

Intensity of *Schistosoma Mansoni*, Hepatitis B, Age, and Sex Predict Levels of Hepatic Periportal Thickening/Fibrosis (PPT/F): A Large-Scale Community-Based Study in Ethiopia

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Abstract. To elucidate determinants of morbidity in schistosomiasis mansoni, a community-based study was undertaken involving 2,451 subjects (mean age, 18.8 ± 15.3 [SD] years) from four endemic sites in Ethiopia. Overall prevalence of infection was 65.9%, reported blood in stools was 35.8%, and schistosomal periportal thickening/fibrosis (PPT/F) was 4.6%. Similarly, 43.2% were positive for at least one marker of hepatitis B virus (HBV), 5.3% were HBsAg positive, and 1.3% were anti-hepatitis C virus (HCV) positive. Prevalence of PPT/F increased significantly with increasing community prevalence and intensity of *S. mansoni* infection. In a multiple logistic regression analysis, intensity of egg excretion, markers of HBV infection, age, and male sex were significantly associated with PPT/F, whereas co-infection with other intestinal helminths was associated with lower odds for PPT/F. HCV was not associated with *S. mansoni* infection or with schistosomal PPT/F. In conclusion, integrated helminth control targeting school-aged children, who have the highest burden infection, should be used to substantially reduce the risk of periportal fibrosis.

INTRODUCTION

Among parasitic infections, schistosomiasis is only second to malaria in terms of public health importance, with > 200 million people currently infected worldwide.¹ Based on recent estimates, ~54 million people in Sub-Saharan Africa are considered to be currently infected with *S. mansoni*, resulting blood in stools in 4.4 million, hepatomegaly in 8.5 million, and an annual mortality of 130,000.²

Several earlier studies have reported disparities between prevalence of infection and levels of morbidity. For example, in Egypt^{3,4} and the Sudan,^{5,6} prevalence of periportal fibrosis is considerably high compared with countries like Kenya^{3,4} and Mali,⁷ where the prevalence of periportal fibrosis is markedly low despite having higher prevalence and intensity of *S. mansoni* infections. Furthermore, even adjacent communities with comparably high levels of *S. mansoni* infection may exhibit considerable difference in their prevalence of periportal fibrosis.⁸ Among possible explanations for the observed differential morbidity patterns, duration and intensity of *S. mansoni* infection^{4,6,9} and host genetic background^{10,11} are among some, but only a few, of the factors implicated in the development of schistosomal hepatic morbidity, although some studies are not in agreement with these claims.¹²

In Ethiopia, although there is an extensive body of literature addressing the distribution of *S. mansoni* infection in the country, there are only a few published works on morbidity related to schistosomiasis mansoni, and these were limited to comparisons of clinical symptoms with intensity of egg excretions.^{13,14} The aim of this study was to elucidate on the patterns and determinants of *S. mansoni*-related liver diseases in Ethiopia.

MATERIALS AND METHODS

Study subjects, morbidity questionnaire, and parasitologic examination. This study was conducted from June 2000 to

August 2002 in Worke-Mado, Cheretee, and Chekorso villages (Kemisse administrative zone, Wollo, Northeast Ethiopia) and in Sille-Elgo villages (Northern Omo Administrative zone, Southern Ethiopia). Over the last 10 years, there has not been mass chemotherapy with anti-schistosomal or anti-helminthic drugs in any of the study sites. However, provision of anti-schistosomal chemotherapy was available on-pay in higher health care facilities situated ~20–30 km away from our study sites. Malaria is a leading health problem in all study villages, but more so in Chekorso and Sille-Elgo villages. Residents of Cheretee, Worke-Mado, and Chekorso are predominantly Muslim whose livelihood is largely dependent on subsistence farming, whereas residents of Sille-Elgo are mostly Christians who are employees of a government-owned irrigation farm. The study communities were of a fairly comparable socioeconomic and nutritional status, with the exception of the Sille-Elgo community, which has better access to fruits and vegetables.

