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Original Article

Study on Prevalence of Parasitic Infections Among Hepatitis C Virus Patients in Egypt

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ABSTRACT

Introduction: Hepatitis C virus (HCV) is a viral infection affecting 71 million people worldwide. A high prevalence of co-infection has been observed with parasitic infections, such as *Schistosoma mansoni*, *Fasciola* sp., and *Toxoplasma gondii*, all of which can contribute to the progression of liver disease. This study aimed to investigate the prevalence of co-parasitic infections with HCV-positive individuals within Egyptian populations and the resulting biochemical changes in liver and kidney biomarkers.

Materials and Methods: A total of three hundred and thirty-seven blood samples were screened molecularly for HCV and immunologically for parasitic infections using PCR and ELISA, respectively. Liver functions were monitored by measuring serum levels of glutamic oxaloacetic aminotransferase (GOT), glutamate pyruvate alanine aminotransferase (GPT), gamma-glutamyl transferase (GGT), total protein (TP), albumin (Alb), total bilirubin (T Bil), and alkaline phosphatase (ALK). Kidney functions were evaluated by measuring creatinine, uric acid, urea, sodium (Na), and potassium (K) levels. Patients were categorized by gender and age <21, 21-50, and >50 years. Results indicated that 120 out of 287 HCV-infected cases (41.8%) have *Schistosoma* infection, of which 57, 31, 24, and 8 cases were mono-infected and co-infected with *Fasciola*, *Toxoplasma*, and *Fasciola*/*Toxoplasma*, respectively Additionally, 99 patients (34.5%) were infected with *Fasciola hepatica* infection, of which 51 were mono-infected and 9 were co-infected with *Toxoplasma*.

Results: A total of 87 patients (30.3%) tested positive for *T. gondii* infection, of which 46 cases were mono-infected. Additionally, the proportion of male patients with monoparasitic infection ranged from 78.2% (*Toxoplasma*) and 84.3% (*S. mansoni* or *F. hepatica*). On the other hand, the highest incidences of single infections among males (*Fasciola* and *Toxoplasma*) were over

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the age of 50 years for *Fasciola* (43.1%) and *Toxoplasma* (39.1%), respectively. In contrast, *S. mansoni* mono-infection was most prevalent (42.1%) among males aged 21–50 years.

Conclusion: Liver enzyme levels (GPT, GOT, Alk, and GGT) and kidney parameters (creatinine and urea) were significantly affected by the type (mono or mixed) and species of parasitic infections in HCV patients. Additionally, most serological parameters were significantly in cases of viral/parasitic co-infections, especially, among patients with high viral loads.

1. Introduction

Hepatitis C (HCV) is a life-threatening viral infection, particularly in several developing countries. According to the World Health Organization (WHO), approximately 71 million people worldwide are chronically infected with HCV, and HCV-related liver disease accounts for over 350,000 deaths annually [1]. Egypt has the highest HCV prevalence worldwide; a 2018 meta-analysis reported an antibody prevalence of 11.9% [2]. Chronic HCV infection generally progresses slowly, with limited advanced liver disease during the first 10 –15 years. The primary causes of mortality in HCV patients included liver-related diseases such as cirrhosis and hepatocellular carcinoma, co-infection with human immunodeficiency virus (HIV), and drug overdose [3].

Parasitic co-infections may also accelerate liver disease progression. *Schistosoma mansoni* infection is the main causative agent of granulomatous reactions in the liver, resulting in splenomegaly, portal hypertension, and hepatomegaly [4]. Also, it has been found that both acute and chronic types of toxoplasmosis involve the liver [5]. The disease is caused by *Toxoplasma gondii*, a widespread protozoal infection distributed all over the world. Its diagnosis relies on serological examinations because the clinical manifestations interfere with many other diseases, and microscopic examination of the parasite from patients is usually difficult. Over the past three decades, human fascioliasis has raised emerged as a public health, prompting the WHO the WHO to designate it as a neglected tropical disease [6]. Apart from several indications, *Fasciola* infection has also been associated with liver fibrosis in both people and animals [7]. Clinical complications may include acute cholecystitis, biliary blockage, and liver abscesses, often requiring surgical intervention [8]. The co-occurrences and associated morbidities of parasitic diseases with HCV infection have directed our attention to studying the prevalence and risk factors, as well as related liver and kidney morbidities among study participants. Therefore, the present study aimed to investigate the prevalence of co-parasitic infections with HCV and associated serum biochemical changes in terms of liver and kidney functions.

2. Materials and Methods

2.1. Demographic characteristics of the study population

A total number of 337 HBV free samples were screened for HCV with or without parasitic infections. As described in Table 1, the tested samples were categorized according to gender and age. The number of male samples was 267 out of 337, and the number of females was 70, while the ratio between them was nearly 4:1. The age distribution of the screened individuals was as follows: 30 individuals (8.9%) aged <21 years, while 132(39.16%) were between 21 and 50 years, and finally, 175 individuals (51.9%) were >50 years old.

2.2. Collection of blood samples and the viral detection

A total of 350 blood samples were collected from patients atthe laboratories of the Armed Forces for Medical Research (AFLMR). Clear sera were separated from the blood samples by centrifugation at 3000 rpm. HCV was detected molecularly using the QIAsymphony assay, which integrates an automated polymerase chain reaction (PCR) process, alongwith the QIAsymphony DSP Virus Kit (QIAGENCAPANY, Germany). Sera samples that tested positive for HCV were subsequently immunologically retested to HBV infection using enzyme-linked immunosorbent assay (ELISA) on the VITROS® 3600 Immunodiagnostic System (QuidelOrtho™, USA). Samples that tested positive for HBV were excluded from this study. All abovementioned tests were achieved in the Virology Department of AFLMR.

