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RESEARCH ARTICLE

Effect of Direct-Acting Antiviral Drugs on Erectile Functions among Hepatitis C Patients: A Prospective Interventional Study

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Abstract: ***Background & Objective*:** Erectile dysfunction (ED) is one of the extrahepatic manifestations of hepatitis C virus infection that greatly affects patients' quality of life. Unfortunately, some of the drugs used for HCV treatment may have a negative impact on the patient's erectile function, such as the pegylated interferon. Currently, with the introduction of direct-acting antiviral drugs, there is scarce data in the literature about its potential impact on erectile function. In these settings, we aimed to assess the impact of sofosbuvir-based therapy on male erectile function.

***Methods*:** This prospective interventional study was carried out in Benha University hospitals between January 2019 and May 2020. The study included all consecutive HCV patients with simultaneous ED coming to the hepatology outpatient clinic. Patients were divided into a study group who received sofosbuvir-based therapy (group A) or a control group who received silymarin therapy (group B). The International Index of Erectile Function-5 (IIEF-5) was used for the assessment of erectile function at different time points (pretreatment, 6 months, and 12 months after treatment). Different variables in both groups have been statistically analyzed.

***Results*:** Overall, 75 patients who received sofosbuvir-based therapy and a control group (n = 35) matched for age and pretreatment variables (Child–Turcotte–Pugh score and Fibrosis□4 score). There was no significant difference between both groups in the pretreatment data. On the other hand, the posttreatment IIEF-5 was significantly higher in the sofosbuvir arm compared to the silymarin arm both at six months ($p<0.001$) and at 12 months ($p<0.001$). Furthermore, the age and the stage of liver fibrosis were negatively correlated with IIEF-5 at all-time points.

***Conclusion*:** The age and the stage of liver fibrosis are significantly correlated with the degree of ED. Furthermore, sofosbuvir-based therapy may be associated with significant improvement in patients with erectile function.

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1. INTRODUCTION

Erectile Dysfunction (ED) is a significant healthcare problem in adult males. A community-based study showed that the overall prevalence of ED is 23.5% among married Egyptian men. Furthermore, this study demonstrated that complete ED is significantly correlated with patients' age (ranging from 8.5% to 52% among men in their 40s to 70s, respectively) [1]. Several risk factors are associated with increased risk of ED, including an unhealthy lifestyle and systemic diseases (like diabetes mellitus, hypertension, and cardiovascular disease) [2]. Interestingly, ED was found to be more prevalent among hepatitis C virus (HCV) patients compared to the general population [3, 4]. Hunter SS *et al*. [4], demonstrated that ED was found in 29.3% of chronic HCV patients in Egypt with significantly higher prevalence in patients with cirrhosis compared to chronic HCV patients without cirrhosis (92.3% versus 16.12%, respectively) [4]. Yet, ED is still considered an underrated condition in HCV patients as the physicians usually tend to concentrate more on life-threatening diseases, and/or it may be embarrassing for the patient to discuss their sexual life and performance [5]. The relation between HCV infection and ED may be explained by several theories, including the psychological and endocrinological disturbances in those patients, the effect of antiviral therapy like interferon, and the fear of the probability of HCV transmission through sexual intercourse [3, 6-8].

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HCV infection represents a major health and economic burden in Egypt. According to the Egyptian national committee for the control of viral hepatitis (NCCVH), approximately 4.61% of the Egyptian population above the age of 18 years tests positive for HCV [9]. HCV is not just a liver disease as it may be accompanied by different extra-hepatic manifestations (mostly diabetes and depression in 15% and 25% of patients, respectively), rendering it a systemic disease that significantly affects the patients' quality of life (QoL) [10]. Considering the nature and the high prevalence of HCV in Egypt, it should be included in the differential diagnosis of ED [4, 5]. The treatment of HCV in Egypt passed through several eras. By 2006, the Egyptian Ministry of Health established the NCCVH with the aim of HCV eradication by 2030 [11]. Before the era of direct-acting antiviral drugs (DAAs), pegylated interferon (PEG-IFN) formed the backbone of HCV treatment between 2006 and 2018; however, it was associated with low sustained virologic response (60%) and high rates of sexual side effects [3, 12]. The introduction of DAAs (Sofosbuvir-based therapy) dramatically changed the landscape of HCV treatment [13]. By 2018, DAAs were adopted as the treatment of choice for chronic HCV patients due to their lower side effects and higher sustained virologic response (up to 90%) [9]. Interestingly, Elshimi *et al*., reported that treatment of HCV with DAAs may result in significant improvement in male sexual function unlike PEG-IFN [14]. In these settings, we aimed to assess the impact of Sofosbuvir-based therapy on male erectile function.