The total population of the study community was 5,248, which was made up of 904 households. Household was used as the sampling frame. Using random numbers generated from an EPI-6 statistical module (WHO/CDC, Atlanta, GA), ~50% of the households (a total of 451 households) were taken from the list of households in census data of each study village, and all members of the selected households were enrolled as study subjects. Based on this, a total of 2,451 subjects (1,277 men and 1,174 women; mean age, 18.8 ± 15.3 [SD] years) from the four *S. mansoni* endemic villages were enrolled in the study. Because we had no background information on the prevalence of periportal thickening/fibrosis (PPT/F) in Ethiopia, we took a figure of 2% as the expected prevalence of PPT/F based on estimates from other African countries with a low prevalence of PPT/F. Thus, for a total population of 5,248 subjects, our sample size of 2,451 provides a power of > 90% to detect a prevalence ranging from 1% to 3%, with 95% confidence.

A day before the date of examination, field assistants visited all households selected for the study and invited all household members to provide morning stool specimens. Stool samples were processed using 41.7-mg templates according to the modified Kato-Katz technique,¹⁵ and quintet

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thick smears were prepared for each subject to optimize detection of *S. mansoni* infection.¹⁶ In addition, for each participant, a pre-tested questionnaire on signs and symptoms of ill health was administered, in the local language, by trained local high school graduates. For underaged children, the guardians were the respondents of the questionnaire.

Furthermore, to obtain information on sero-prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection in a community not endemic for malaria and schistosomiasis, 50% of Sheno high school students (232 men and 117 women; mean age, 17.5 ± 2.5 years) were taken at random from the list of students in the school and were enrolled as non-endemic controls. Sheno town is situated 80 km north of Addis Ababa at an altitude of 2,825 m above sea level.

Clinical examination. A brief clinical examination of each study subject was done with emphasis on detection of pallor, jaundice, fever, splenic/liver enlargement, and superficial abdominal collateral veins. Enlargement of the liver was measured at the mid-sternal and right mid-clavicular line, whereas the spleen was measured at the left anterior-axillary line, all in centimeters below the costal margins, with the subject in supine position. A liver edge and/or splenic tip extending > 2 cm below the costal margins were considered enlarged.

Ultrasonography. Details on ultrasonographic examinations have been described elsewhere.¹⁷ However, briefly, using the WHO-Niamey protocol,¹⁸ standard ultrasonographic livers scans were performed using Hitachi EUB 405 portable ultrasound equipment (Tokyo, Japan), fitted with a 3.5-MHz convex abdominal probe. In subjects with image patterns suggestive of PPT/F, the liver picture was compared with standard images,¹⁸ and the corresponding image pattern score was recorded. In addition, assessment of the periportal thickening was made by taking inner to inner and outer to outer portal branch wall thickness (PBWT) measurements of two to three second branching portal veins. These measurements were close to branching point of the vessels, and the arithmetic mean differences between outer and inner wall thickness were taken as the individual's PBWT value. The summation of the image pattern and PBWT scores gave the final PPT/F grading of each individual. Accordingly, subjects with non-specific diffuse echogenic liver pattern associated with minimal wall thickening were classified as having "incipient PPT/F," those with image patterns suggestive of PPT/F but with wall thickness less or equal to mean ± 2 SD of normal PBWT-for height standard were classified "probable/possible PPT/F," and those with definite or advanced PPT/F by both image pattern and PBWT measurements were classified as "definite/advanced PPT/F." In subjects with definite and advanced forms of PPT/F, inner to inner diameter of the portal vein was measured at its entry point to the liver, and a search for collateral veins was made in subjects with advanced PPT/F.

Serologic tests. Using disposable syringes and needles, venous blood was collected from subjects ≥ 5 years of age who consented (or whose parents consented) to provide blood samples. Among an eligible 1,901 subjects (≥ 5 years of age), 1,707 volunteered to provide blood samples. Subjects who did not provide blood samples were mostly children and young adults from Cheretee and Sille-Elgo villages, which also included five pregnant women. Among these, only two had PPT/F. Sera collected during each survey period were stored

in deep freezers (about -20°C) of the respective health institutions and finally transported cool, in iceboxes, to the Institute of Pathobiology (Addis Ababa University) and stored at -20°C until use. All sera were tested for markers of HBV (anti-HBcAg and HBsAg) and for anti-HCV antibodies. Reactive samples on either of the test panels were repeated. Markers of HBV were assessed using Hepanostica Enzyme Immunoassay kits from Organon Teknika and from Biomèriex (Boxtel, The Netherlands). Anti-HCV tests were done using Ortho HCV 3.0 Enzyme Immunoassay kits (Ortho-Clinical Diagnostics, Bucks, UK), and reactive samples were cross-checked using Architect Anti-HCV test kits (Abbott Laboratories, Chicago, IL).

