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Liver

Does steatosis affect the performance of diffusion-weighted MRI values for fibrosis evaluation in patients with chronic hepatitis C genotype 4?

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Original Article

ABSTRACT

Background/Aims: To evaluate the effect of hepatic steatosis on the apparent diffusion coefficient (ADC) of hepatic fibrosis in patients with HCV genotype 4-related chronic hepatitis.

Materials and Methods: Overall, 268 chronic hepatitis C patients (164 males and 104 females) underwent liver biopsy for fibrosis assessment by the METAVIR score and grading for hepatic steatosis. They were classified into early fibrosis stage (F1, F2) and advanced fibrosis stage (F3, F4). Diffusion-weighted MRI (DWI) of the liver was performed using 1.5-Tesla scanners, and the ADC value of the patients with and without steatosis in different stages of fibrosis was estimated and compared.

Results: In patients with early fibrosis, the ADC value significantly decreased in patients with steatosis ($1.52\pm0.17\times10^{-3}$ mm^2/s) compared to that in patients without steatosis ($1.65\pm0.11\times10^{-3}$ mm^2/s) ($p<0.001$). In those with an advanced stage of fibrosis, the ADC value was also significantly decreased in patients with steatosis ($1.07\pm0.16\times10^{-3}$ mm^2/s) compared with that in patients without steatosis ($1.35\pm0.11\times10^{-3}$ mm^2/s) ($p\leq0.001$). The cutoff value for ADC for steatosis prediction in the early fibrosis group was 1.585 according to the AUROC curve, with a sensitivity of 76.8% and a specificity of 73.5%. The cutoff value for ADC for steatosis prediction in patients with an advanced stage of fibrosis was 1.17×10^{-3} mm^2/s, with a sensitivity of 97% and a specificity of 88.5%

Conclusion: Histologically detected hepatic steatosis should always be considered when assessing hepatic fibrosis using diffusion-weighted MRI to avoid the underestimation of the ADC value in patients with chronic hepatitis C genotype 4.

Keywords: Steatosis, diffusion-weighted MRI, fibrosis, chronic hepatitis C Genotype 4

INTRODUCTION

Hepatitis C virus (HCV) is a positive-strand RNA virus responsible for chronic hepatic infection in 150-200 million people worldwide (1). Egypt has the highest HCV prevalence. Chronic liver disease causes aberrant formation of fibrous tissue that impairs normal liver function, resulting in hepatic fibrosis, cirrhosis, portal hypertension, and hepatocellular carcinoma (2).

Early detection of hepatic fibrosis has important clinical implications for chronic viral hepatitis because antiviral treatment can reduce hepatic decompensation and increase patient survival (3). Despite the well-known problems and potential morbidity, liver biopsy remains the gold standard method for staging of liver fibrosis (4). Hence, it is important to develop non-invasive methods for the evaluation of hepatic fibrosis to reduce the risks associated with liver biopsy and for better monitoring of disease progression.

Magnetic resonance imaging (MRI) is a non-invasive method that can quantify and grade liver fibrosis (5-7).

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Diffusion-weighted MRI (DW-MRI) is one of the promising techniques that measure the motion of water in the extracellular space, and the diffusion of water can be quantified by calculating the apparent diffusion coefficient (ADC). This method may enhance the diagnostic accuracy of hepatic fibrosis; however, the results reported in previous studies are conflicting (8,9).

Hepatic steatosis is a usual histological feature in HCV-related chronic hepatitis patients, but it is unclear whether steatosis has a direct relationship with HCV itself or it results from host-related factors (10-13). Up to 50% of these patients have varying degrees of hepatic steatosis even in the absence of steatogenic risk factors (14). Currently, the impact of liver steatosis on the ADC value of DW-MRI is unclear. Therefore, this study aimed to assess the impact of histologically detected hepatic steatosis on the ADC value of DW-MRI used for the diagnosis of liver fibrosis in HCV genotype 4-related chronic hepatitis.

MATERIALS AND METHODS

Ethics Statements

This intervention study was approved by the institutional review board of Mansoura Faculty of Medicine, and written informed consent was obtained from all the patients.