Table 1. The demographic characteristics of the tested patients

Sample No.	No. (%)		
	Sex		Total
Age (y)	Male	Female	
<21	23(6.82)	7(2)	30(8.9)
21-50	106(31.45)	26(7.7)	132(39.16)
>50	138(40.94)	37(10.97)	175(51.92)
Total	267(79.2)	70(21.3)	337(100)

2.3 Detection of the parasitic infections

2.3.1 Preparation of *S. Mansoni* and *Fasciola hepatica* antigens

Adult worms of *S. mansoni* were obtained from the Schistosome Biological Supply Program (SBSP) at Theodor Bilharz Research Institute, Giza, Egypt. Whole worms were homogenized in phosphate-buffered saline (PBS, 1:3 w/v). Centrifugation of the homogenate was carried out at 10000 rpm for 15 minutes. The resulting supernatant, containing the crude antigen, was kept at -80 ˚C until use.

Adult *Fasciola* sp. worms were collected from naturally infected sheep at El-Basaten slaughterhouse in Cairo, Egypt. The whole worms were isolated from the common bile ducts, gall bladders, and main hepatic ducts of naturally infected sheep. All worms were washed three times with normal saline solution and repeatedly rinsed with distilled water. They were then incubated in 0.85% NaCl at room temperature for 6 hours to remove adherent host cells and empty intestinal caeca. Phosphate buffer (pH 7.2) was added to the worms in a mortar in a ratio of 3:1 (v/w), then the worms were grinded manually for 5 minutes, and centrifuged for 10 minutes at 10000 rpm at 4 ˚C. The supernatant was taken, transferred to a clean tube, and stored at -80 ˚C. Protein concentrations in the *S. mansoni* and *Fasciola* homogenates were determined using the Bio-Rad Kit for total protein (TP) measurement at a wavelength of 570–580 nm.

2.3.2 ELISA for detection antibodies of parasitic infections

An ELISA was performed to detect the parasitic infections with Schistosomiasis and/or Fascioliasis in HCV-positive sera samples. Polystyrene 96-well plates were coated with a standardized quantity (1 µg/mL) of crude antigens (extracted from adult *S. mansoni* and *Fasciola* spp.), diluted in 0.05 M bicarbonate buffer (pH 9.6), and incubated overnight at 4 ˚C. Plates were washed three to five times with PBS/0 containing 05% Tween-20 (PBST), then blocked with 1% (v/v) bovine serum albumin (BSA) (Win Lab., UK) in PBST (BSA-PBST) at room temperature for 2 hours. After washing, 100 µL of each serum sample (diluted 1:100) in phosphate buffered saline (1×) was added to each well, and the plates were incubated at 37 ˚C for 1 hour. The plates were then washed and incubated at 37 ˚C for 1 hour with anti-human-IgG horseradish peroxidase-conjugated antibody (Sigma-Aldrich, St. USA) diluted in washing solution at 1:10000 in washing solution. After a final wash, 100 µL of substrate solution, ortho-phenylenediamine (OPD) (Sigma) substrate, for 30 minutes was added to each well. The reaction was stopped by adding 50 µL of 4 N sulfuric acid per well. The absorbance was estimated at 450 nm (ELx808, BioTek Instruments Inc, Vermont, USA).

All HCV serum samples were also tested for the presence of anti-*T. gondii* antibodies, IgG using the VITROS® 3600 immunological integrated System and Architect™ PLUS I1000SR immunoassay analyzer (ABBOTT company, Germany).

2. 4. Clinical chemical determination

Liver function was evaluated using the Vitros® 4600 chemistry system and VITROS 5600 integrated System (QuidelOrtho™, USA,). The following serum parameters were measured: Glutamate oxaloacetate aspartate aminotransferase (GOT), Glutamic-pyruvic transaminase (GPT), gamma-glutamyl transferase (GGT), TP, albumin (Alb), total bilirubin (T Bil), and alkaline phosphatase (ALK). Kidney functions were evaluated by estimating serum levels of creatinine, uric acid, urea, sodium (Na), and potassium (K) using the same system and its specific kits, according to the instructions provided for each kit.

Table 2. Parasitic infections frequencies among HCV patients

Parasite	No. of Samples with Single and Mixed Parasitic Infections/No. of Inf. with Specific Parasite (%)				Total Specific Parasitic inf.) % from 287 HCV-infected Cases)
	F	T	S	S+T+F	
Shcistosoma	31/120 (25.8%)	24/120 (20%)	57/120 (47.5%)	8/120 (6.66%)	120 (41.80%)
Fasciola	51/99 (51.51%)	9/99 (9%)	31/99 (31.3%)	8/99 (8.08%)	99 (34.49%)
Toxoplasma	9/87 (10.34%)	46/87 (52.87%)	24/87 (27.58%)	8/87 (9.19%)	87 (30.31%)

Abbreviations: S: *Shcistosoma*; F: *Fasciola*; T: *Toxoplasma*.

Note: Total mono-infected samples=57+46+51=154; Total double-infected samples=31+24+9=34; Total trible-infected samples=8.

2.5. Statistical analysis

ANOVA and a non-parametric t-test (Mann-Whitney test) were used. The $P<0.05$ was considered statistically significant and highly significant when it was <0.001, according to GraphPad Prism software, version 8.0.2.

3. Results

3.1. Detection of viral infection using PCR

Out of 337 tested samples for HCV infections using the VITROS® 3600 Integrated System, 50 samples were found to be free from both HCV and HBV (Hepatitis B virus) infections. The remaining 287 sera samples were individually tested for antibody titer reactivity against the antigens of *S. mansoni*, *F. hepatica*, and *T. gondii*.