Furthermore, to obtain information on sero-prevalence of HBV and HCV infection in a community not endemic for malaria and schistosomiasis, sera were collected from 349 Sheno high school students.

Statistical analysis. Statistical analysis was done using SPSS statistical software, version 10 (SPSS, Chicago, IL). For each study subject, *S. mansoni* egg count per Kato-Katz thick smear was calculated taking the average count of five Kato-Katz thick smear slides. Normality and equality of variances were assessed 1) before using parametric tests and (2) after regression analysis to check the validity of assumptions of regression modeling. Because *S. mansoni* egg counts per gram of stool (epg) were not normally distributed, the data were transformed to natural logarithms, using $\log(\text{epg} + 1)$ to allow computing for subjects with zero counts. Mean intensities of *S. mansoni* epg expressed in text or tables are geometric means. One-way analysis of variance (ANOVA) with a Welch test for equality of means was used for comparisons of geometric mean *S. mansoni* egg loads by categories of age and study site. Comparison of geometric mean *S. mansoni* egg loads by sex was done using an independent sample *t* test. Comparisons of proportions between groups were made using the χ^2 test. After univariate analysis, multiple logistic regression analysis was used to quantify association of specific risk factors with development of PPT/F. Results were considered significant for $P < 0.05$. Assessment of the logistic regression model showed that the model correctly predicted 93% of cases. The area under the receiver operating characteristic (ROC) curve (95% CI) was 0.74 (0.69, 0.77). The Hosmer-Lemeshow goodness-of-fit χ^2 was 8.7, with $P = 0.42$ indicating that the model fit the data reasonably well.

Ethical consideration. This study was part of a larger research project entitled "Control of schistosomiasis with local production and use of the Ethiopian soap-berry Endod," which had ethical clearance from the Institutional and National Ethical Clearance committees of Ethiopia and from the Norwegian Board of Medical Research Ethics. The aims of this study were initially explained during a meeting of community leaders and heads of households. All diagnostic and treatment procedures were carried out after obtaining informed consent from each subject or his/her guardians. Free treatment was offered to all subjects with schistosomiasis and/or other helminth infections. All subjects who were positive for *S. mansoni* were treated with a single dose of praziquantel at 40 mg/kg body weight. Subjects with *Taenia* spp. or *Hymenotepis nana* infections were treated with a 3-day course of albendazole 400 mg/d or with praziquantel if they had *S. mansoni* co-infection. Other helminth infections were treated with a single dose of albendazole 400 mg.

RESULTS

A total of 2,451 subjects from *S. mansoni*-endemic villages (1,277 men and 1,174 women; mean age, 18.8 ± 15.3 years) and 349 high school students from a non-endemic site (232 boys and 117 girls; mean age, 17.5 ± 2.5 years) participated in the study. All non-endemic controls were free from *S. mansoni* infection and had normal ultrasonographic image patterns of the liver. Table 1 shows prevalence and intensities of *S. mansoni* and other helminth infections by study site, age, and sex categories. Overall prevalence of *S. mansoni* infection in the endemic study sites was 65.9%, and the geometric mean egg excretion of all examined was 27.9/g of stool. A total of 1,088 (44.4%) subjects harbored one or more other intestinal helminth infections. There was a trend of increasing prevalence and intensity of *S. mansoni* infection in our northeast Ethiopia study villages of Wollo: Cheretee had the lowest, Worke-Mado had an intermediate, and Chekorso had the highest burden of infection. The Sille-Elgo village (south Ethiopian study site in northern Omo) had burdens of schistosomiasis in the lower range (between Cheretee and Worke-Mado). On the other hand, an opposite trend was noted regarding prevalence of other helminth infections, with Sille-Elgo having the heaviest burden. Peak prevalence and intensity of *S. mansoni* infection was in the age group of 11–20 years and declined sharply thereafter, whereas the prevalence of other helminth infections was high until > 30 years of age and declined thereafter (Table 1). Based on ultrasonographic image patterns and PBWT-for-height standard, 2,119 (86.5) had a normal image pattern, 128 (5.2%) had incipient PPT/F, 46 (1.9%) had probable/possible PPT/F, 112 (4.6%) had definite/advanced PPT/F, and 46 (1.9%) had other non-schistosomal image patterns (Table 2). The proportion of subjects with hepatomegaly and splenomegaly increased significantly with advancing stages of PPT/F (Table 2). Among subjects with definite/advanced PPT/F, 83.9% had demonstrable *S. mansoni* eggs in at least one of five Kato-Katz thick smear slides at the time of initial evaluation (Table 2).