Patients

This cross-sectional comparative study included 268 histologically-proven chronic hepatitis C genotype 4 (CHC G4) patients from January 2013 to December 2015. All patients fulfilled the inclusion and exclusion criteria mentioned below. Of these 268 patients, 60 patients had biopsy-proven steatosis. CHC G4 patients were defined by positive serum anti-HCV antibodies and the detection of serum HCV-RNA. The exclusion criteria were as follows: patients with Child-Pugh B and C cirrhosis, hepatocellular carcinoma, other causes of hepatic parenchymal disease as metabolic or autoimmune liver diseases, coinfection with HBV or HIV, and a history of the use of potentially hepatotoxic drugs.

Demographic data were obtained at the time of liver biopsy. Diabetes was diagnosed according to the revised criteria of the American Diabetes Association (15). The levels of serum bilirubin, serum albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum cholesterol, triglycerides (TGs) high-density lipoprotein, and glucose were determined after an overnight fast.

Hepatitis C Virus Genotyping

Extraction of RNA was performed by QIAamp Viral RNA Mini (Qiagen, Valencia, CA). The PyroMark Q24 (Qiagen) uses pyrosequencing technology for real-time, sequence-based detection and quantification of sequence variants and epigenetic methylation. The PyroMark Q24 is highly suited for the analysis of CpG methylation, SNPs, insertion/deletions, STRs, variable gene copy number, as well as for microbial identification and resistance typing. Primers and dispensation order was performed according to Elahi et al. (16).

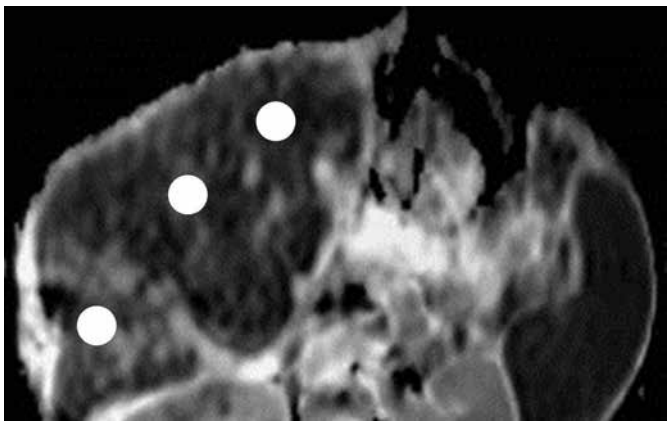

Figure 1. Axial ADC map of hepatic parenchyma with localization of three regions of interest
ADC: apparent diffusion coefficient

Diffusion-Weighted MRI Measurement

Magnetic resonance imaging examination was performed using a 1.5-Tesla scanner (Magnetom symphony; Siemens, Erlangen, Germany), which was equipped with a gradient set (30 mT/m maximum gradient strength and 120 T/m/s slew rate). Axial T1-weighted MRI images with TR/TE=600/20 ms and axial true FISP with TR/TE=4.3/2.1 ms of the abdomen was obtained. The field of view (FOV) was 25×25 cm, thickness of the section was 7 mm, and interslice gap was 1 mm.

Diffusion-weighted MRI of the abdomen was performed using echoplanar imaging. Automatic shimming and chemical shift selective fat-suppression technique were performed to reduce artifacts. The parameters used were b values of 0, 400, and 800 S/mm^2, TR of 2900 ms, TE of 80 ms, FOV of 25×25 cm, section thickness of 7 mm, interslice gap of 20%, and acquisition matrix of 192×154. The ADC map was reconstructed. The time of examination for DW-MRI was 1 min.

Image Analysis

Image analysis was performed by a single radiologist with an experience of more than 25 years in performing MRI (AA).

A circular region of interest (ROI) measured 5-7 cm2 was placed on the ADC map at three different regions of hepatic parenchyma, on three consecutive slices away from the biliary and vascular structures and more than 2 cm far from the surface of the liver (Figure 1) (17,18). The mean of nine regions was calculated, which represents the ADC value of the liver in each patient.

