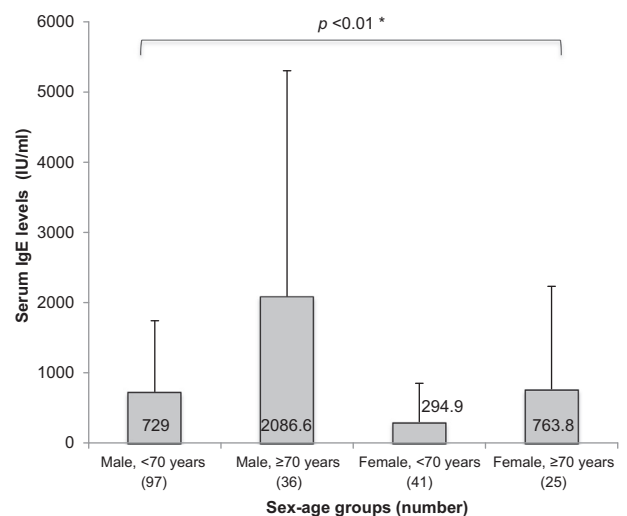


Fig. 2. Evaluation of potential relationships between sex-age groups and serum IgE levels. *One-way ANOVA was used to compare serum IgE levels (IU/ml) among groups. Data are expressed as the mean $\pm$ SD; $n = 199$.

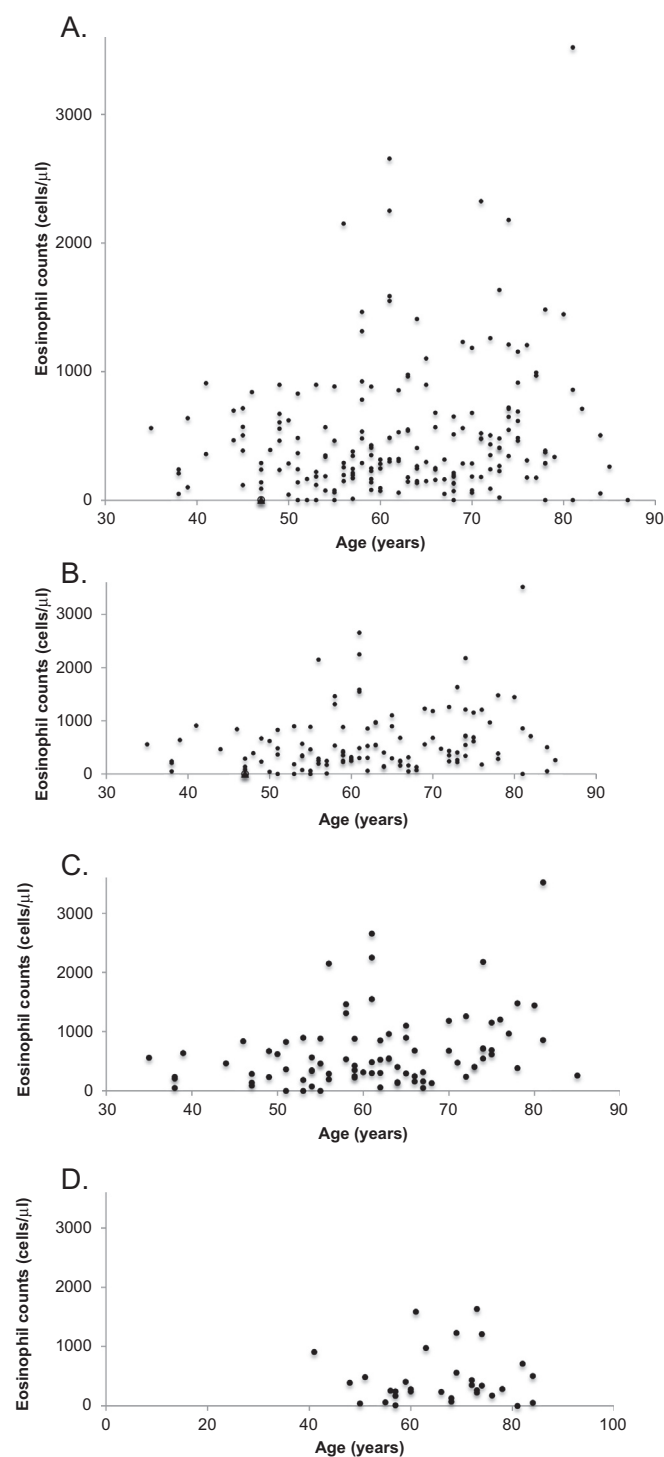


Fig. 3. (A) Correlation between eosinophil counts and age in the second cohort ($\rho = 0.19$, $p < 0.01$, $n = 199$). (B) Correlation between eosinophil counts and age in HTLV-1 negative patients ($\rho = 0.23$, $p < 0.05$, $n = 118$). (C) Correlation between eosinophil counts and age in male patients without HTLV-1 infection ($\rho = 0.32$, $p < 0.01$, $n = 86$). (D) Correlation between eosinophil counts and age in female patients without HTLV-1 infection ($\rho = 0.14$, $p < 0.05$, $n = 32$).