3.2. Detection of parasitic infection using ELISA

Sera samples from HCV-infected patients were subjected to ELISA to detect antibodies against *S. mansoni*, *Fasciola*, and/or *Toxoplasma* antibodies. A total of 120 out of 287 samples of HCV-infected cases, with a percentage of 41.8%, were found to have developed *Schistosoma* antigen-specific antibodies. Among these cases, single schistosomiasis infections were recorded in 57 samples (47.5%), followed by samples from patients with co-infections: 31(25.8%) with *Fasciola*, 24(20%) with *Toxoplasma*, and 8(6.6%) with both *Fasciola* and *Toxoplasma* (Table 2).

In parallel, 99 out of 287 samples (34.5%) tested positive for *F. hepatica* antibodies. Among these, 51 samples (51.5%) were single infections, while mixed infections with *Schistosoma* and/or *Toxoplasma* were also recorded as, 31(31.3%), 9(9%), and 8(8%) out of 99 samples, respectively (Table 2).

Additionally, 87 out of 287 samples (30.3%) were positive for *T. gondii*-specific IgG antibodies. Of these, 46 samples (52.8%) represented single toxoplasmosis infections. Co-infections were observed in 24 samples (27.5%) with Schistosoma, 9 samples (10.3%) with *Fasciola*, and 8 samples (9.1%) with both Schistosoma and *Fasciola* (Table 2).

3.3. Group categories according to parasitic infection

Based on the data presented in Tables 3 and 4, the evaluated samples for parasitic infection were classified into 9 groups according to the presence of HCV, monoparasite, or co-infection. Each group was further categorized by age and gender. The age categories were: <21 years old, 21-50 years old, and >50 years old. Group (A): Samples free from both free from both HCV and parasitic infections, considered as healthy control (HCV-ve, P-ve). Group (B) comprised HCV positive samples but were free from any parasitic infection (HCV+ve, P-ve). Group (C) included HCV positive combined with *S. mansoni* infection (HCV+ve, S+ve).

Group (D) HCV viral infection combined with *F. hepatica* infection (HCV+ve, F+ve). Group (E) consisted of individuals with HCV viral infection combined with the parasitic infection of *T. gondii* (HCV+ve, T+ve). Groups (F), (G), (H), and (I) were positively infected with HCV accompanied by mixed parasitic infections including *S. mansoni* and *F. hepatica* (HCV+ve, SF+ve)., *S. mansoni* and *T. gondii* (HCV+ve, ST+ve), *F. hepatica* and *T. gondii* (HCV+ve, FT+ve), *S. mansoni*, *F. hepatica* and *T. gondii* (HCV+ve, SFT+ve), respectively. Additionally, all groups from B to I were further categorized referring to the viral load (quantitative PCR [qPCR] results) into two subgroups: Patients with low viral load (103 to 105

Table 3. Prevalence of single parasitic infections in HCV patients according to gender and ages

Group	No. (%)									
	A		B		C		D		E	
Age (y)	M	F	M	F	M	F	M	F	M	F
<21	-	1(2)	6(9.83)	2(3.2)	6(10.52)	-	4(7.84)	-	1(2.17)	2(4.34)
21–50	13(26)	5(10)	18(29.5)	3(4.91)	24(42.1)	1(1.75)	17(33.33)	2(3.92)	17(36.95)	3(6.52)
>50	28(56)	3(6)	27(44.26)	5(8.19)	18(31.57)	8(14.03)	22(43.13)	6(11.76)	18(39.13)	5(10.86)
Total	41(82)	9(18)	51(83.6)	10(16.3)	48(84.2)	9(15.7)	43(84.3)	8(15.6)	36(78.2)	10(21.7)

F: Famale; M: Male.

Note: A: Healthy; B: HCV +ve; C: HCV & *Schistosoma* +ve; D: HCV & *Fasciola* +ve; E: HCV & *Toxoplasma* +ve.

copies/mL) and patients with high viral load (>105 copies/mL) group (Table 5).

The percentage of males in groups with mono-parasitic infection ranged from 78.2% (*Toxoplasma*) and 84.3% (*S. mansoni* or *F. hepatica*). Among these, the highest proportion of males over the age of 50 was observed in the *Toxoplasma* and *Fasciola* groups, accounting for 39 and 43.1%, respectively. However, the *Schistosoma*-infected group showed the highest male percentage in the 21–50 age category (42.1%). In general, the age group under 21 consistently had the lowest male percentage representation across all mono-parasitic infection groups. Likewise, in the HCV-infected group, the majority of patients belonged to the age group over 50 years, comprising 44.2% and 8.1%, totaling 52.2% (Table 3).

The same profile was identical in the patient groups with mixed parasitic infection,where the number of males was greater than the number of females. On the other hand, most of patients co-infected with both *Schistosoma* and *Fasciola* (group F, 29%+19.3%=48.2%) were in the 21-50 age group, while the remaining patients with mixed parasitic infection belonged to the age group above 50 years (Table 4).

Most HCV patients in this study, whether infected with the virus alone or even co-infected with one or more parasites, showed a high viral load (>105 copies/mL). However, the highest viral load was observed in patients with mixed parasitic infections involving both *Fasciola* and *Toxoplasma* (group H, 88.8%) (Table 5).