Prevalence of PPT/F had a sharp rise in the age group 11–20 years, reached its peak in the 21- to 30-year age group,

and started to decline thereafter (Table 3). Prevalence and intensity of *S. mansoni* infection and prevalence of schistosomal PPT/F was significantly higher in men than in women (Table 3). Overall prevalence of reported blood in stool, hepatomegaly, and splenomegaly were 35.8%, 11.0%, and 21.8%, respectively, and these values varied significantly by study site and by categories of age, sex, and intensity of *S. mansoni* infection (Table 3).

Prevalence estimates for markers of HBV and HCV infections are shown in Tables 4 and 5. Overall, 43.2% of subjects were positive for at least one serum marker of HBV infection, 5.3% were positive for HBsAg, and 1.3% were positive for anti-HCV antibodies. Prevalence of overall markers of HBV infection varied significantly by study sites and by categories of age and PPT/F (Table 4). However, the proportion of anti-HCV positives did not vary across these categories (Table 4). Neither *S. mansoni* infection status nor intensity of egg excretion was associated with markers of HBV or HCV infection (data not shown). The proportion of subjects who tested positive for at least one serum marker of HBV, HBsAg, and anti-HCV antibodies among 349 high school students in Sheno (non-endemic for schistosomiasis and malaria), was 19.2%, 0.9%, and 0.3%, respectively. The corresponding figures for the same age category in our *S. mansoni* and malaria-endemic communities were 40.8%, 4.8%, and 1.3%, respectively (data not shown).

Table 5 shows the results of logistic regression analysis. Among study variables, intensity of *S. mansoni* egg excretion > 100 epg, markers of HBV infection, increasing age, and male sex were significantly associated with higher odds for PPT/F. Furthermore, after controlling for age and *S. mansoni* infection status, subjects with other helminth infections had lower odds for the development of schistosomal PPT/F than those who were uninfected.

Presence of PPT/F (adjusted odd ratio [OR] = 4.6, 95% CI = 3.0, 7.0; *P* < 0.001), history of clinical malaria (adjusted OR = 2.1; 95% CI = 1.6, 3.0; *P* = 0.001), and male sex (adjusted OR = 2.2; 95% CI = 1.8, 2.9; *P* = 0.001) were associated with a higher risk for splenomegaly. Similarly, presence of PPT/F (adjusted OR = 2.3, 95% CI = 1.4, 3.8;

TABLE 1

Prevalence and intensities of *S. mansoni* and other helminth infections by study site, age, and sex among 2,451 subjects from *S. mansoni*-endemic villages

Study variables	N	<i>S. mansoni</i>			Other helminth infections [N (%)]
		Prevalence [N (%)]	Mean epg* (95% CI)	Epg > 100 [N (%)]	
Study sites					
Chekorso	207	176 (85.0)	134.8 (97.9,185.6)	143 (69.1)	40 (19.3)
Worke-Mado	557	445 (79.9)	55.7 (46.0, 67.5)	260 (46.7)	208 (37.3)
Cheretee	703	353 (50.2)	12.4 (10.2, 15.2)	199 (28.3)	334 (47.5)
Sille-Elgo	984	641 (65.1)	24.1 (20.5, 28.3)	333 (33.8)	506 (51.4)
<i>P</i> value		< 0.001	< 0.001†	< 0.001	0.0001
Age category- (years)					
< 10	1,029	582 (56.6)	18.6 (15.7, 22.0)	354 (34.4)	469 (45.6)
11–20	557	468 (84.0)	89.9 (74.1,108.2)	314 (56.4)	257 (46.1)
21–30	355	233 (65.6)	21.7 (16.9, 28.0)	113 (31.8)	170 (47.9)
31–40	279	186 (66.7)	21.4 (16.2, 28.2)	81 (29.0)	109 (39.1)
> 40	231	146 (63.2)	20.6 (14.9, 28.5)	73 (31.6)	83 (35.9)
<i>P</i> value		< 0.001	0.001†	0.001	0.01
Sex					
Male	1,277	905 (70.9)	39.1 (33.8, 45.8)	558 (43.7)	536 (42.0)
Female	1,174	710 (60.5)	19.3 (16.7, 22.5)	377 (32.1)	552 (47.0)
<i>P</i> value		< 0.001	0.001‡	0.001	0.01
Total (%)	2,451	1,615 (65.9)	27.9 (25.1, 31.0)	935 (38.1)	1,088 (44.4)

