

Impact of Gender Difference on Characteristics and Outcome of Chronic Hepatitis C

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Abstract

Gender difference in chronic hepatitis C (CHC) infection is not previously well studied. We aimed to analyze the effect of gender difference on the risk factors of CHC, disease progression, and outcome after oral direct acting antiviral (DAA) therapy. The study was conducted at Tropical Medicine and Gastroenterology Department, Sohag University, Egypt, in the period between 2018 and 2020. 775 patients were evaluated for hepatitis C virus (HCV) risk factors. Laboratory investigations, abdominal ultrasound and liver Shear wave elastography (SWE) were done. The patients were given antiviral therapy and followed up to assess the response and side effects of DAA therapy. 434 (56%) of study patients were males and 341 (44%) were females. Catching infection from blood transfusion and intravenous (IV) injection of tarter emetic was significantly higher in males, while catching infection from surgical operation was significantly higher in females. Hepatic fibrosis was significantly more extensive in males. Side effects were reported more in females. Sustained virological response (SVR) 12 was reported in 98.6%. Females had a slightly better SVR12 than males (99.4% versus 97.9%). In conclusion males were different from females in exposure to HCV risk factors. After introduction of blood screening and stoppage of parenteral anti-bilharzial therapy the risk of HCV infection could be greatly prevented in males, while the exposure of females to obstetric procedure is increasing nowadays which hides a risk of ongoing infection in females. So, HCV surveillance programs in females retain their importance in early detection and management of CHC. Although hepatic fibrosis progression was more in males, females were more liable to adverse events of DAA therapy. So, researchers should consider the gender of their patients in drug design and administration.

Keywords

Chronic HCV, Risk Factors, Gender Difference, DAA Therapy

1. Introduction

Hepatitis C virus infection is a global health problem. The prevalence rate of HCV infection in 2015 was 1% worldwide [1]. Egypt has the highest prevalence rate of HCV in the world [2]. The national seroprevalence of HCV in 2008 was 14.7% in people aged 15 - 59 years and was higher in males than in females [3]. This seroprevalence decreased in 2015 to 6.3%. This decrease in the prevalence may be due to the significant decrease in HCV new infections; also the group of patients who received parenteral anti-bilharzial therapy in the 1950s and 1960s, that had the highest prevalence, had been aged much [4].

Parenteral anti-bilharzial therapy and blood transfusion were associated with HCV infection in Egypt. Nowadays, parenteral anti-bilharzial therapy is obsolete [5], and the risk of transmission through blood transfusion is greatly declined with the application of blood screening technology [6] [7].

The recent development of highly efficacious oral DAA therapy provides opportunities for reducing the burden of chronic liver disease (CLD) related to HCV infection [8]. Gender difference affects HCV progression and outcome; for instance, clearance of HCV infection in females is higher than males [9]. Females had a decreased rate of decompensated cirrhosis, and less commonly have malignant liver tumors [10]. CHC progression is known to be worse in males [11]. Also, males had 2 folds more risk to die from CLD than females [10]. The aim of this work is to analyze the effect of gender difference on risk factors of CHC, disease progression and outcome after oral DAA therapy.

2. Patients and Methods

This is a prospective cohort study conducted at Tropical Medicine and Gastroenterology Department, Sohag University hospitals, Egypt, on patients with CHC who are candidate for sofosbuvir-based antiviral therapy between 2018 and 2020. According to the standards of the Local Ethical Committee, written informed consents were obtained from all participants. The exclusion criteria were age below 18 years, HCV and hepatitis B virus co infection, other causes of CLDs, advanced liver disease and patients with chronic kidney disease. The patients were subjected to:

- Detailed history taking for assessment of the risk factors of HCV infection.
- Ten milliliters of blood were drawn from each patient; 1.8 ml in Plastic Citrated tube (9NC sodium citrate vacutainer, 3.2%) 2 ml in an K₃-EDTA vacutainer for Complete blood count (CBC), 3 ml in lithium heparin vacutainer for liver function tests, and the rest in gel vacutainer for serology and quantitative polymerase chain reaction (PCR). Vacutainers were (BD); (Becton Dick-

inson Systems, San Jose, CA, USA).