3.4. Liver functions parameters

Tables 6 and 7 illustrate the tested parameters of the liver functions for all examined groups, including both low and high viral loaded sample categories, respectively. All

Table 4. Prevalence of mixed parasitic infections in HCV patients according to gender and age

Group	No. (%)							
	F		G		H		I	
Age (y)	M	F	M	F	M	F	M	F
<21	3(9.67)	-	3(12.5)	2(8.33)	-	-	-	-
21-50	9(29.03)	6(19.35)	3(12.5)	5(20.83)	1(11.11)	2(22.22)	2(25)	1(12.5)
>50	8(25.8)	5(16.12)	7(29.16)	4(16.66)	5(55.55)	1(11.11)	5(62.5)	-
Total	20(64.5)	11(35.4)	13(54.1)	11(45.8)	6(66.6)	3(33.3)	7(87.5)	1(12.5)

M: Males, F: Females.

Note: F: HCV; *Schistosoma* & *Fasciola* +ve; G: HCV; *Schistosoma* & *Toxoplasma* +ve; H: HCV; *Fasciola* & *Toxoplasma* +ve; I: (HCV; *Schistosoma*; *Fasciola* & *Toxoplasma* +ve).

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Table 5. Distribution of parasitic and HCV infections according to HCV viral loads

Group (No. of Patients)	No. (%)	
	Low Viral Load*	High Viral Load**
B (HCV+ve) (61)	21(35)	40(65)
C (*Schistosoma*) (57)	24(42.11)	33(57.89)
D (*Fasciola*) (51)	15(29.42)	36(70.58)
E (*Toxoplasma*) (46)	19(41.31)	27(58.69)
F (S+F) (31)	9(29.04)	22(70.96)
G (S+T) (24)	6(25)	18(75)
H (F+T) (9)	1(11.1)	8(88.8)
I (F+S+T) (8)	4(50)	4(50)

Chi square=5.608, P>0.05, non-significant.

*(10000-100000 copies/mL), **(>100000 copies/mL) according to qPCR results.

low viral loaded samples showed no significant variation in GOT level in comparison with group A (-ve control) (P>0.05) (Table 6). On the other hand, as illustrated in Table 7, high viral loaded samples of groups C (HCV +ve with *S. mansoni*), D (HCV +ve with Fascioliasis) and I (HCV +ve with F, S, T) showed significantly increased GOT levels (P<0.05). However, the other groups did not show statistically significant difference from the negative control group (P>0.05).

Analysis of liver enzyme GPT levels using a non-parametric ANOVA test showed statistically high significant variations among all groups (P<0.01). When comparing each group to group A using the Mann–Whitney test, the following groups showed highly significant increases in GPT levels (P<0.01): Group B (high viral loads), group C (low viral load), group E (high viral load), group H (high viral load) and group I (high viral load), while groups C (high viral load), D (high viral load) and F

Table 6. Liver-specific serum parameters for the different groups with low viral loaded samples

Group Parameter	Mean±SD							
	A (HCV-ve)	B (HCV +ve)	C (*Schistosoma*)	D (*Fasciola*)	E (*Toxoplasma*)	F (S+F)	G (S+T)	I (F+S+T)
GOT (u/L)	43±20	34.95±20.7	53.36±35.6	50.86±27.9	52.47±33	51.13±29	50.8±28.8	34.5±3.69
GPT (u/L)	31.24±15.3	45.3±20	47.75±30.37**	42.07±26.8	44.69±31.75	43.13±32.38	46±26.24	17.33±3.05*
TP (g/dL)	7.211±1.26	7.142±1.04	7.79±0.99	7.4±1.55	7.41±1.02	6.52±0.97	8±0.95	7.6±0.94
ALK (IU/L)	63.21±17.7	66.38±17.2	90.14±36.2**	81.58±38	91.61±35.17**	72.14±27.6	85±12.4**	97.75±41.1**
T Bil (mg/dL)	0.615±0.2	0.862±0.4	1.468±1.6**	0.946±0.66*	0.883±0.72*	0.844±0.66*	1.217±1.12**	0.7±0.1
Alb (g/dL)	3.907±0.8	4.25±0.73	4.25±0.91	4.63±0.7	3.76±0.67	3.74±0.68	4.6±0.56	4.05±0.46
GGT (U/L)	26.97±9.75	66.75±50.9***	93.13±53.5***	53.6±24.96***	62.08±35***	49.5±29.1**	49±34.48*	61.75±39.3***

Note: GOT: Glutamic oxaloacetic transaminase (normal level 8-45 u/L), GPT: Glutamic-pyruvic transaminase (normal range 7-56 u/L), TP: Total proteins (normal range 6-8 g/dL), ALK: Alkaline phosphatase (normal range 44-147 IU/L), T Bil: Total bilirubin (normal range 0.1-1.2 mg/dL), Alb: Albumin (normal range 3.4-5.4 g/dL), GGT: Gamma-glutamyl transferase (normal range 5-40 U/L).

*P<0.05 (significant), **P<0.01 (very significant), ***P<0.001 (highly significant).

Table 7. Liver-specific serum parameters for the different groups with high viral loaded

Group / Parameter	Mean±SD								
	A (HCV-ve)	B (HCV +ve)	C (*Schistosoma*)	D (*Fasciola*)	E (*Toxoplasma*)	F (S+F)	G (S+T)	H (F+T)	I (F+S+T)
GOT (u/L)	43±20	50.18±39	59.75±53.7*	55±32.6*	49.12±26.8	50.83±26	41.36±18.3	43.63±20.5	66.25±22.6*
GPT (u/L)	31.24±15.3	62±61.2**	44.7±23.5*	55.2±27.1*	58.25±38**	47.57±26*	33.18±15.4	56.86±29**	57.5±20.36**
TP (g/dL)	7.21±1.26	7.39±0.91	7.7±1.27	7.3±1.27	7.6±0.91	6.98±1.3	7.67±1.07	7.58±1.55	8.24±0.47
ALK (IU/L)	63.2±17.8	84.38±53.7	98.82±66.8*	103.1±45.1**	109±78.2*	100.7±41.1**	81.3±28.4	91.63±41.1	90±36
T Bil (mg/dL)	0.615±0.2	0.78±0.38	1.461±1.4**	1.06±0.86*	0.892±0.34*	0.958±0.46*	1.24±1.61**	1.07±0.57*	0.9±0.35*
Alb (g/dL)	3.9±0.8	4.13±0.66	4.4±0.69	4.1±0.64	4.25±0.7	4.07±1.15	4.28±0.7	4.36±0.9	3.95±0.7
GGT (U/L)	26.97±9.75	69.26±54.2***	81.59±99.9***	81.11±66.1***	101.1±83.2***	56±30.1***	64.69±24.56***	59.67±23.8**	53.2±14***