Fig. 2 shows the comparison of serum IgE among four distinct sex and age categories. Serum IgE levels were significantly elevated in all patients ≥ 70 years old ($p < 0.01$). Furthermore, serum IgE levels were considerably lower in female patients < 70 years old ($p < 0.01$), suggesting a synergistic effect of these two variables. **Table 5A** shows the evaluation of potential relationships between sex-age categories and serum IgE levels in patients co-infected with HTLV-1. Serum IgE levels were

Table 4

Logistic regression analyses of normal eosinophil count in the second cohort ($n = 199$).

Factor		Number	OR	95% CI	p values
Serum IgE level	High	120	0.4	0.19–0.83	<0.05
	Normal	79	2.52	1.20–5.30	
Sex	Male	133	0.57	0.28–1.16	0.12
	Female	66	1.76	0.86–3.57	
HTLV-1	Positive	81	1.68	0.84–3.37	0.14
	Negative	118	0.59	0.30–1.19	
Age	< 70 years old	138	1.45	0.73–2.88	0.29
	≥ 70 years old	61	0.69	0.35–1.37	
Symptoms	+	22	1.46	0.75–2.85	0.27
	–	177	0.69	0.35–2.40	

Logistic regression analyses of factors identified as significant using the chi-square test. Eosinophil count (dependent variable) was coded so that 0 = elevated eosinophil count ($n = 69$) and 1 = eosinophil count ($n = 130$). Model $\chi^2 = 14.9$, $p < 0.01$, pseudo $R^2 = 0.07$, $n = 199$. OR: odds ratio, 95% CI: 95% confidence interval.

significantly elevated in all patients ≥ 70 years old ($p < 0.01$). Furthermore, serum IgE levels were considerably lower in female patients < 70 years old ($p < 0.01$), suggesting a synergistic effect of these two variables. **Table 5B** shows the evaluation of potential relationships between sex-age categories and serum IgE levels in patients without HTLV-1 infection. Both serum IgE levels and eosinophil counts were affected by sex and age in patients without HTLV-1 infection.

3.3. Investigation of factors affecting eosinophil counts in systemic blood

Fig. 3 shows the correlation between eosinophil counts and age. A slightly positive correlation was observed overall between eosinophil counts and age ($\rho = 0.19$, $p < 0.01$, $n = 199$). A significantly positive correlation was also observed between eosinophil counts and age in HTLV-1 negative patients ($\rho = 0.23$, $p < 0.05$, $n = 118$) and male patients without HTLV-1 infection ($\rho = 0.32$, $p < 0.01$, $n = 86$). A slightly positive correlation was also observed between eosinophil counts and age in female patients without HTLV-1 infection ($\rho = 0.14$, $p < 0.05$, $n = 32$). However, this correlation was not observed in HTLV-1 positive patients ($\rho = 0.10$, $p = 0.37$, $n = 81$). Interestingly, only patients with normal IgE levels were likely to have low eosinophil counts in the blood serum ($p < 0.05$) (**Table 4**).

Fig. 4 shows the comparison of eosinophil counts among four distinct sex and age categories. Similar trends to those observed for serum IgE levels were observed, likely because serum IgE levels are dependent on eosinophil counts. In particular, males and patients ≥ 70 years of age exhibited significantly higher eosinophil counts than any other group ($p < 0.05$ for each). **Table 5A** shows the evaluation of potential relationships between sex-age categories and eosinophil counts in

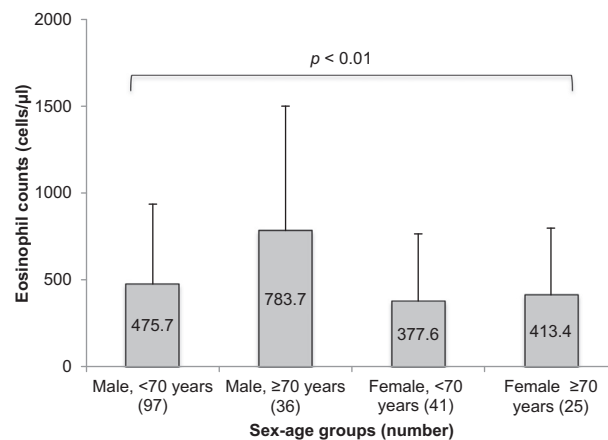


Fig. 4. Evaluation of potential relationships between sex-age groups and eosinophil counts. *One-way ANOVA was used to compare eosinophil counts (cells/ml) among groups. Data are expressed as the mean $\pm$ SD; $n = 199$.

Table 5A

Evaluation of potential relationships between sex-age groups and serum IgE levels and eosinophil counts in patients co-infected with HTLV-1.