2. METHODS

2.1. Study Design and Participants

This was a prospective interventional study that was carried out at Benha University Hospital between January 2018 and April 2019. The study included all the consecutive HCV male patients (between 18 and 60 years old) with simultaneous ED coming to the hepatology outpatient clinic. All the included patients signed written informed consent, and the study has been approved by the local ethical committee with approval number RC-2-9-2017 and has been conducted in accordance with the principles outlined in the Helsinki Declaration.

All the patients with a history of HCV treatment, hepatitis B virus (HBV), or human immunodeficiency (HIV) virus, or patients with other major health problems that may contribute to ED like diabetes mellitus, renal insufficiency, and hypertension were excluded from the study.

2.2. Randomization

The included patients were randomized in a 2:1 ratio either to group A (Sofosbuvir-based therapy) or group B (supportive liver therapy only), respectively. Unequal allocation of patients is acceptable in clinical trials as long as the ratio does not exceed 3:1 as it is not associated with a significant reduction in the statistical power [15]. The block randomization technique was performed using Excel 365 software (Microsoft Inc., Redmond, Washington, USA). An independent nurse (not included in the study) was responsible for the randomization. The current study was not blinded. Fig. (**1**) summarizes the flow of patients in the current study.

2.3. Pretreatment Assessment

Data of the included patients were included in a specifically designed excel database. The pretreatment assessment of all the patients included age, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood sugar (FBS), serum glutamic pyruvic transaminase (SGPT), serum albumin, serum bilirubin, and liver

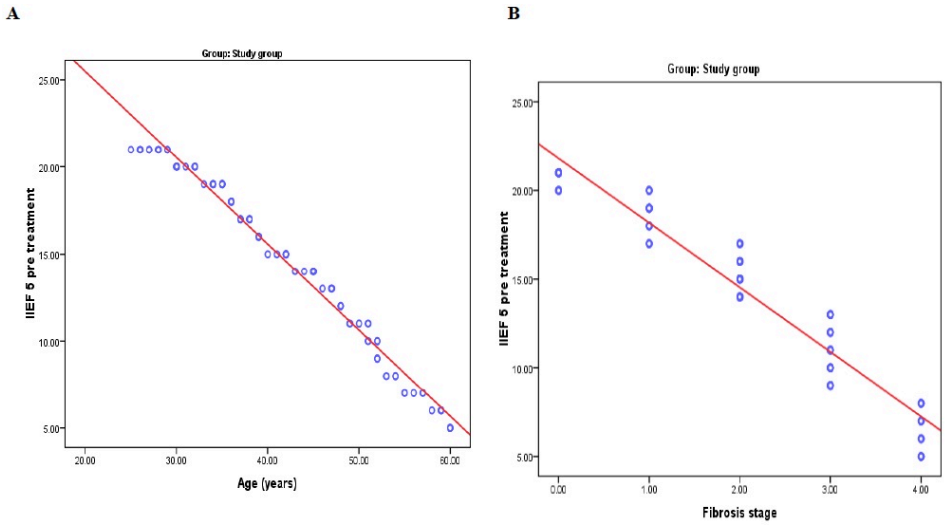

Fig. (1). (**A**) Scatter graph showing significant negative correlation between age and IIEF5 score; (**B**) Scatter graph showing significant negative correlation between fibrosis stage and IIEF5 score. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

fibroscan. Furthermore, the METAVIR score of liver fibrosis was collected for each patient [15, 16].

2.4. international Index for Erectile Function-5 (IIEF-5)

The validated Arabic version of the IIEF-5 (also known as sexual health inventory for men) was used for the evaluation of the erectile function at three-time points (pretreatment, 6- and 12-months posttreatment). This score consists of five questions with a possible score ranging from 5-25, where ED can be divided into five grades based on the final score including; no ED (22-25), mild (17-21), mild to moderate (12-16), moderate (8-11), and sever (5-7) [17].