Note: GOT: Glutamic oxaloacetic transaminase (normal level 8-45 u/L), GPT: Glutamic-pyruvic transaminase (normal range 7-56 U/L), TP: Total proteins (normal range 6-8 g/dL), ALK: Alkaline phosphatase (normal range 44-147 IU/L), T Bil: Total bilirubin (normal range 0.1-1.2 mg/dL), Alb: Albumin (normal range 3.4-5.4 g/dL), GGT: Gamma-glutamyl transferase (normal range 5-40 U/L).

*P<0.05 (significant), **P<0.01 (very significant), ***P<0.001 (highly significant).

(high viral load) revealed slightly significant increases (P<0.05). All remaining groups showed no significant differences in GPT level compared to groups A and B (low and high viral loads) (P>0.05). No significant variations were observed in TP and Alb serum levels across all groups.

Regarding ALK level, groups C, E, G, and I (with low viral loads) and groups D and F with high viral loads showed highly significant increases where the P<0.01. However, groups C and E (high viral load) showed less significant increases in ALK level (P<0.05). In contrast, serum level of GGT showed fluctuations in the degree of significant increase for all groups of low and high viral loaded samples in comparison with -ve control group (Tables 6 and 7).

For T Bil, groups D, E, and F with low viral loads showed significant increases in comparison with group A (P<0.05), while groups C and G showed a highly significant increase (P<0.01). Similarly, the same groups with high viral loads in addition to groups G, H, and I showed significant increases with different degrees (P<0.05 and 0.001), particularly group C, which was co-infected with *Schistosoma* sp.

Overall,liver enzyme levels (GPT, GOT, Alk, and GGT) were more affected by the type (mono or mixed) and species of parasitic infections in HCV patients.

Most liver function parameters were significantly elevated in cases of viral/parasitic co-infection, with more pronounced increases observed in patients with high viral loads.

3.5 Kidney functions parameters

Tables 8 and 9 present the kidney function parameters across all examined groups, including low and high viral loaded samples categories, respectively. As shown in Table 8, when comparing serum creatine levels in patients with low viral loads from groups B, E, D, and F versus group A, there were less significant (group B & E, P<0.05) and highly significant (group D & F, P<0.01) increases. Similarly Table 9 shows that patients with high viral loads in groups E and F showed highly significant increases in creatine levels (P<0.01 & P<0.001, respectively), whereas groups G and H showed less significant increases (P<0.05). However, no significant differences were observed in the remaining groups.

Uric acid levels were generally not significant different from group A, except for group F with low viral load (Table 8), and groups H and I with high viral loads (Table 9), where they showed the least significant increases in blood uric acid levels (P<0.05).

Regarding blood urea levels, groups B, D, and F (with low viral load) showed very significant increases (P<0.01), while the groups C and E showed the least sig-

Table 8. Kidney-specific serum parameters for the different groups with low viral loaded samples

Group Parameter	Mean±SD							
	A (HCV-ve)	B (HCV +ve)	C (*Schistosoma*)	D (*Fasciola*)	E (*Toxoplasma*)	F (S+F)	G (S+T)	I (F+S+T)
Creatinine (mg/dL)	0.75±0.158	2.75±2.9*	1.81±2.6	2.25±2.7**	2.36±2.9*	2.73±2.6**	0.86±0.16	1.97±2
Uric acid (mg/dL)	5.01±1.2	5.98±1.53	5.68±1.22	4.98±1.21	5.22±1.53	6.92±2.55*	5.15±1.73	5.4±0.77
Urea (mg/dL)	32.77±15.2	72.65±60**	48.19±30.2*	60.15±37.7**	49.75±25.6*	60.29±32.4**	32±3.87	50.5±26.8
Na (mmol/L)	134±6.17	127.2±11.5	135±3.432	125.9±11.2	126±14.33	126.1±12	128.2±18.3	128±12.4
K (mmol/L)	4.41±0.59	5.31±1.68**	4.98±1.08	4.86±0.53	4.8±0.85	4.77±0.53	4.94±1.03	5.45±2.4**

*P<0.05 (significant), **P<0.01 very significant).

Note: Creatinine (normal range 0.6-1.3 mg/dL), uric acid (normal range 3.5-7.2 mg/dL), urea (normal range 5-20 mg/dL), Na (normal range 136-145 mmol/L), K (normal range 3.5-5.2 mmol/L).

nificant increases (P<0.05) (Table 8). On the other hand, in the high viral load groups, groups E and F exhibited highly significant increases (P<0.001). Groups B, C, and D showed less significant increases (P<0.05) (Table 9).