Histology Assessment

The METAVIR scoring system was used for staging of all biopsies by experienced pathologists as follows: F0=absence of fibrosis; F1=perisinusoidal or portal; F2=perisinusoidal and portal/periportal; F3=septal or bridging fibrosis; and

Table 1. Comparison between patients with and without steatosis

		Steatosis		
	Total (268) Mean±SD	No (208) Mean±SD	Yes (60) Mean±SD	Significance
Age (years)	45.3±9.4	45.0±9.5	46.2±9.1	p=0.4
Body mass index	28.4±3.4	28.3±3.4	28.9±3.4	p=0.3
S. albumin (g/dL)	4.1±0.6	4.1±0.6	4.1±0.4	p=0.3
Creatinine(mg/dL)	0.9±0.3	0.9±0.3	0.9±0.2	p=0.3
Hb (g/dL)	12.9±1.9	12.8±2.0	13.3±1.7	p=0.15
WBC (10^9/L)	6.1±2.0	5.9±2.0	6.7±1.9	p=0.008
INR	1.2±0.2	1.2±0.2	1.1±0.1	p=0.3
S. cholesterol (mg/dL)	181.9±21.4	181.9±21.9	182.2±20.1	p=0.9
S. triglyceride (mg/dL)	111.3±20.4	112.0±21.1	109.0±17.6	p=0.3
Fasting blood glucose (mg/dL)	94.1±24.7	89.8±13.6	108.9±42.8	p≤0.001
	Median (min-max)	Median (min-max)	Median (min-max)	
ALT (IU/L)	42.5 (13.3-285)	41 (13.3-285)	48 (20-112)	p=0.2
AST (IU/L)	42.5 (10-209)	42 (10-209)	47.5 (20-98)	p=0.15
Total bilirubin (mg/dL)	0.8 (0.2-8.0)	0.8 (0.2-8.0)	0.8 (0.2-1.7)	p=0.6
Platelet (10^9/L)	179 (45-414)	177 (45-414)	186 (83-325)	p=0.045
AFP (ng/mL)	3.73 (0.2-81.9)	3.8 (0.2-81.9)	2.9 (0.9-30.2)	p=0.6
HCV PCR IU/mL	316990 (1218-12639049)	595900 (1218-12639049)	427960 (8614-7511732)	p=0.4
	N (%)	N (%)	N (%)	
Male sex (N&%)	164 (61.2)	140 (67.3)	24 (40.0)	χ^2=14.6, p≤0.001
DM (N&%)	21 (7.8)	11 (5.3)	10 (16.7)	χ^2=8.3, p=0.004
HTN (N&%)	11 (4.1)	8 (3.8)	3 (5.0)	χ^2=0.2, p=0.69
Fibrosis: F1	128 (47.8)	106 (82.8)	22 (17.2)	
F2	47 (17.5)	35 (74.5)	12 (25.5)	χ^2=14.1,
F3	45 (16.8)	26 (57.8)	19 (42.2)	p=0.003
F4	48 (17.9)	41 (85.4)	7 (14.6)	

ALT: alanine transaminase; AFP: alfa fetoprotein; AST: aspartate transaminase; HB: hemoglobin; HCV: hepatitis C virus; INR: international normalized ratio; PCR: polymerase chain reaction; WBC: white blood cell; DM: diabetes mellitus; HTN; hypertension
Z of Mann-Whitney test

F4=cirrhosis (19). Stage 0 was excluded from our study. Steatosis was defined as the percentage of liver cells containing fat droplets. Histologically, steatosis is classified as score 0 (<5%), score 1 (5%-33%), score 2 (33%-66%), and score 3 (>66%). In this study, patients were classified into two groups: non-steatotic (<5%) and steatotic (≥5%).

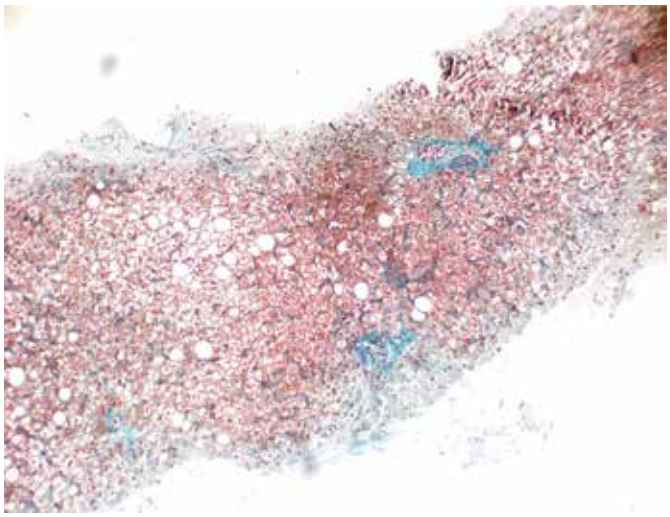

Figure 2. Presence of mild macro-vesicular steatosis, mild peri-cellular fibrosis, and mild portal fibrosis (Masson Trichrome staining 100x)