- Serology: HCV antibody was carried out using the Architect® i2000SR anti-HCV (CIA) chemiluminescence system (Abbott Laboratories, Diagnostics Division, Abbot Park, IL, USA).
- Quantitative HCV RNA level by Real-time PCR using QIAcube system (Qiagen, Hilden, Germany) with Spin tubes protocols (Qiagen) and The StepOne™ Real-Time PCR System (Applied Biosystems, Life Technologies, Foster City, CA, USA).
- Abdominal ultrasounds and liver real-time Shear wave elastography (SWE) using (Toshiba Aplio 500) done for the study purpose at Radiology Department, Sohag University Hospital. All cases were done by a single operator, with placing the patient in a supine position, the right arm is in a maximum abduction to widen the intercostal spaces, and to acquire a stable image the patient asked to hold his breath in the expiration, then the convex probe placed in the intercostal spaces. The SWE box placed 2 cm sub-capsular in a uniform zone to avoid reverberation artifacts. Also, the operator avoided the perivascular areas as they may alter the estimations of liver stiffness. The color map is used but it is not dependable to assess liver stiffness because it is not quantitative. We mainly depended on liver stiffness measurement in m/s. For each patient the elastography acquisition was repeated five times. Freeze of real-time SWE 2D color map of the stiffness (in m/s) after a stabilization of at least 3 s for each acquisition was done. SWE color box size was about 4 × 4 cm. The measurements were performed in a 2 to 3 cm diameter region of interest (ROI). For each patient, liver stiffness was considered as the median of multiple SWE successful measurements (**Figure 1**).

The patients were given Sofosbuvir-based antiviral therapy, for 12 weeks duration, according to the modified protocol of Egyptian national program for treatment of HCV (**Figure 2**).

Patients' follow up was done in Tropical Medicine and Gastroenterology outpatient clinic every 4 weeks until the end of therapy, and then at 12 weeks thereafter. CBC and liver function tests were repeatedly assessed every 4 weeks. All patients were assessed for the possible side effects of DAA therapy as headache, fatigue, GIT upset, diarrhea and dyspnea. Patients who were negative for serum



Figure 1. SWE measurement of liver in cirrhotic patient.

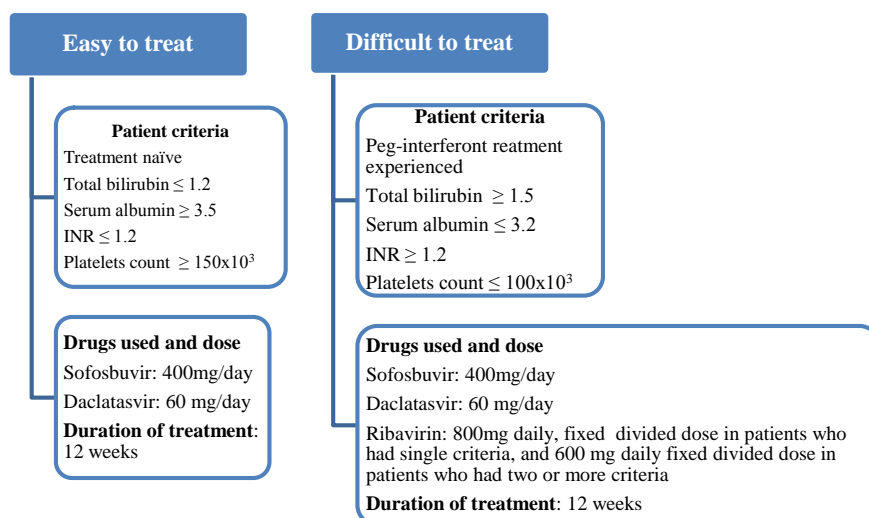


Figure 2. Flowchart for the modified national program for treatment of HCV in Egypt provided by National Committee for Control of Viral Hepatitis.