Number	Male		Female		p value ^a
	<70 years	≥70 years	<70 years	≥70 years	
Serum IgE levels (IU/ml)	388.5 ± 714.1	1655.3 ± 1851.7	86.7 ± 88.0	227.7 ± 248.2	<0.01
Eosinophils (cells/μl)	349.8 ± 208.5	487.3 ± 583.9	326.7 ± 340.0	345.6 ± 273.9	0.84

^a One-way ANOVA was used to compare serum IgE levels (IU/ml) and eosinophil counts (cells/μl) among groups. Data are expressed as the mean ± SD; n = 81.

patients co-infected with HTLV-1. Eosinophil counts were not affected by sex or age ($p = 0.84$). Table 5B shows the evaluation of potential relationships between sex-age categories and eosinophil counts in patients without HTLV-1 infection. Eosinophil counts were significantly elevated in all patients ≥70 years old ($p < 0.01$). Furthermore, serum IgE levels were considerably lower in female patients <70 years old ($p < 0.01$).

4. Discussion

S. stercoralis intestinal infection typically causes gastrointestinal symptoms. Our study showed that abdominal pain, diarrhea, and general fatigue were improved after ivermectin treatment. Tanaka reported that *S. stercoralis* can also cause rash, cough, and sore throat immediately after infection [5], and Tsai et al. reported that diarrhea, fever, abdominal pain, cough, dyspnea, and constipation were symptoms of severe *S. stercoralis* infection [7]. Despite this documentation, we did not observe such symptoms. A potential explanation for this difference may be that subjects in our cohort only suffered from mild infection, and hospitalized patients with severe *S. stercoralis* infection were not included.

In agreement with previous studies [1,16], our results also showed that serum IgE levels were normal in patients co-infected with *S. stercoralis* and HTLV-1. Porto et al. reported that HTLV-1 infection decreases Th2 type immune responses, and this same mechanism is likely responsible for the lower serum IgE levels in co-infected patients [16]. Our study, however, showed that eosinophil counts of HTLV-1 positive patients were not significantly different from that of HTLV-1 negative patients. Although this information is not novel based on Th2 pathway improvements [19], the mechanism of IgE production and the crosstalk between eosinophils and Th2 lymphocytes remains unclear.

To our knowledge, this is the first report to describe a relationship between sex and serum IgE levels in patients infected with *S. stercoralis*. However, other studies have reported a similar relationship among female patients with bronchial asthma and allergies [20] and in umbilical cord blood IgE levels [21]. Hunninghake et al. reported variations in IgE levels among asthmatics. Increased transcription of the interleukin-17 receptor B gene was found to increase IgE levels in males. However, a significant correlation between gene transcript abundance and serum IgE levels was not found in females [22]. To our knowledge, no other studies

Table 5B

Evaluation of potential relationships between sex-age groups and serum IgE levels and eosinophil counts in patients without HTLV-1 infection.

Number	Male		Female		p value ^a
	<70 years	≥70 years	<70 years	≥70 years	
Serum IgE levels (IU/ml)	904.6 ± 1093.2	2361.1 ± 3854.6	536.0 ± 732.4	1258.6 ± 1908.6	<0.05
Eosinophils (cells/μl)	540.6 ± 536.4	973.3 ± 741.3	436.5 ± 436.8	475.9 ± 466.4	<0.01

^a One-way ANOVA was used to compare serum IgE levels (IU/ml) and eosinophil counts (cells/μl) among groups. Data are expressed as the mean ± SD; n = 118.

investigating the correlation between serum IgE levels and IL-17RB in asthmatics have been conducted, nor have any other reports compared serum IgE levels between males and females with helminth infections.

Our study also found that as age may affect serum IgE levels. Patients younger than 70 years of age frequently present with normal IgE levels, rather than anticipated elevated levels. Mutapi et al. also reported a positive correlation between serum IgE levels and age in patients infected with *Schistosoma mansoni* [23]. Here, we speculate that the age-antibody relationship might be caused by the increased duration of parasitic infection. However, there were no significant correlations between serum IgE levels and age in females or HTLV-1 co-infected patients. These results further suggest that female sex and HTLV-1 are inhibitive factors on serum IgE levels in *S. stercoralis* infection.

We speculated that serum IgE levels are dependent on eosinophil counts, and similar results were observed in univariate analyses. In previous studies [15,16], eosinophil counts were found to be decreased in patients co-infected with *S. stercoralis* and HTLV-1. The statistical analyses used and inherent cohort differences may explain the differences between our results and that of previous studies.

There are some limitations associated with this study. It is well known that allergies, immunosuppressants, steroid use, human immunodeficiency virus infection, and other parasitic infections can also affect serum IgE levels and eosinophil counts. Unfortunately, these confounders were not included in the survey and, thus, their effects could not be analyzed.

5. Conclusions

Our study showed that serum IgE levels were normal, rather than elevated as is typical during parasitic infections, in *S. stercoralis*-infected patients who were female, younger than 70 years, or co-infected with HTLV-1. Therefore, physicians should not eliminate *S. stercoralis* infection from the differential diagnosis solely according to findings of normal or low serum IgE levels. Mechanisms regulating IgE, eosinophils, and Th2 antihelminthic responses need further research.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

Acknowledgements

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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