2.5. Treatment Protocols

The Sofosbuvir-based therapy (the treatment group) consisted of a combination of 400 mg Sofosbuvir and 60 mg Daclatasvir daily for three months. During the treatment course, all the patients were followed up by clinical examination and laboratory investigations at monthly intervals. Subsequently, the patients were followed up with scheduled outpatient clinic visits for one year. On the other hand, patients in the control group were given only liver support. Noteworthy, all the patients in the liver support group were offered Sofosbuvir-based therapy at the end of the study.

2.6. Endpoints

The primary endpoint of the study was the impact of HCV treatments on erectile function. On the other hand, the secondary endpoint was to determine the independent predictors of posttreatment erectile function.

2.7. Statistical Analysis

The collected data were tabulated and analyzed using SPSS version 16 software (SPSS Inc, Chicago, IL, USA). All the variables were tested for normality using the Kolmogorov-Smirnov test. Categorical data were presented as numbers and percentages, and Fisher's Exact test (FET) was used to detect the differences between the two groups. Similarly, McNemar's test was used to detect the differences between paired data (pretreatment and posttreatment values). On the other hand, continuous data were expressed as mean and standard deviation (in case of normally distributed data) or median and interquartile range (in case of the non-normal distribution of data). The difference between the three-time points was assessed using ANOVA (F test). If ANOVA showed a significant difference between groups, post hoc multiple comparisons were done using the Bonferroni test to determine the significant pairs. Correlations were tested by Pearson's correlation coefficient (r) for parametric variables or Spearman's coefficient (rho) for rank. The accepted level of significance in this work was stated at <0.05.

3. RESULTS

Overall, 105 patients were included in the study, of which, 70 patients were allocated to the treatment (Sofosbuvir-based therapy) arm and the remaining 35 patients were allocated to the control (liver-support) arm. Following the allocation of patients into either group, five patients in the control arm refused the liver-support therapy and were re-allocated to the treatment arm. Finally, 75 patients were included in the treatment arm, and 30 patients were included in the control arm.

3.1. Patients' Demographic and Pretreatment Clinical and Laboratory Investigations

There was no significant difference between both groups with regard to the patients' demographics and the pretreatment data. The mean age of patients was 41.8 ± 9.93 and 41.3 ± 10.60 in the treatment and the control groups, respectively. The patients' blood pressure, FBS, serum albumin, and total bilirubin were in the normal range. Furthermore, the stage of liver fibrosis was not significantly different between both groups. Table **1** shows a summary of the pretreatment baseline data.

3.2. Erectile Function

The mean pretreatment IIEF-5 score and the degree of ED were not statistically significant between both arms ($p=0.84$, and $p=1.0$, respectively). On the other hand, the posttreatment IIEF-5 was significantly different between the treatment and the control groups, both at six months ($p<0.001$) and 12 months ($p<0.001$) (Table **2**). Furthermore, the degree of erectile function was significantly improved at six months ($p<0.001$) and 12 months ($p<0.001$) in the treatment group. On the contrary, the erectile function was not significantly improved at any time point in the control group ($p=1.0$) (Table **2**).

3.3. Correlation Between Different Variables And Iief-5 Scores

We performed a sub-group analysis of the degree of pretreatment ED in relation to age and stage of liver fibrosis for all the patients included in the Sofosbuvir arm to provide a better insight into the correlation of these variables and the degree of ED. Generally, patients with higher degrees of ED were significantly older (Table **3**). Similarly, the degree of ED was significantly affected by the stage of liver fibrosis, where all the patients with F4 stage (cirrhosis) suffered from either moderate (25%) or severe (75%) ED compared to 40% mild to moderate and 60% moderate ED in patients with F3 stage (Table **4**).

Noteworthy, age and stage of liver fibrosis were negatively correlated with IIEF-5 at all-time points (Table **5**). There was a negative correlation between the IIEF-5 score and age and fibrosis stage.

4. DISCUSSION

Egypt is known for having the highest prevalence of HCV infections worldwide [14]. Current evidence supports that HCV infection may contribute to the development of male sexual dysfunction depending on the characteristics of

Table 1. Summary of patients' demographics and pretreatment assessments.