* Geometric mean of all examined.

† Based on one-way ANOVA with the Welch test for equality of means.

‡ Independent samples *t* test.

TABLE 2
Categories of PPT/F by parasitologic and clinical characteristics among 2,451 subjects from *S. mansoni* endemic villages

Variables	Category of PPT/F based on image pattern and PBWT-for-height					Total
	No PPT/F	Incipient	Possible/probable	Definite/advanced	Others	
Number of subjects	2,119	128	46	112	46	2,451
<i>S. mansoni</i> Infection [N (%)]	1,359 (64.1)	101 (78.9)	29 (63.0)	94 (83.9)	32 (69.6)	1,615 (65.9)
Epg > 100 [N (%)]	774 (36.5)	57 (44.5)	17 (37.0)	70 (62.5)	17 (37.0)	935 (38.1)
Mean* Epg (95% CI)	24.9 (22.3, 27.8)	60.6 (39.2, 93.5)	22.2 (10.2, 48.2)	102.0 (65.6, 158.0)	32.9 (15.6, 69.5)	27.9 (25.1, 31.0)
Hepatomegaly [N (%)]†	195 (9.2)	26 (20.3)	9 (19.6)	30 (26.8)	10 (21.7)	270 (11.0)
Splenomegaly [N (%)]†	397 (18.7)	38 (29.7)	18 (39.1)	67 (59.8)	14 (30.4)	534 (21.8)

* Geometric mean of all examined.

† More than 2 cm below costal margin.

$P = 0.001$), history of clinical malaria (adjusted OR = 2.0; 95% CI = 1.3, 3.0; $P = 0.002$), intensity of *S. mansoni* egg excretion (adjusted OR = 1.9; 95% CI = 1.2, 2.8; $P = 0.003$), and male sex (adjusted OR = 1.8; 95% CI = 1.3, 2.5; $P = 0.001$) were associated with a higher risk for hepatomegaly (data not shown).

Figure 1 shows the proportion of subjects with PPT/F in relation to categories of age and intensity of *S. mansoni* infections. Among subjects with a high intensity of infections, the proportion of subjects with PPT/F had a sharp peak in the age category of 21–30 years.

DISCUSSION

This large-scale study involved communities from geographic areas with differing endemicity of *S. mansoni* infection. Our overall prevalence estimate of 4.6% for schistosomal periportal fibrosis is comparable to figures reported from neighboring countries such as Kenya^{3,4,12} and Tanzania.¹⁹ The peak prevalence and intensity of *S. mansoni* infection, observed in the age category of 11–20 years, preceded by 10 years the peak for the proportion of subjects with PPT/F among those with high intensity infection that was observed in the age category of 21–30 years. These findings are in line with earlier studies^{5,6,12} and emphasize the importance of in-

tensity and duration of infection (as reflected by age of the subject) in the development of schistosomal periportal fibrosis. Furthermore, presence of hepatosplenomegaly was related to intensity of infection and levels of periportal fibrosis in addition to its relation with history of clinical attacks of malaria.

Similar to previous studies,^{6–8} the prevalence and intensity of *S. mansoni* infections and prevalence of schistosomal PPT/F were significantly higher among men than women. Because men do most of the farming activities in our study communities, the observed high prevalence of PPT/F is probably related to sex-related behavioral and occupational differences of exposures to potentially infected water bodies, which put men at higher risk of acquiring *S. mansoni* infection.