HCV RNA at the EOT and 12 weeks thereafter were defined as responders achieving SVR12. A positive HCV RNA 12 weeks after end of treatment (EOT) was defined as relapse [12].

Statistical Analysis

Data were analyzed using SPSS version 16. Quantitative data were represented as mean \pm standard deviation, median and interquartile range (IQR). The data were tested for normality using Shapiro-Wilk test. Students'-T-test was used for normally distributed data while Mann-Whitney test was used when the data were not normally distributed. Paired data were compared by Wilcoxon rank test. Qualitative data were presented as number and percentage. Comparison of data was done by Chi-square test and Fischer Exact test when suitable. Interaction between gender, stage of hepatic fibrosis and age was tested by two-way ANOVA and the interaction plots were obtained. Logistic regression was used to analyze variables which had a statistical impact on SVR. Graphs were produced by SPSS program. p value < 0.05 was considered significant.

3. Results

Seven hundred seventy-five patients with CHC were included in the study, 434 (56%) were males and 341 (44%) were females.

Gender difference regarding exposure to HCV risk factors:

The most frequent risk factors of HCV infection were previous history of hospital admission, blood transfusion and exposure to needle stick. In males the most common risk factors were blood transfusion (28.6%), hospital admission (24.7%) and IV injection of tarter emetic (18.7%). In females the most common risk factors were hospital admission (26.7%), exposure to needle stick (18.2%) and previous operation (17.3%). The risk of infection from blood transfusion

and IV injection of tartar emetic were significantly higher in males ($p < 0.001$), while the risk of infection from surgical operation was significantly higher in females ($p = 0.007$) (**Table 1**).

Gender and baseline laboratory characteristics in CHC patients:

In patients with CHC the mean age was closely comparable between the two gender groups. Males had significantly higher hemoglobin, albumin, prothrombin time and bilirubin levels but significantly lower platelets count compared to females (**Table 2**).

Gender distribution in different stages of hepatic fibrosis:

Hepatic fibrosis measured by SWE was significantly more extensive in males than in females ($\chi^2 = 10.20$, $p = 0.037$) (**Table 2**). There was a significant difference in hepatic fibrosis stages in males compared to females when considering the patients' age ($p = 0.016$). The mean ages of males with different stages of hepatic fibrosis (F0-F3) were closely related, while in females advanced fibrosis (F3) was present in old age. F4 was positively correlated with old age in both gender groups and females with F4 were older than males with F4 stage ($p < 0.001$) (**Figure 3**).

Hematological and biochemical changes after sofosbuvir-based antiviral therapy:

At EOT there were highly significant increase in white blood cells (WBCs) count, platelets count, and total bilirubin level ($p = 0.003$, $p = 0.015$, $p < 0.001$ respectively), and there were a highly significant decrease in hemoglobin ($p = 0.019$), albumin, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels ($p < 0.001$) compared to the baseline laboratory data. The increase in platelets count was significantly more in males ($p = 0.049$), while the increase in total bilirubin level and decrease in albumin level significantly more in females ($p = 0.001$, $p < 0.001$ respectively) (**Table 3**).

Side effects of DAA therapy:

Fatigue was the most frequent reported side effect (42%) followed by headache (24%), gastrointestinal tract (GIT) upset (16%) and few cases of mild anemia (3%). Side effects were reported more in females. Fatigue and GIT upset were significantly higher in females (**Table 4**).

Table 1. Gender difference regarding exposure to HCV risk factors.

Risk factors	Total n = 775	Males with CHC n = 434	Females with CHC n = 341	p value
Hospital admission	198 (25.5%)	107 (24.7%)	91 (26.7%)	0.52
Blood transfusion	171 (22%)	124 (28.6%)	47 (13.8%)	0.000
Exposure to needle stick	131 (17%)	69 (15.9%)	62 (18.2%)	0.413
Operation	105 (13.5%)	46 (10.6%)	59 (17.3%)	0.007
Endoscopy	101 (13%)	48 (11.1%)	53 (15.5%)	0.069
IV injection of tartar emetic	93 (12%)	81 (18.7%)	12 (3.5%)	0.000

CHC: Chronic hepatitis C, N: Number.