Statistical Analysis

Data was analyzed using Statistical Package for Social Sciences version 16 (SPSS Inc.; Chicago, IL, USA). For statistical analysis, the stages of fibrosis were classified into early fibrosis (F1, F2) and advanced fibrosis (F3, F4). Categorical variables were presented as numbers and percentages. The chi-square test was used for comparisons between groups. Quantitative variables were tested for normality distribution using the Shapiro test. Normally distributed variables were presented as mean and standard deviation. Unpaired t-test or ANOVA (F) test was used for group comparisons, as appropriate. Non-parametric variables were presented as median (minimum-maximum). The Mann-Whitney test was used for group comparisons. ADC performance was assessed using the receiver operator characteristic (ROC) curve. Based on the ROC curve, a cutoff value was designated for ADC to maximize the sensitivity and specificity of the assay for the prediction of advanced fibrosis (F3&F4) in total patients and in patients with and without steatosis. The spearman correlation coefficient was used to calculate the correlation between the ADC of necroinflammatory activity and fibrosis and different variability in each group. p≤0.05 was considered statistically significant.

RESULTS

Demographic Finding

Table 1 summarizes the baseline patients' characteristics. This study included 268 patients with a median age of 45.3±9.4 years and a male predominance of 61.2% (164). The mean BMI was 28.4±3.4 kg/m^2. The median values for AST, ALT, and total bilirubin were 42.5 IU/L (10-209), 42.5 IU/L (13.3-285), and 0.8 mg/dL (0.2-8.0), respectively. The mean value for albumin, glucose, cholesterol, and triglyceride levels were 4.1±0.6 g/dL, 94.1±24.7 mg/dL, 181.9±21.4 mg/dL, and 111.3±20.4 mg/dL, respectively. Eleven patients (4.1%) were hypertensive, and diabetes was present in approximately 21 patients (7.8%).

Table 2. ADC values in patients with early and advanced fibrosis with and without steatosis

Fibrosis	ADC				
	No steatosis		Steatosis		
	N	Mean±SD	N	Mean±SD	Significance
Early (F1&F2)	141	1.65±0.11	34	1.52±0.17	≤0.001
Advanced (F3&F4)	67	1.35±0.11	26	1.07±0.16	≤0.001
Significance		<0.001*		<0.001*	

ADC: apparent diffusion coefficient

Table 3. Correlation between ADC values and different parameters in total patients, no steatosis, and steaosis groups

	ADC		
	Total r	No steatosis r	Steatosis r
S. Cholesterol	0.124*	0.151*	0.128
S. Triglyceride	-0.020	-0.030	-0.269*
Body mass index	-0.237***	-0.232**	-0.221
Fibrosis	-0.756***	-0.824***	-0.858***

ADC: apparent diffusion coefficient
*, **, ***significant correlation at p≤0.05, ≤0.01, and ≤0.001, respectively

Histological Finding

The distribution of the fibrosis stage in the total patients (n=268) was as follows: F1 (n=128) (47.8%), F2 (n=47) (17.5%), F3 (n=45) (16.8%), and F4 (n=48) (17.9%). The patients were also classified into early (METAVIR score ≤ F2) fibrosis [175 patients, of them 141 patients had histological fat content <5% (non-steatotic subgroup) and 34 patients with liver fat content ≥5% (steatotic subgroup)] and those with advanced fibrosis (F3, F4) [93 patients, of them 67 patients non-steatotic and 26 patients with liver steatosis. Median hepatic fat content was 25% (Figure 2)].

Apparent Diffusion Coefficient Values in Different Groups of Fibrosis

Diffusion-weighted MRI values (ADC) significantly decreased according to the fibrosis stage: $1.66\pm0.12\times10^{-3}$ mm^2/s in F1; $1.53\pm0.14\times10^{-3}$ mm^2/s in F2; $1.29\pm0.21\times10^{-3}$ mm^2/s in F3; and $1.26\pm0.14\times10^{-3}$ mm^2/s in F4; p≤0.001) (data not shown in tables).