Our prevalence estimate of HBsAg positives of 5.3%, in *S. mansoni*- and malaria-endemic communities, is comparable to some earlier studies from Ethiopia.^{20,21} However, the prevalence of HBsAg positives among healthy controls from Sheno high school (not endemic for schistosomiasis and malaria) was 0.9%, which is 5-fold lower than the corresponding figure of 4.8% for the same age category in our *S. mansoni*- and malaria-endemic study community. Similarly, other studies from Ethiopia have also reported considerable geographic variations of HBV infections^{22,23} and, taken together, these findings suggest the possible existence of important differ-

TABLE 3
Morbidity signs by study site, age, sex, and levels of *S. mansoni* egg excretion among 2,451 subjects from *S. mansoni*-endemic villages

Variables	Total N	Blood in stools [N (%)]	Hepatomegaly* [N (%)]	Splenomegaly* [N (%)]	Definite/advanced PPT/F [N (%)]
Study site					
Chekorso	207	138 (66.7)	55 (26.6)	121 (58.5)	55 (26.6)
Worke-Mado	557	203 (36.4)	48 (8.6)	56 (10.1)	33 (5.9)
Cherete	703	192 (27.3)	11 (1.6)	14 (2.0)	18 (2.6)
Sille-Elgo	984	344 (35.0)	156 (15.9)	343 (34.9)	6 (0.6)
<i>P</i> value		< 0.001	< 0.001	< 0.001	< 0.001
Age category (years)					
< 10	1,029	414 (40.2)	71 (6.9)	151 (14.7)	18 (1.7)
11–20	557	232 (41.7)	96 (17.2)	173 (31.1)	39 (7.0)
21–30	355	87 (24.5)	37 (10.4)	95 (26.8)	28 (7.9)
31–40	279	83 (29.7)	32 (11.5)	67 (24.0)	18 (6.5)
> 40	231	61 (26.4)	34 (14.7)	48 (20.8)	9 (3.9)
<i>P</i> value		< 0.01	< 0.001	< 0.01	0.001
Sex					
Male	1,277	499 (39.1)	183 (14.3)	354 (27.7)	74 (5.8)
Female	1,174	378 (32.2)	87 (7.4)	180 (15.3)	38 (3.2)
<i>P</i> value		< 0.01	< 0.001	< 0.001	0.003
<i>S. mansoni</i> EPG categories					
0	836	221 (26.0)	46 (5.5)	123 (14.7)	18 (2.2)
1–100	680	218 (32.1)	83 (12.2)	160 (23.5)	24 (3.5)
> 100	935	438 (46.8)	141 (15.1)	251 (26.8)	70 (7.5)
<i>P</i> value		< 0.001	< 0.001	0.01	< 0.001
Overall	2,451	877 (35.8)	270 (11.0)	534 (21.8)	112 (4.6)

* More than 2 cm below the costal margin.

TABLE 4

Serum markers of HBV and HCV by study site, sex, categories of age, and PPT/F among 1,707 study subjects from *S. mansoni*-endemic villages

Study variables		N	Any HBV marker positives [N (%)]	HBsAg positives [N (%)]	Anti-HCV positives [N (%)]
Study site	Chekorso	171	94 (55.0)	14 (8.2)	5 (2.9)
	Worke-Mado	412	183 (44.4)	21 (5.1)	6 (1.5)
	Cherete	405	165 (40.7)	10 (2.5)	6 (1.5)
	Sille-Elgo	719	296 (41.2)	46 (6.4)	6 (0.8)
<i>P</i> value			0.007	0.01	0.052
Sex	Male	906	392 (43.3)	44 (4.9)	11 (1.2)
	Female	801	346 (43.2)	47 (5.9)	12 (1.5)
<i>P</i> value			0.9	0.3	0.7
Age category (years)	< 10	461	167 (36.2)	24 (5.2)	7 (1.5)
	11–20	487	189 (38.8)	23 (4.7)	7 (1.4)
	21–30	315	161 (51.1)	22 (7.0)	5 (1.6)
	31–40	250	133 (53.2)	14 (5.6)	2 (0.8)
	> 40	194	88 (45.4)	8 (4.1)	2 (1.0)
<i>P</i> value			< 0.001	0.6	0.9
Patterns of PPT/F	No PPT/F	1,416	592 (41.8)	63 (4.4)	20 (1.4)
	Incipient	108	42 (38.9)	6 (5.6)	1 (0.9)
	Possible/probable	37	17 (45.9)	3 (8.1)	1 (2.7)
	Definite/advanced	104	68 (65.4)	14 (13.5)	1 (1.0)
	Other image pattern	42	19 (45.2)	5 (11.9)	0 (0)
<i>P</i> value			< 0.001	0.001	0.8
Overall		1,707	738 (43.2)	91 (5.3)	23 (1.3)