Table 2. Demographic, baseline laboratory characteristics and fibrosis staging in males compared to females in CHC patients.

	Male patients with HCV	Female patients with HCV	p value
Age (years)			
Mean ± SD	51.19 ± 13.55	51.17 ± 14.29	0.623
Median (IQR)	56 (49 - 62)	55 (41 - 62)	
BMI			
Mean ± SD	26.76 ± 3.95	28.61 ± 4.07	0.000
Median (IQR)	24 (26 - 28)	25 (28 - 31)	
WBCs (×10³/mL)			
Mean ± SD	6.64 ± 2.34	6.50 ± 2.26	0.401
Median (IQR)	6.2 (4.8 - 8.5)	6.2 (4.9 - 8)	
Hemoglobin (g/dL)			
Mean ± SD	15.03 ± 1.44	13.77 ± 1.52	0.000
Median (IQR)	15.2 (14.2 - 15.9)	13.9 (13 - 14.8)	
Platelets count (×10³/mL)			
Mean ± SD	213.68 ± 67.89	235 ± 82.61	0.000
Median (IQR)	201 (171 - 238)	227 (174 - 271)	
ALT (U/L)			
Mean ± SD	53.77 ± 37.86	51.74 ± 55.68	0.385
Median (IQR)	45 (31 - 77)	42 (31 - 70)	
AST (U/L)			
Mean ± SD	54.96 ± 37.06	55.10 ± 43.69	0.421
Median (IQR)	43 (37 - 73)	40 (33 - 68)	
Albumin (g/dL)			
Mean ± SD	4.08 ± 0.48	3.9 ± 0.455	0.000
Median (IQR)	4 (3.7 - 4.4)	3.9 (3.6 - 4.2)	
Prothrombin time (Sec)			
Mean ± SD	13.05 ± 1.48	12.50 ± 1.20	0.04
Median (IQR)	12.9 (12 - 14.5)	12.20 (11.30 - 13)	
Total bilirubin m (g/dL)			
Mean ± SD	0.69 ± 0.32	0.61 ± 0.31	0.004
Median (IQR)	0.68 (0.2 - 2.20)	0.6 (0.2 - 1.87)	
PCR (IU/mL)			
Mean ± SD	2.16 ± 2.6 × 10 ⁶	1.98 ± 2.2 × 10 ⁶	0.596
Median (IQR)	9.4 × 10 ⁵ (2.57 × 10 ⁵ - 2.68 × 10 ⁶)	8.22 × 10 ⁵ (3.02 × 10 ⁵ - 2.54 × 10 ⁶)	
Stage of hepatic fibrosis:			
n (%) within fibrosis stage			
F0	87 (50.9%)	84 (49.1%)	0.037
F1	116 (60.7%)	75 (39.3%)	
F2	100 (57.5%)	74 (42.5%)	
F3	46 (67.6%)	22 (32.4%)	
F4	85 (49.7%)	86 (50.35)	

CHC: Chronic hepatitis C, SD: Standard deviation, IQR: Interquartile range, WBC: White blood cells, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, PCR: Polymerase chain reaction.

Table 3. Hematological and biochemical changes after sofosbuvir-based therapy.

	All patients				Males		Females	p value
	Baseline	EOT	EOT-Baseline change	p value	EOT-Baseline change	EOT-Baseline change		
WBCs	6.58 ± 2.30	6.79 ± 2.09	0.21 ± 0.07	0.003	0.12 ± 0.09	0.34 ± 0.11	0.276	
Hemoglobin	14.42 ± 1.69	13.77 ± 6.94	-0.65 ± 0.28	0.019	-1.02 ± 0.09	-0.21 ± 0.60	0.626	
Platelets	216.41 ± 76.23	221.45 ± 72.12	5.40 ± 2.07	0.015	8.23 ± 3.07	1.21 ± 2.67	0.049	
Total bilirubin	0.65 ± 0.32	0.80 ± 0.31	0.15 ± 0.01	0.000	0.10 ± 0.39	0.2 ± 0.36	0.001	
Albumin	3.98 ± 0.50	3.86 ± 0.31	-0.11 ± 0.02	0.000	-0.05 ± 0.38	-0.17 ± 0.48	0.000	
ALT	52.76 ± 36.90	16.73 ± 7.78	-36.02 ± 28.12	0.000	-36.67 ± 37.98	-35.20 ± 35.21	0.682	
AST	55.02 ± 40.08	19.89 ± 9.26	-35.13 ± 30.72	0.000	-34.49 ± 37.44	-35.96 ± 42.04	0.815	

EOT: End of treatment, WBC: White blood cells, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase.