Variable	Treatment arm (N=75)		Control arm (N=30)		p value
	Value	Range	Value	Range	
Age in years (mean ± SD)	41.8 ± 9.93	25-60	41.3 ± 10.60	25-60	0.82
Duration of HCV infection years (mean ± SD)	10.5±7.45	3-20	11.5±6.01	4-19	0.78
Duration of ED in years (mean ± SD)	8.4±5.03	3-15	7.1±4.04	3-13	0.64
BMI in kg/m^2(mean± SD)	25.4 ±2.42	23-31	26.1 ± 2.37	23-31	0.63
SBP in mmHg (mean ± SD)	123.3 ± 2.94	120-130	123.6 ± 3.32	120-130	0.66
DBP in mmHg (mean ± SD)	81.1 ± 1.65	79-85	81.3 ± 1.72	79-85	0.61
FBS in mg/dl (mean± SD)	83.9 ± 5.89	72-99	83.5 ± 5.53	73-98	0.72
SGPT (mean± SD)	59.0 ± 16.53	39-89	58.3 ± 13.46	42-88	0.84
Albumin (mean± SD)	4.11 ± 0.56	3-5.3	4.23 ± 0.65	3.1-5.2	0.34
Bilirubin (mean± SD)	0.80 ± 0.11	0.5-1.0	0.82 ± 0.11	0.5-1.0	0.39
METAVIR fibrosis stage (N, %) F0 (No fibrosis) F1 (portal fibrosis without septa) F2 (Septal fibrosis [portal-portal]) F3 (Septal fibrosis [portal-central) F4 (cirrhosis)	 12 (16%) 18 (24%) 18 (24%) 15 (20%) 12 (16%)	NA	 5 (16.7%) 7 (23.3%) 8 (26.7%) 6 (20.0%) 4 (13.3%)	NA	0.99
Viral clearance (%)	70 (93%)	NA	NA	NA	NA

N = Number; SD = standard deviation; BMI = body mass index; NA = Not available; SBP = systolic blood pressure; DBP = diastolic blood pressure; FBS = fasting blood sugar; SGPT = serum glutamic pyruvic transaminase; IIEF-5 = International Index of Erectile Function.

Table 2. Posttreatment IIEF-5 at 6 months and 12 months in both groups.

Variable	Treatment arm (N=75)		Control arm (N=30)		p value
	Value	Range	Value	Range	
Baseline IIEF-5 (mean ± SD)	14.7 ± 4.96	5-21	14.9 ± 5.14	5-21	0.84
Degree of ED (N, %) Mild [17-21] Mild to Moderate [12-16] Moderate [8-11] Severe [5-7]	 33 (44%) 21 (28%) 12 (16%) 9 (12%)	NA	 14 (46.7%) 8 (26.7%) 5 (16.7%) 3 (10%)	NA	1.0
6 mo IIEF-5 (mean± SD)	19.4 ± 5.38	5-25	14.7 ± 5.10	5-21	**<0.001***
Degree of ED (N, %) No ED [22-25] Mild [17-21] Mild to Moderate [12-16] Moderate [8-11] Severe [5-7]	 45 (60%) 14 (18.7%) 4 (5.3%) 8 (10.7%) 4 (5.3%)	NA	 0 (0%) 14 (46.7%) 8 (26.7%) 5 (16.7%) 3 (10.0%)	NA	**<0.001***
12 mo IIEF-5 (mean ± SD)	20.3 ± 5.24	6-25	14.4 ± 5.04	5-21	**<0.001***
Degree of ED (N, %) No ED [22-25] Mild [17-21] Mild to Moderate [12-16] Moderate [8-11] Severe [5-7]	 54 (72%) 7 (9.3%) 3 (4%) 8 (10.7%) 3 (4%)	NA	 0 (0%) 14 (46.7%) 8 (26.7%) 5 (16.7%) 3 (10.0%)	NA	**<0.001***
p value 1 for degree of ED between pretreatment and 6 mo	**<0.001***		1.0		NA
p value 2 for degree of ED between pretreatment and 12 mo	**<0.001***		1.0		NA
p value 3 for degree of ED between 6 mo and 12 month	**0.011***		1.0		NA

mo = months; IIEF-5 = International Index of Erectile Function.
* statistically significant.