Concerning Na levels, serum samples from patients with high viral loads (Table 9), except for groups G and I, showed significant decreases when compared to group A (P<0.05). However, no significant differences were observed among the remaining groups with low viral load (Table 8). In addition, K levels in patients' blood samples in groups B and I (with low viral load, Table 8) showed significant increases (P<0.01), similarly, groups C, D, F, G and H (with high viral loads), showed relatively high significant elevations in K levels compared to the healthy group A (P<0.01). However, the remaining groups did not show significant differences from the healthy group A (Tables 8 and 9). In summary, kidney parameters (Creatinine, Urea, Na, K), were more affected in patients with HCV with a high viral load and parasitic co-infections (*Schistosoma*, *Fasciola* and *Toxoplasma*) than the parameters (creatinine and urea) in patients with low viral load.

4. Discussion

An ELISA assay was carried out to detect three parasitic infections (schistosomiasis, fascioliasis, and toxoplasmosis) in all tested samples of HCV patients. ELISA is a powerful immunological tool for estimating parasitic infection in HCV-positive samples [9]. According to gender, the present study showed that the prevalence of all parasitic infections among male HCV patients was higher than among females with no significant varia-

Table 9. Kidney-specific serum parameters for the different groups with high viral loaded samples

Group Parameter	Mean±SD								
	A (HCV-ve)	B (HCV +ve)	C (*Schistosoma*)	D (*Fasciola*)	E (*Toxoplasma*)	F (S+F)	G (S+T)	H (F+T)	I (F+S+T)
Creatinine (mg/dL)	0.75±0.15	1.41±1.9	1.62±2.6	1.841±2.33	2.5±2.9***	3.12±2.9***	2.44±2.8*	2.17±2.6*	0.95±0.31
Uric acid (mg/dL)	5.01±1.23	5.61±1.26	5.59±1.24	5.52±1.27	5.28±1.25	5.23±1.78	4.98±1.2	6.2±0.89*	6.52±1.2*
Urea (mg/dL)	32.7±15.2	50.23±43.8*	49.59±34.6*	50.29±39*	60.24±38***	63±28.5***	49±23.1	43.43±30.9	33.5±17.3
Na (mmol/L)	134±6.17	129.6±9.2*	129.8±8.4*	129.2±8.83*	129±7.9*	130.1±7.47*	131.2±9.08	127.3±7.9*	134±4.35
K (mmol/L)	4.41±0.59	4.68±0.83	5.12±1.05**	5.49±1.75**	4.67±0.67	5.17±0.99**	5±0.728**	6.16±2.01**	4±0.65

*P<0.05 (significant), **P<0.01 very significant), ***P<0.001 highly significant.

Note: Creatinine (normal range 0.6-1.3 mg/dL), uric acid (normal range 3.5-7.2 mg/dL), Urea (normal range 5-20 mg/dL), Na (normal range 136-145 mmol/L), K (normal range 3.5-5.2 mmol/L).

tions. This finding agreed a study on schistosomiasis by Chisango [10], who suggested that males are more likely to be infected with schistosomiasis than females. One plausible explanation is that men spent more time fishing and practicing irrigation farming, so they are at an increased risk of exposure to contaminated water bodies [11, 12]. However, the distribution of fascioliasis by sex shows variable results. A large study by Parkinson [13] in the Bolivian Altiplano, involving almost 8000 subjects of all ages, found no significant association between fascioliasis and sex. Conversely, a study of over 21,000 children in Egypt [14] reported that females had a significantly higher prevalence of fascioliasis among females, who also passed more eggs in their stool than males. Nonetheless, it should be emphasized from the findings of the present study that men represented the majority of the clinic's patient population. Regarding *Toxoplasma* infection, previous research has identified rural residence and increased age as risk factors for toxoplasmosis, while gender was not found to be a significant factor.

In the current study, the age groups of the screened individuals were represented in three age categories. The distribution of parasitic infections among HCV patients according to age showed that the most infected samples were among patients aged more than 50 years old, while the percentages of mono-parasitic infections were more prominent than the mixed infections (26/175, 28/175, and 23/175 infected with *S. mansoni*, *Fasciola*, *Toxoplasma*, respectively). These findings are consistent with those reported by Raso [16].

This trend may be explained by age-related changes in immune function, which reduce resistance to parasitic infections [17]. Additionally, occupational shift later in life could lead to an increase in water contact, potentially causing the second peak (especially in *S. mansoni* and *Fasciola* infections). Furthermore, older patients may delay seeking medical attention until symptoms become severe, leading to higher detection rates in advanced age. Significant elevations in GPT, TBIL, and GGT were observed in most experimental groups, especially among patients with high viral loads., In contrast, no significant changes were recorded in serum levels of Alb or TP throughout the study. Some studies agreed with our results [18]. Possible causes might be damage to the membrane of the liver, hepatic manifestations originating from the deposition of viral infection or parasite inside the small vessels of the liver. This can lead to an intense inflammatory response and subsequent functional changes, a situation which presumably may be responsible for significant elevation of these circulating liver enzymes. Many studies reported elevated levels of GOT and GPT as well as increased enzyme activities in the sera of samples of HCV patients [19].

Bil, the primary bile pigment resulting from the breakdown of red blood cells, can cause jaundice when elevated. Numerous types of liver or biliary illnesses can result in high Bil levels. When liver cells are damaged by hepatitis, the liver may release both indirect and direct Bil into the bloodstream, resulting in higher levels. Similarly, the host liver is harmed during the *F. hepatica* invasion. Hepatic tissue is broken down by parasite, leading to significant parenchymal loss, severe hemorrhagic lesions, and immune responses. Besides, juvenile flukes that migrate, are the cause of mechanical liver injury [20]. In HCV patients with schistosomiasis, liver function gets worse more quickly, often resulting in severe, irreversible periportal fibrosis and a faster progression to end-stage liver disease [21]. In this study, we found that infection with schistosomiasis caused the highest increase in Bil than other infections, due to the possible role of surface egg antigens (SEA) in inhibiting some important genes in Bil metabolism, such as *UGT1A1* [22].