Table 4. Side effects of DAA therapy in both gender groups.

	Fatigue	Headache	GIT upset	Anemia
Sex: Male	139 (32%)	82 (19%)	34 (8%)	9 (2%)
Female	188 (55%)	106 (31%)	116 (34%)	14 (4%)
Total	327 (42%)	188 (24%)	150 (16%)	23 (3%)
Chi-square	$\chi^2 = 6.17, p = 0.012$	$\chi^2 = 2.07, p = 0.154$	$\chi^2 = 15.17, p = 0.000$	$\chi^2 = 1.62, p = 0.204$

GIT: Gastrointestinal tract.

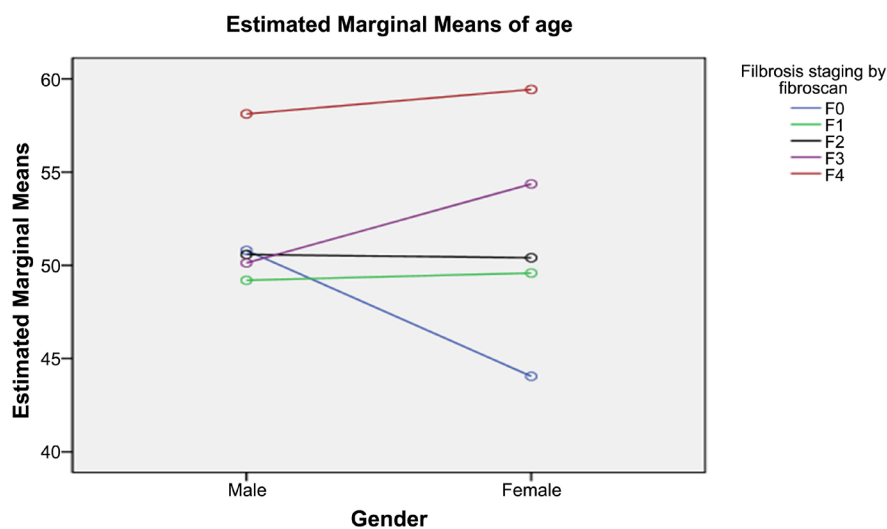


Figure 3. Interaction plots: The effect of patients' mean ages on different stages of hepatic fibrosis ($f = 18.17, p < 0.001$) and in interaction with patients' gender ($f = 3.04, p = 0.016$) test by two-way ANOVA.

Gender effect on treatment outcome:

All patients who received DAA had undetectable virus level at the EOT, but SVR12 was achieved in 98.6% of them. Females had a better SVR12 than males (99.4% versus 97.9%). Most of the relapsers were males [9 (2.1%) versus 2 (0.6%)] (Table 5).

Table 5. Gender effect on treatment outcome.

		Response	
		SVR	Relapse
Males	Count	425	9
	% within sex	97.9%	2.1%
	% within responders	55.6%	81.8%
Females	Count	339	2
	% within sex	99.4%	0.6%
	% within responders	44.4%	18.2%
Total	Count	764	11
	% within responders	98.6%	1.4%

SVR: Sustained virological response.

Variables predicting relapse of HCV:

Univariate logistic regression analysis showed that male gender and the presence of advanced hepatic fibrosis and cirrhosis were the significant risk factors associated with relapse of HCV ($p = 0.042$, 0.011 respectively). However, in multivariate analysis, the only independent predictor of relapse was the presence of advanced hepatic fibrosis and cirrhosis ($p = 0.007$) (Table 6).