ences related to routes of transmission that may influence the overall prevalence of HBV in the respective localities. Our overall prevalence estimate of HCV infection was comparable to figures reported from earlier studies in Ethiopia.^{24,25} In our series, neither the presence of markers of HBV infection nor the presence of anti-HCV antibodies was associated with *S. mansoni* infection status or intensity of *S. mansoni* egg excretion. However, markers of HBV infection were significantly associated with schistosomal PPT/F.

Studies that addressed the association/interaction of *S. mansoni* with HBV/HCV infections are varied and at times conflicting. Some studies from Egypt have reported higher prevalence of HBsAg among subjects with schistosomiasis and schistosomal periportal fibrosis,^{26,27} and subjects with co-infection had increased risk of hepatocellular carcinoma.²⁸ A similar association was also observed between schistosomiasis mansoni and HCV.²⁹ Furthermore, subjects with co-infection had significantly more advanced liver disease^{30,31} and exhibited higher titers of HCV RNA.³⁰ A similar pattern was also

observed in some case-control studies from Brazil.^{32,33} On the other hand, other studies reported no association of HBV/HCV infection with either *S. mansoni* infection or with periportal fibrosis.^{3,34–37} Furthermore, the high frequencies of HCV infections observed among Egyptian subjects with a history of schistosomiasis were largely considered to be related to possible iatrogenic transmissions that may have resulted from the use of poorly sterilized equipment during parenteral anti-schistosomal treatment campaigns.^{38,39}

Our multiple logistic regression analysis showed that intensity of *S. mansoni* egg excretion > 100 epg, presence of markers for HBV infection, age, and male sex were significantly associated with the development of PPT/F. On the other hand, after controlling for age and *S. mansoni* infection, presence of other intestinal helminth infections was associated with lower odds of developing schistosomal PPT/F. Similarly, other researchers have also reported intensity of *S. mansoni* infection, male sex, and age/duration of exposure to be independent risk factors associated with the development of

TABLE 5

Results of logistic regression analysis with estimates of crude and adjusted odds ratios of risk factors associated with schistosomal periportal thickening/fibrosis

Variables		Crude OR (95% CI)	<i>P</i> value	Adjusted OR (95% CI)	<i>P</i> value
Age category (years)	> 10	1		1	
	11–20	4.6 (2.6–8.1)	< 0.001	2.6 (1.4–4.9)	0.003
	21–30	5.3 (2.9–9.7)	< 0.001	4.7 (2.4–9.2)	< 0.001
	31–40	4.3 (2.2–8.3)	< 0.001	3.0 (1.4–6.2)	0.003
	> 40	2.6 (1.1–5.8)	0.02	2.0 (0.9–4.7)	0.1
Sex	Female	1		1	
	Male	1.9 (1.3–2.8)	0.002	1.9 (1.2–2.9)	0.004
<i>S. mansoni</i> EPG category	0	1		1	
	1–100	1.7 (0.9–3.2)	0.08	1.0 (0.5–2.0)	0.9
	> 100	3.7 (2.2–6.1)	< 0.001	2.5 (1.4–4.5)	0.001
Other helminth	Negative	1		1	
	Positive	0.5 (0.3–0.8)	0.002	0.5 (0.3–0.8)	0.002
HBsAg	Negative	1		1	
	Positive	3.3 (1.8–6.2)	< 0.001	3.5 (1.9–6.7)	< 0.001
Any HBV marker	Negative	1		1	
	Positive	2.3 (1.5–3.6)	0.001	2.1 (1.4–3.3)	0.001