Effect of Steatosis on the Apparent Diffusion Coefficient Value in Chronic Hepatitis C Virus Patients with Early and Advanced Fibrosis

Table 2 shows the ADC values in patients with early and advanced fibrosis with and without steatosis. In patients with early fibrosis, the ADC value was significantly decreased in steatotic patients ($1.52\pm0.17\times10^{-3}$ mm^2/s) in comparison that in non-steatotic patients ($1.65\pm0.11\times10^{-3}$ mm^2/s) (p≤0.001). In patients with advanced fibrosis, there was also a significant decrease in the ADC value in steatotic patients ($1.07\pm0.16\times10^{-3}$ mm^2/s) versus that in non-steatotic patients ($1.35\pm0.11\times10^{-3}$ mm^2/s) (p≤0.001).

Correlation Analysis

When correlation analysis was performed between the ADC value in the studied cases as shown in Table 3, it was found that the ADC value showed a significant inverse correlation with fibrosis stages (p≤0.001) and a negative correlation with BMI (p<0.001), whereas a positive correlation was observed with cholesterol (p≤0.05) and there was no significant correlation with TG.

Table 4 shows the cutoff values for the prediction of fibrosis in patients with and without steatosis. The area under ROC curve was 0.74 for the detection of advanced fibrosis in total cases, and the optimal ADC cutoff value was 1.52×10^{-3} mm^2/s, with a sensitivity and specificity of 0.88 and 0.6, respectively. In non-steatotic cases, the ADC cutoff value was 1.56×10^{-3} mm^2/s, with a sensitivity and specificity of 0.89 and 0.71, respectively (positive predictive value: 0.87 and negative predictive value: 0.75). However, the cutoff value for the prediction of fibrosis in patients with steatosis was 1.39×10^{-3} mm^2/s with an area under ROC curve of 0.55 (positive predictive value: 0.56 and negative predictive value: 0.43). Area under curve (AUC) of ADC for the detection of advanced fibrosis is significant in total cases and in cases with no steatosis but not significant in cases with steatosis. At the specified cutoff points, the sensitivity, specificity, and predictive values are higher in cases without steatosis than in those with steatosis.

DISCUSSION

Hepatic fibrosis is a wound-healing response to various types of chronic liver diseases (20). In addition, liver fibrosis seems to have a direct role in the pathogenesis of cirrhosis and its complications, resulting in increased morbidity and mortality (21). In chronic hepatitis patients, the diagnosis of hepatic fibrosis is crucial for therapeutic and prognostic implications. In addition, the grade of inflammation is correlated with the cirrhosis progression rate and the response to therapy (22).

Diffusion-weighted MRI of the liver is well established for the detection and characterization of hepatic lesions (23-25). DWI represents the mobility of water molecules (molecular diffusion) in a tissue, which can be described by the ADC value or the intravoxel incoherent motion model (26).

Previous studies reported contradictory results with respect to liver fibrosis and DWI using 1.5-Tesla scanners. In this study, our findings showed decreased hepatic ADC values in patients with fibrosis owing to HCV- related chronic hepatitis. In our study, the ADC value changed according to the stages of fibrosis and was significantly decreased as fibrosis progressed. There was also a significant difference in the ADC value between early and advanced hepatic fibrosis (p£0.001). Our findings were similar to most other studies, for example Bakan et al. (8) showed that advanced fibrosis stages were associated with lower ADC values in the group of patients with chronic hepatic paryncheml disease. Sandrasegaran et al. (27) also

Table 4. The AUC, sensitivity, specificity and predictive values of ADC in patients with the presence and absence of steatosis

	Total patients (268)	Steatosis (60)	No steatosis (208)
AUC	0.74	0.55	0.81
p	≤0.001	0.08	≤0.001
Cutoff	1.52	1.39	1.56
Sensitivity	0.88	0.54	0.89
Specificity	0.6	0.47	0.71
Positive predictive value	0.81	0.56	0.87
Negative predictive value	0.73	0.43	0.75

ADC: apparent diffusion coefficient; AUC: area under curve

showed the ADC value to be lowered significantly in cirrhotic versus nonfibrotic livers. Moreover, Taouli et al. (23) reported that in chronic liver disease patients, there was a significant inverse correlation between ADC and liver fibrosis. Because the DWI represents the molecular diffusion of the tissue, which can be described by the ADC value, the decrease in the ADC value reported in our study can be explained by the restricted diffusion in advanced fibrosis, which was deemed to be multifactorial mostly due to diminished hepatic perfusion and, to some extent, to the presence of increased connective tissues, which contains fewer protons.