4. Discussion

Generally, males and females are different in their health and disease state. This difference could be explained by the difference in exposure to risk factors, sexual hormones, genetic effect and different corporal structures. In addition, CLD may produce different consequences in both genders [13].

In this prospective study which analyzes the characteristics of HCV infection in males compared to females, we found a preponderance of male gender in patients with chronic HCV which was documented by several previous studies [14] [15] [16] [17]. This higher HCV prevalence in males is multifactorial. Males were the main target of parenteral anti-schistosomal therapy campaigns [18]. This may be related to occupational exposure to bilharziasis during farming. In addition, the possibility of clearance of HCV acute infection is higher in females [9] [19]. Also, there is variance in sex dependent susceptibility to infectious diseases due to the effect of sexual hormones [20] [21]. Estrogens have immune stimulating effect, while androgens have immune suppressing effect resulting in stronger humoral and cellular immune responses to viral infections in females [22]. Similarly, genetic variation had an impact on the outcome of HCV infection. Most immune related genes that determine the response to viral infection are located on X chromosome [13] [23]. In females the activation of X-linked genes related immune cells is greater than males [23], and male patients with chronic HCV carry IL-6 promoter polymorphisms more likely than females [24], while certain polymorphisms in Ctl4, an inhibitory T cell receptor which is more common in females exposed to infection, are associated with resolution of HCV infection [25].

Table 6. Univariate and multivariate analysis of variables predicting relapse of HCV.

Baseline variables	Univariate analysis		Multivariate analysis		
	Odds ratio (95% CI)	p value	Significant variable	Odds ratio (95% CI)	p value
Age (years)	0.98 (0.92 - 1.04)	0.555	Male versus Female	3.75 (0.82 - 17.50)	0.09
Sex: Male versus Female	5.84 (1.05 - 32.41)	0.042	Stages of fibrosis	6.32 (1.67 - 24.12)	0.007
BMI	1.19 (0.95 - 1.26)	0.142			
PCR (IU/mL)	1 (1)	0.875			
WBCs ($\times 10^3$ /mL)	0.89 (0.66 - 1.21)	0.325			
Hemoglobin (g/dL)	1.4 (0.68 - 1.6)	0.613			
Platelets count ($\times 10^3$ /mL)	1.01 (0.99 - 1.02)	0.465			
Total bilirubin (mg/dL)	0.78 (0.11 - 5.53)	0.713			
Serum albumin (g/dL)	0.33 (0.10 - 1.08)	0.112			
Prothrombin time (Sec)	0.21 (0.001 - 1.01)	0.423			
ALT (IU/L)	0.97 (0.94 - 1.01)	0.222			
AST (IU/L)	1.01 (0.98 - 1.04)	0.563			
Stages of fibrosis:					
- Mild to moderate	5.27 (1.20 - 23.10)	0.011			
- Advanced fibrosis and cirrhosis					

SVR: Sustained virological response, PCR: Polymerase chain reaction, WBC: White blood cells, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase.

In our study, the risk of HCV infection from blood transfusion and IV injection of tartar emetic was significantly more in males. This could be explained by that males were overrepresented in trauma and need more units of all blood products in massively transfused traumatized patients [26] [27]. History of parenteral anti-bilharzial therapy was more common in males. Other authors found similar result [9]. We found the risk of HCV infection from surgical operation was higher in females. This may be due to the role of obstetric procedures, which is increasing nowadays, as a risk for infection [28].

In our study, males had significantly higher mean values of hemoglobin and albumin levels compared to females. This may be due to sex related difference in mean hemoglobin and albumin levels. Males have mean levels approximately 12% higher in hemoglobin level and higher overall red blood cell count than females [29]. Serum albumin level is higher by approximately 2 g/L in males due to hormonal factors [30] [31]. Another explanation from our point of view is the periodic menstrual blood loss in fertile females and the poor nutritional state in females compared to males. Therefore, decreased albumin level in females did not reflect impaired synthetic liver function in this group of patients. On the other hand, we found a significant alteration of liver function test and worse hepatic fibrosis progression in males reflected in higher bilirubin level, lower platelets count, and more extensive hepatic fibrosis than females. Similarly, in patients with CLD Narciso-Schiavon *et al.* found more altered liver function

tests and more progressive fibrosis in males [32]. Poynard *et al.* reported that males have a twofold greater progression of hepatic fibrosis than females [33]. Several studies documented that progression of HCV infection is worse in males [11] [16]. Also, progression of hepatic fibrosis is reflected in gradual decrease in platelets count [34].