GGT, an enzyme primarily found in the liveris influenced by hepatic destruction in chronic viral hepatitis [23]. Some authors have proposed that these alterations could be caused by damage to the bile ducts, the advancement of liver disease, or an inadequate reaction to interferon (IFN) treatment [24]. Despite these hypotheses, the exact significance of the GGT changes in chronic HCV infection remains unknown [19].

In line with Giannini [25], it was observed that the elevated GGT levels were linked to bile duct lesions in chronic HCV patients. However, no significant correlation was found between serum GGT levels and HCV viral load. These findings were consistent with those of [26], who reported that there was no correlation between serum GGT elevation and neither the HCV genotype nor serum HCV RNA titer.

The relationship between *T. gondii* infection and liver disease was assessed by Babekir [27] using the Mantel-Haenszel risk ratio (RRMH), Rho-Scott chi-square bivariate analyses, design-based t-tests, and linear and logistic regression models. The present data indicated that the patients co-infected with the parasite *Toxoplasma* and the C virus have greater values of GGT, possibly due to the fact that parasite's ability to cause DNA damage, shape distortion, and disruptions in the hepatocyte's metabolic activities when upon invasion [28]. The quantity of hepatic stellate cells (HSCs) and *T. gondii* antigens

also significantly correlate, suggesting an active involvement of HSCs in liver pathology and the pathobiology of *T. gondii*-related hepatitis.

On the other hand, the parasites (*Schistosoma* and *Fasciola*) are known to be in the liver of the host and induce pathological alterations, leading to necrosis, granuloma, and hepatomegaly [29]. Infestation of *S. mansoni* can cause portal hypertension, liver fibrosis, and possibly even an increase in liver enzymes such as GGT [30]. After *Fasciola* enters the bile duct, it damage to the bile duct epithelium results in the release of GGT into the bloodstream, which increases the GGT level in serum [31]. This significant rise in GGT level is linked to bile duct injury and cholestasis [18]. The possible causes might be due to hepatic manifestations originating from the deposition of parasite/viral infection inside the small vessels of the liver, leading to an intense inflammatory response and subsequent functional changes, a situation that presumably may be responsible for the significant elevation of these circulating liver enzymes.

In the present study, we found that there is a varying signification between parameters of kidney function (creatinine, uric acid, urea, Na and K) among the viral samples when compared to group A (HCV-ve). A significant medical burden for patients with chronic renal disease is HCV infection. Patients with chronic kidney illness are more likely to contract HCV infection, even though HCV infection itself can induce chronic kidney disease (CKD), primarily mixed cryoglobulinemia, glomerulonephritis, and membranoproliferative glomerulonephritis (MPGN) [32]. A larger HCV viral load has the potential to induce more serious glomerulopathy. Patients with CKD have weakened immune systems, increasing their risk of infection [33]. What exactly causes the reduction in renal function associated with Schistosoma infection remains unclear. Several theories have been considered, including immune-mediated glomerular and tubular disease, changes in the renal microcirculation, fluid loss through a variety of pathways, and mechanical obstruction by infected erythrocytes [34]. It is possible that immune complex deposition has a role in the pathophysiology of renal involvement [35].

There are similarities in the pathophysiology of the glomerular lesion in schistosomiasis and other parasitic illnesses, such as malaria. In schistosomiasis, the glomerular lesion has immunological character. Human and animal sera infected with *S. mansoni* include antigens from the parasite that appear to be linked to glomerulopathy [36]. Besides, the infected humans and animals have also shown to have antibodies against the parasite, which appears to be connected to the onset of glomerular damage [37]. The majority of the isolated circulating antigens involved in the pathophysiology of glomerulopathy originate from the adult parasite's digestive tract [38].

The presence of *T. gondii* IgG antibodies was used to measure *T. gondii* exposure, while CKD biomarkers were used to determine the state of the disease. Multivariable regression models were employed [27] to examine association between CKD biomarkers and *Toxoplasma* infection, while controlling clinical, anthropometric, behavioral, and sociodemographic variables, frequently linked to renal failure. The findings revealed that participants with positive *T. gondii* IgG antibodies showed noticeably higher levels of CKD biomarkers.

How exposure to *T. gondii* harms the renal system remains unknown. Prior research has indicated that *Toxoplasma* infection causes cells to produce more reactive oxygen species (ROS) and nitric oxide, subsequently resulting in oxidative stress [39]. This oxidative stress, associated with renal failure, sets off an initial inflammatory response that is mediated by the transcription factor nuclear factor-κB (NF-κB), proinflammatory mediators, tumor necrosis factor (TNF-alpha), interleukin (IL-1b), and proinflammatory mediators. Extracellular matrix is synthesized, as a result of increased transforming growth factor beta (TGF-beta) production during the later stages of inflammation [40]. Therefore, inflammation and consequent tissue damage are the mechanisms by which the long-term effects of oxidative stress on kidney tissues are conveyed, ultimately resulting in organ dysfunction. We also note in our results that the group that is the co-infection of samples from patients with C virus and the *Toxoplasma* parasite has a higher value than the rest of the groups.