Concomitant liver steatosis and fibrosis are frequently observed in liver fibrosis patients, particularly those with nonalcoholic and alcoholic liver diseases and viral hepatitis C and B (28,29). However, only few and conflicting data are available regarding the influence of liver steatosis on the diffusion parameters. Conflicting results have been obtained from previous studies on assessing the influence of hepatic fat on ADC. For example, Poyraz et al. (30) reported that the ADC value was significantly decreased in the group of patients with hepatic fat content in comparison to that in the normal group. In normal parenchyma, Poyraz et al. reported an ADC value of 1.32×10^{-3} mm^2/s, while a decrease in the ADC value to 1.17×10^{-3} mm^2/s was observed in patients with a signal fat fraction of 10%-20%; however, in a study between the two similar groups by d`Assignies et al. (31), there was no significant change in the ADC value. The source of discrepancy in the ADC value between those two prior studies is unclear. In this study, we investigated the influence of hepatic steatosis on ADC values in patients with HCV-related chronic hepatitis with early and advanced fibrosis stages. Our results demonstrated a significant decrease in the ADC value in the subgroups of patients with steatosis in both groups of patients with early and advanced fibrosis stages in comparison to that in patients without steatosis. Our results are in agreement with those reported by Poyraz et al. (30), wherein it was reported that hepatic fat has an influence on the ADC value. The decrease in the ADC value observed in our study can be explained by hepatocyte swelling and the changes in the architectural structure of the liver that results from the accumulation of fat droplets in the liver cells (32). Another probable explanation is that protons associated with intra- and extracellular fat have reduced diffusivity, thus resulting in a lower ADC compared with normal parenchyma (33).

Our study showed a significant inverse correlation between liver fibrosis and ADC values taken using 1.5-Tesla DWI in total cases and in those with and without steatosis. The presence of steatosis was associated with a significant decrease in the ADC value and consequently was associated with a more significant inverse correlation between ADC values with liver fibrosis.

The ADC cutoff value of 1.56×10^{-3} mm^2/s was shown to predict advanced fibrosis in patients with no steatosis, thus providing a potentially useful tool for the assessment of these patients. In the presence of steatosis, the ability to predict advanced fibrosis is poor (area under ROC curve, 0.55).

Accordingly, the results of our study suggest that steatosis can act as a potential confounder when assessing fibrosis stages using DW-MRI as steatosis significantly affects molecular diffusion.

Few limitations are present in our study. First, there was a small number of patients with hepatic steatosis in different fibrosis stages; therefore, we divided the study subjects into two groups: non-steatotic and steatotic. Therefore, a large-scale study with an adequate number of steatotic patients in each stage of fibrosis is needed to achieve statistically significant results. Second, with respect to particularly considering liver biopsy and METAVIR scoring as a diagnostic gold standard method, some problems are present such as interobserver variability and sampling errors. In addition, METAVIR is not a continuous scale, and the increased accumulation of fibrous tissue upon different stages of fibrosis is not linear (34). Third, this study performed DW-MRI of the liver; however, future studies using diffusion tensor MRI and MR spectroscopy will achieve better results (35-37).

In conclusion, assessment of the ADC value was influenced by biological factors such as hepatic steatosis. Such effects may be the result of changes in the diffusion of water or alteration of residual fat signals in steatotic hepatic parenchyma, suggesting that steatosis has confounding effects on the ADC value of the liver. Therefore, hepatic steatosis should always be considered when assessing hepatic fibrosis using DW-MRI in patients with CHC G4 to avoid underestimation of the ADC value.

Ethics Committee Approval: Ethics committee approval was received for this study from the Institutional Review Board of Mansoura Faculty of Medicine (Decision Date: 18.01.2011).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - T.B., H.E., A.A.; Design - M.A., A.A., T.B., H.E.; Supervision - M.E., H.Z., T.B.; Resource - S.T.D.F., M.U.H.; Materials - T.B., H.E., M.E., A.A.; Data Collection and/or Processing - A.E., T.B., H.E., M.A., M.E.; Analysis and /or Interpretation - A.E., A.A., K.Z., W.E., H.Z.; Literature Search - M.A., T.B., H.E., M.E., A.A.; Writing - M.A., T.B., H.E., A.A., K.Z., W.E., H.Z.; Critical Reviews - T.B., A.A., M.A., H.E., M.E., A.E.

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