In our study, hepatic fibrosis measured by SWE was significantly more extensive in males than in females. There was significant difference in hepatic fibrosis stages in males compared to females when considering the patients' age. The mean ages of males in different stages of hepatic fibrosis (F0-F3) were closely related, while in females advanced fibrosis (F3) was present in old age. Most of the stages of hepatic fibrosis in females during the reproductive age were mild and moderate fibrosis, while advanced stage of fibrosis was present in old females. Female sex hormones particularly estradiol have important role in limiting hepatic fibrosis progression through their anti-fibrotic properties and inhibition of hepatic stellate cells which are responsible for fibrogenesis beside the protective role against hepatic necroinflammation, apoptosis and oxidative stress [16] [22] [35]. In HCV related CLD and hepatocellular carcinoma the decreased expression of estrogen receptor alfa in males could explain the worse outcome of HCV infection in males [22].

The blood counts were improved apart from mild decrease in hemoglobin level due to the effect of ribavirin, and the liver enzymes were normalized at EOT. Similarly, Ahmed *et al.* found significant reduction in ALT and AST levels at EOT [36]. Also, we found a slight increase in total bilirubin level, decrease in serum albumin level and appearance of some clinical side effects (fatigue and GIT upset) after initiation of DAA therapy which were significantly more in females. Similar to our results, the most recorded adverse events of DAA in several previous studies were fatigue, headache, nausea and diarrhea [36] [37]. Generally, females experienced greater adverse events to antiviral drugs than males [38] [39]. In contrast, Attia *et al.* reported that male gender was significantly associated with the occurrence of adverse events to DAA therapy as anemia and hyperbilirubinemia [40].

Since introduction of DAA therapy the outcome of chronic HCV infection was markedly improved [36]. The efficacy and safety of sofosduvir based DAA regimens have been proven in several Egyptian studies, and the combination of sofosbuvir/daclatasvir with and without ribavirin showed high SVR rates between 92% and 98.9% [12] [41] [42]. However, the gender effect on the potential efficacy and safety of DAA therapy is not sufficiently studied.

In our study, all patients who received DAA therapy had undetectable virus level at the EOT. SVR12 was achieved in 98.6% of all studied patients; although females had a better SVR12 than males and most of the relapsers were males, this difference is not clinically relevant. Similarly, some studies found that female sex and less hepatic fibrosis were independently associated with higher rates of SVR. Also, fertile women with genotypes 2 or 3 have a better response to

therapy [43] [44] [45] [46]. However, these studies were on interferon-based therapy. On the other hand, Yang *et al.* found that SVR was high in patients treated with DAA therapy regardless of age, gender or hepatic fibrosis stage [47].

In univariate analysis we found that male gender and the presence of advanced hepatic fibrosis and cirrhosis were significant predictors of relapse after DAA therapy. While in multivariate analysis we found that the only independent predictor of relapse was the presence of advanced hepatic fibrosis and cirrhosis, but still male patients have 3.75 times more risk to relapse than females.

5. Conclusion and Recommendation

Males were different from females in exposure to HCV risk factors. After introduction of blood screening and stoppage of parenteral anti-bilharzial therapy the risk of HCV infection could be greatly prevented in males. On the other hand, the exposure of females to obstetric procedures is increasing nowadays which hide a risk of ongoing infection in females. So, HCV surveillance programs in females retain their importance in early detection and management of CHC. Although hepatic fibrosis progression was more in males, females were more liable to adverse events of DAA therapy than males. So, researchers should consider the gender of their patients in drug design and administration.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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