Table 3. Summary of pretreatment ED according to patients' age.

Pre ttt ED	number	Age in years		P value
		Mean± SD	Range	
Mild ED	33	32.5±4.0	25-38	**<0.001**
Mild to moderate ED	21	43.7±3.07*	39-48	
Moderate ED	12	51.8±1.46*†	49-54	
Severe ED	9	58.2±1.85*†‡	55-60	

* significant in comparison with mild ED.
† significant in comparison with mild to moderate ED.
‡ significant in comparison with moderate ED.

Table 4. Summary of pretreatment ED according to the stage of fibrosis.

		Pretreatment IIEF5				Total	P value
		Mild ED	Mild to moderate ED	Moderate ED	Severe ED		
F0	**Count**	12	0	0	0	12	**<0.001**
	%	100.0%	0%	0%	0%	100.0%	
F1	**Count**	18	0	0	0	18	
	%	100.0%	0%	0%	0%	100.0%	
F2	**Count**	3	15	0	0	18	
	%	16.7%	83.3%	0%	0%	100.0%	
F3	**Count**	0	6	9	0	15	
	%	0%	40.0%	60.0%	0%	100.0%	
F4	**Count**	0	0	3	9	12	
	%	0%	0%	25.0%	75.0%	100.0%	
Total	**Count**	33	21	12	9	75	
	%	44.0%	28.0%	16.0%	12.0%	100.0%	

Table 5. Summary of correlation between ED score, and age and stage of liver fibrosis.

With	Age		F stage	
	R	P	rho	P
IIEF5 Pretreatment	-0.991	**<0.001***	-0.977	**<0.001***
IIEF5 after 6 m	-0.804	**<0.001***	-0.815	**<0.001***
IIEF5 after 12 m	-0.790	**<0.001***	-0.843	**<0.001***

patients and the degree of liver impairment [3, 18]. The relation between chronic HCV infection and ED may be explained by one of the following pathways. Firstly, some of the extrahepatic manifestations of chronic HCV may induce ED, such as depression, psychological disturbance, and fatigue [14]. Secondly, the progressive course of the disease and the associated disturbance of the metabolic and endocrinological functions may play a role in the development of ED in chronic HCV patients [19]. For instance, advanced liver disease in men is associated with a decrease in the testosterone estradiol ratio, rendering male HCV patients more vulnerable to ED [20, 21]. Furthermore, like the normal population, approximately 2% of middle-aged men with early liver dysfunction experience decreased libido and ED. On the other hand, men with advanced liver disease are more prone to manifestations related to hormonal disturbance like testicular dysfunction, loss of body hair, gynecomastia, decreased libido, decreased muscle mass, female configuration of pubic hair, redistribution of body fat, and ED [22]. Thirdly, many of the medications used for the treatment of HCV (PEG-IFN) and the extrahepatic manifestations (antidepressants) may increase the risk of ED [3]. Finally, ED may result from an inflammatory-based pathway, in which, nonstructural proteins may stimulate the production of mitochondrial reactive oxygen species (ROS), resulting in oxidative stress and inflammation, which, in turn, increase the calcium release from the endoplasmic reticulum. Subsequently, ROS and inducible nitric oxide synthase (iNOS) are increased as a result of calcium accumulation with a consequent increase in the production of NO and its derivatives that are capable of activating inflammatory process, DNA damage, and cell death. As a result of the chronic systemic inflammation and the increase in the C reactive protein level, endothelial NO production is decreased. In these settings, the chronic inflam-

mation together with the nitric oxide dysfunction may explain the HCV associated ED [23]. Interestingly, chronic HCV infection may cause endothelial dysfunction with aggravation of the atherosclerotic process, even in the absence of any cardiovascular risk factors [24].