Generally, Na levels decreased in most HCV-patient groups with high viral loads. A common side effect of advanced cirrhosis is hyponatraemia, caused by a reduction in the renal ability to eliminate solute-free water. This leads to an excessive retention of water compared to Na, resulting in lowered serum Na concentration and hypo-osmolality. The primary pathogenic mechanism linked to circulatory dysfunction,which causes hyponatraemia, is a non-osmotic hypersecretion of arginine vasopressin (AVP), also known as antidiuretic hormone, from the neurohypophysis. In cirrhosis, hyponatraemia is linked to higher morbidity and death rates [41]. The generation of free radicals and modifications to liver antioxidant levels during host-parasite contact lead to fibrosis and other metabolic disorders [42]. Dendritic cells

have also been demonstrated to upregulate and utilize voltage-gated K (KV) channel activity for cytokine production, major histocompatibility complex (MHC) class II expression, chemotaxis, and phagocytosis [43]. Additionally, nitric oxide (NO) generation in macrophages in response to antimicrobial agents requires K channel activation [44].

Urea levels were significantly elevated in groups with low viral loads (B (HCV+), D (HCV+F), and F (HCV+S+F)). In patients with high viral loads, urea levels were significantly elevated in groups E (HCV+T) and F (HCV+S+F). The most common cause of elevated urea levels is abnormal urea production or excretion. One of the liver's primary roles in maintaining the body's overall nitrogen balance is ureagenesis, dealing with the ultimate, irreversible conversion of amino nitrogen to urea nitrogen [45].

Purine metabolism, derived from both endogenous and external sources, culminates in uric acid (hyperuricemia) [46]. It is catalyzed by xanthine oxidase (XO) and processed by the muscles, intestines, and liver. Roughly two- thirds of uric acid is eliminated via urine, with the other third being expelled through feces [47]. Due to higher plasma estrogen levels, female individuals may exhibit greater plasma estrogen levels than male patients, possibly leading to a better urate clearance in urine and lower serum uric acid levels. Numerous additional risk factors have also been reported to be connected to hyperuricemia [48]. Patients with chronic HCV are thought to be a unique group with metabolic disorders. Similar risk factors for hyperuricemia were found in both the general population and HCV-infected patients in this study.

The harmful effects of *Toxoplasma* on the kidney may be the cause of the rise in urea concentration. These effects include decreased urea excretion from the body and increased blood urea levels. The afflicted mice's kidneys contained *Toxoplasma* cysts, leading to several pathological alterations. Kidney damage from *Toxoplasma* infection can result in increased protein excretion in the urine and hypoalbuminemia [49].

Kidney injury associated with parasitic diseases may arise from direct parasite damage, immunological phenomena such as immune complex deposition and inflammation, and systemic symptoms such as hemolysis, hemorrhage, and rhabdomyolysis [50].

This study found that the sera levels of liver markers (GPT, T Bil, and GGT) and kidney parameters (creatinine, urea, Na, and K) were more affected by the type (mono or mixed) or species of parasitic infections, and that most of these biochemical parameters in this study were significantly elevated with viral/parasitic infections. Regarding the effect of parasitism on HCV patients, it was found that GGT has remarkably increased in HCV patients with *Schistosoma* and *Toxoplasma* infections in the low and high viral load groups, respectively,while GPT clearly has decreased in HCV patients with triple and double (*Schistosoma*/ *Toxoplasma*) parasitic infections in the low and high viral load groups, respectively.

ALK has significantly increased in HCV patients with triple parasitic and *Toxoplasma* infections in the low and high viral loaded groups, respectively. In a striking way, T Bil has increased in HCV patients (low and high viral load groups) with single infection (*Schistosoma*). Creatinine has decreased in HCV patients (low viral load) with double parasitic infections (*Schistosoma*/ *Toxoplasma*), while it has remarkably increased in HCV patients (high viral load) with double parasitic infections (*Schistosoma*/ *Fasciola*). Moreover, urea has remarkably decreased in HCV patients (low viral load) with double parasitic infections (*Schistosoma*/ *Toxoplasma*), as well as in HCV patients (high viral loaded) with tribble parasitic infections. Besides, the highest viral load in experimental groups was in patients with mixed parasitic infections with both *Fasciola* and *Toxoplasma* (88.8%). Exceptionally, the TP and Alb show insignificant changes in their serum levels either in patients with low or high viral load. Moreover, the urea, and K showed decreasing changes in their levels in patients with the high viral loads. It is an urgent need to conduct studies for a deeper understanding of the metabolic interactions in the human body in the case of parasitic infections with the presence of any viral infection (as HCV), especially when the organ is a common target for both pathogens.

Compliance with ethical guidelines

All human procedures and experimental protocols were reviewed and approved by the Scientific Research Committee of Egypt Center for Research and Regenerative Medicine (ECRRM), Cairo, Egypt. (OHRP Reg. IORG0010559 – IRB00012517 – MOHP: RHDI-RB2021020101-220124-01UC-MD-No.0124).

This cross-sectional study was conducted at Armed Forces Medical Research Laboratories and Blood Bank (AFLMR) between December 2020 and March 2021. Patients confirmed to be HCV-positive with HCV were randomly sampled, including both males and females with an age range between 20 to more than 50 years old. 50 healthy individuals free from HCV and any parasitic

infections served as controls. Patients with hepatitis B were excluded.

Data availability

All data generated or analyzed during this study are included in this published article.

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Authors' contributions

Conceptualization and study design: Hoda A. Taha, Marwa M. Aboueldahab, and Ahmed Hamdy Nigm; Project administration, technical, and material support: Maryam Samwel Garas, Hoda A. Taha, and Marwa M. Aboueldahab; Data analysis and interpretation: Hoda A. Taha and Marwa M. Aboueldahab and Ahmed Hamdy Nigm; Statistical analysis: Hoda A. Taha and Maryam Samwel Garas; Writing the original draft: Hoda A. Taha, Ahmed Hamdy Nigm and Maryam Samwel Garas; Review and editing: Hoda A. Taha, Marwa M. Aboueldahab and Ahmed Hamdy Nigm.

Conflict of interest

The authors declared no conflict of interest.

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