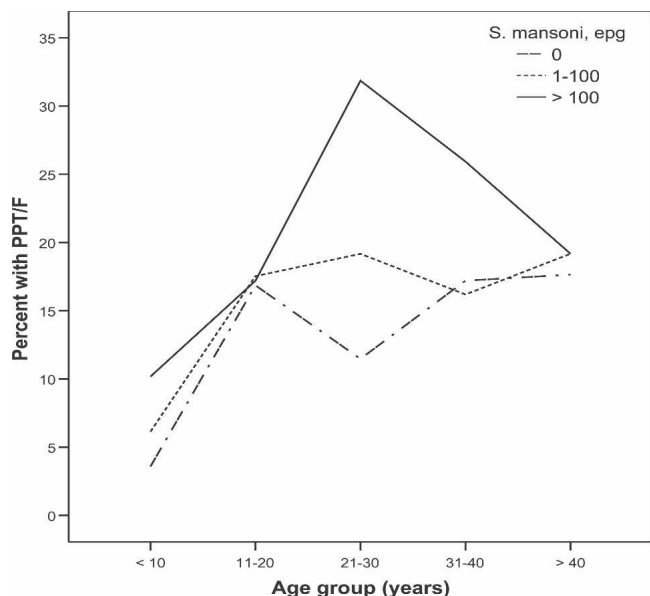


FIGURE 1. Percent with periportal thickening/fibrosis by age and *S. mansoni* Egg category.

PPT/F.^{4,6} Furthermore; Boisier and others⁹ have indicated similar risk factors including the negative association of geohelminth with the development of schistosomal PPT/F. More often than not, morbidity exhibited in subjects with poly-parasitic infections may not be commensurate with what may be expected from the combined morbid effects of the specific infections. Furthermore, it is known that concomitant infections can influence host immune response, and their interaction may result in augmentation or suppression of immunopathology of either or both infections.⁴⁰ Similar associations of reduced morbidity have also been reported for malaria in association with intestinal helminth infections,^{41,42} although not all publications support these observations.⁴³ Thus, although the underlying mechanism, if any, remains to be seen, this negative association of geohelminth with development of schistosomal PPT/F may have important public health implications in *S. mansoni*-endemic areas and provides an additional justification in favor of combining community deworming programs with anti-schistosomal chemotherapy.

Our logistic regression model predicted correctly the PPT/F status of subjects in 93% of the cases. However, after controlling for the above risk factors, study communities still differed in their prevalence of PPT/F, suggesting the probable existence of some micro-geographic peculiarities to these communities that may have important bearings in the overall morbidity levels related to schistosomiasis mansoni. It is to be noted that, although our study communities with higher prevalence and intensity of *S. mansoni* infection generally had higher prevalence of PPT/F, the levels of fibrosis in the Sille-Elgo community were not commensurate with the local prevalence and intensity of *S. mansoni* infection. In our earlier report, we noted high levels of oxidative stress in subjects from *S. mansoni*-endemic areas, and furthermore, although serum concentrations of α -tocopherol among school children in Sille-Elgo were comparable to the levels found in healthy non-endemic highlanders, the corresponding figure in children from the *S. mansoni*-endemic area with high levels of periportal fibrosis were significantly low.⁴⁴ Thus, among oth-

ers, the fact that the Sille-Elgo community has better access to fruits and vegetables, and thus has better antioxidant defense, may have contributed to the observed differential morbidity pattern at a community level.⁴⁴

We are aware that mild forms of PPT/F may be caused by other infectious diseases.⁴⁵ However, we excluded this possibility mainly because our prevalence estimate was based on detection of definite/advanced PPT/F. Similarly, non-cirrhotic portal fibrosis, which is often reported from the Asian sub-continent, may occasionally mimic the ultrasonographic image patterns of mild-moderate schistosomal PPT/F.⁴⁶ Although this possibility cannot be excluded with absolute certainty, none of our patients presented with the typical clinical and ultrasonographic features of non-cirrhotic PPT/F,⁴⁷ thus making it an unlikely cause of PPT/F in our study community.

Obviously, because schistosomal liver pathology is a late disease outcome, cross-sectional studies such as ours can only provide information on associated factors of morbidity, which may not imply causality. Second, our serologic studies on HBV and HCV did not include children < 5 years of age, and the prevalence estimates of these infections may not reflect the actual community levels of these infections. However, with these shortcomings, this study was the first large-scale morbidity study that involved study villages from major endemic sites in Ethiopia.

In summary, because children have the highest prevalence and intensity of infection, school age targeted chemotherapy combined with proper sanitation practices and provision of a safe water supply need to be implemented to substantially reduce the overall prevalence of and morbidity caused by schistosomiasis mansoni.

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