The current evidence in the literature supported that PEG-IFN may contribute to ED; however, when it comes to the newly available DAAs, the evidence is scarce, with only one study (to the best of our knowledge) evaluating the impact of these drugs on male sexual function [14]. The current study showed a significant improvement of the IIEF-5 scores, over the study time frame, in patients allocated to the Sofosbuvir-based therapy as 45/75 (60%) and 54/75 (70%) of the patients reported no ED at 6 months and 12 months, respectively. Furthermore, the IIEF-5 scores were significantly higher in the treatment group compared to the control group at both 6 and 12 months ($p<0.001$). Our results supported the findings of Elshimi E *et al*. [14], who reported that the prevalence and the degree of ED were significantly higher in HCV patients before using DAAs compared to the posttreatment findings, where only 2% of their patients reported no ED before DAAs-based treatment compared to 42.5% without ED after the treatment. Noteworthy, in our study, the ED cure rate was higher (70%) compared to the study by Elshimi E *et al*. [14], (42.5%); however, this may be due to the longer follow up period (6 and 12 months) and the fixed treatment protocol (Sofosbuvir + daclatasvir) in our study. Furthermore, in the study by Elshimi E *et al*. [14], the authors did not comment on systemic diseases (like hypertension and diabetes mellitus) in their cohort, which, might have an impact on the outcome of their study.

Mullhal *et al*., reported that the prevalence of ED in the general population increases with the increase of age [25]. We aimed to explore this correlation in chronic HCV patients. There was a negative correlation between the IIEF-5 scores and the age among our patients (pretreatment $r= -0.991$, $p<0.001$; 6 months $r=-0.804$, $p<0.001$; 12 months $r=-0.790$, $p<0.001$). This finding is in line with the study by Elshimi E *et al*. [14], who demonstrated that the degree of ED increased with the increase in patients' age. Similarly, Dove LM *et al*. [26], reported that older age was among the independent predictors of ED in men with chronic HCV. On the same hand, our study showed that the stage of liver fibrosis was negatively correlated with the IIEF-5 score (pretreatment rho = -0.977, $p<0.001$; 6 months rho= -0.815, $p <0.001$; 12 months rho= -0.843, $p<0.001$). Several authors reported that the degree of ED is significantly correlated with the stage of liver fibrosis in accordance with our results [4, 8, 14, 27-29].

Unlike the PEG-IFN that is associated with significant impairment of sexual function as a result of the direct impact of IFN on the gonads and hypothalamic regulatory centers [20], male erectile function was significantly improved after HCV clearance using the DAAs. This may be explained by different mechanisms, including the improvement of the HCV-related endothelial dysfunction, improvement of liver function and prevention of further liver fibrosis that subsequently improves the testosterone levels, and the improvement of the patients' mental status and QoL. In the same setting, Chien YC *et al.,* [22], showed that living--donor liver transplantation was associated with improvement of patients' erectile function and disappearance of the hypogonadism signs as a result of the significant improvement of liver functions.

Our study is not devoid of limitations, including the small sample size. Furthermore, we did not assess sexual desire and the ejaculatory function, which is considered another limitation. On the other hand, there are multiple strengths in the current study, including the study design as this is the first prospective randomized comparative study to evaluate the impact of HCV DAAs on male sexual function. Moreover, we excluded patients with systemic diseases like hypertension, diabetes mellitus, and renal insufficiency which might have an impact on the prevalence of ED. Finally, the results of the current study should be interpreted with caution as there may be some sort of performance bias as a result of the deviation of five patients from the intention to treat randomization.

CONCLUSION

In conclusion, chronic HCV has a direct impact on erectile function even during the early stages of the disease (before the development of liver cirrhosis). The age and the stage of liver fibrosis are significantly correlated with the degree of ED. Clearance of HCV using DAAs is associated with significant improvements in erectile function.

AUTHORS' CONTRIBUTION

MA, KA and AM developed the idea of the manuscript, SP helped in the methodology development and refining the research idea, AF and AM did the data collection, MA, SA and AM recruited the patients, AH and AE did the statistical analysis, KA, SA and AE wrote the initial draft which was revised by all authors and KA and AE wrote the final version of the manuscript. All authors read and approved the final version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study has been approved by the Local Ethical Committee (IRB Approval Number: RC-2-9-2017).

HUMAN AND ANIMAL RIGHTS

No animals were used for the study. All human procedures were followed in accordance with the Helsinki Declaration of 1975 as revised in 2013 (http://ethics.iit.edu/ecodes/node/3931).

CONSENT FOR PUBLICATION

Written informed consent was obtained from all patients prior to the publication of the study.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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