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RESEARCH PAPER

Real-world results of direct-acting antivirals use for the treatment of chronic hepatitis C in old patients

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Key Summary Points

Aim What are the real-world efficacy and safety of direct-acting antivirals (DAAs) in old chronic HCV population?

Findings The overall sustained virological response rate was 98.9%. Higher albumin, higher platelet count, lower bilirubin and lower stage of fibrosis were among predictors of favorable response.

Message Different DAAs regimens were safe and effective in old patients with chronic HCV.

Abstract

Background and aim Old people with chronic hepatitis C (HCV) were considered a difficult-to-treat category with more frequent adverse events until recently. Interferon-free direct-acting antivirals (DAAs) improved treatment adherence and quality of life of old patients. In this study, we aimed at reporting the real-world efficacy and safety of DAAs, in addition to predictors of sustained virological response (SVR) in old chronic HCV population.

Methods This is a prospective observational intention-to-treat analysis that included old chronic hepatitis C genotype-4 patients (> 65 years) treated in a single specialized viral hepatitis treatment center in Egypt. Treatment regimens were allocated according to national guidelines for treatment of hepatitis C. Primary outcome was undetectable HCV-RNA at 12-week post-treatment by PCR. Secondary outcomes were identification of predictors of SVR and assessment of safety related issues.

Results Our study included 864 patients (64% females) with mean age of 67.7 ± 2.8 years. Overall SVR rate was 98.9% while SVR rates for sofosbuvir/daclatasvir/ribavirin, paritaprevir/ombitasvir/ritonavir/ribavirin, sofosbuvir/daclatasvir, sofosbuvir/ledipasvir/ribavirin, sofosbuvir/simeprevir/daclatasvir/ribavirin, sofosbuvir/simeprevir, interferon/sofosbuvir/ribavirin and sofosbuvir/ribavirin were 100%, 100%, 100%, 100%, 100%, 99.3%, 98% and 94.2%, respectively. DAAs were well tolerated. None of the patients discontinued the treatment due to adverse effects. Higher albumin, higher platelet count, lower bilirubin and lower stage of fibrosis were among predictors of favourable response.

Conclusion Different DAAs regimens were safe and effective in old Egyptian patients with chronic HCV.

Keywords Direct-acting antivirals · HCV · Egypt · Old

Abbreviations

CTP	Child–Turcotte–Pugh
DCV	Daclatasvir
DAAs	Direct-acting antivirals
FIB-4	Fibrosis-4
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
LED	Ledipasvir
NCVHTC	New Cairo Viral Hepatitis Treatment Center
OMP	Ombitasvir
PAR	Paritaprevir
Peg IFN	Pegylated interferon
QoL	Quality of life
RIT	Ritonavir
RBV	Ribavirin
SIM	Simeprevir
SOF	Sofosbuvir
SVR	Sustained virological response

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Introduction

Chronic hepatitis C viral infection (HCV) is a major health problem, responsible for nearly 500,000 deaths every year, with a variable geographic distribution worldwide [1]. In Egypt, HCV and its complications represent a major endemic medical health problem with extraordinary rates of prevalence. In 2015, an Egyptian demographic survey study stated that 6.3% of the population have been tested HCV Antibody (HCV Ab) positive and the rate of infection increases with age reaching 27.6% in those aged (55–59 years) [2, 3]. As a response to this epidemic, and because of the exclusive prevalence of genotype 4 with its hard to treat nature with interferon-based therapies [4, 5], Egypt launched a large program for controlling HCV in the country which utilized a wide network of specialized viral hepatitis treatment centers covering the country to secure access to antiviral medications [6, 7]. Through this program, Egypt was able to treat more than 1 million patients with high success rates [8].

Old people always represent a therapeutic challenge in many aspects because of the associated co-morbidities and the possible used polypharmacy. The age of 65 years and more is agreed as the definition for old population, and the size of this group varies from a country to another [9, 10]. Old people with chronic HCV were considered a difficult-to-treat category to previous standard of care treatment combination of Pegylated interferon (Peg IFN) and ribavirin (RBV), with less success, more treatment failures than younger population, high discontinuation rates and more adverse events [11]. With the recent availability of IFN-free direct-acting antivirals (DAAs), success rates for chronic HCV infection have been markedly improved reaching above 90% [12, 13]. Even though some of the newer drugs give higher chances for aged populations, the numbers of old patients enrolled were limited.

The current study aimed to report the real-world efficacy and baseline predictors of response to different direct-acting antiviral regimens in treatment of chronic HCV old patients in Egypt.

Materials and methods

Patient recruitment

In this prospective observational study, all old patients with chronic HCV genotype who attended New Cairo Viral Hepatitis Treatment Center (NCVHTC) outpatient clinics in the period between January 2016 and July 2017 were enrolled. NCVHTC is one of the centers affiliated to the Egyptian National Committee for Control of Viral Hepatitis (NCCVH) [14]. Eligible patients were 65 years or older, had chronic HCV infection evident by positivity of HCV antibodies and HCV RNA by PCR. Patients with HCV recurrence/reinfection after previous IFN-based regimens were also enrolled.

Patients were included in the study according to the standardized protocol for HCV management issued by NCCVH. Key exclusion criteria were: Child–Turcotte–Pugh (CTP) class C, haemoglobin level < 10 g/dL, platelet count < 50,000/mm^3, hepatocellular carcinoma (HCC) except 6 months following a successful intervention and cure with no proof of recurrence by dynamic imaging (CT, MRI), extra hepatic malignancy except after 2 years of cure, co-infection with hepatitis B or HIV, and hypersensitivity to any of study medications. The study was performed according to the ethical guidelines of the 1975 Declaration of Helsinki after approval from Institutional Review Board (IRB) for human subject research at National Hepatology and Tropical Medicine Research Institute (Serial: 28-2015). A written informed consent was obtained from all enrolled participants before enrolment to the study.

Study design and assessments

This is a prospective observational intention-to-treat cohort analysis of old HCV-infected patients treated at NCVHTC, Cairo, Egypt. Before enrollment into the study, all participants were subjected to detailed physical examination, routine blood workup, and assessment of hepatic fibrosis stage using liver biopsy, FibroScan® or Fibrosis-4 (FIB-4) score. Patients were assigned to receive one of the antiviral regimens according to the available medication at time of enrollment and the applied treatment protocol issued by NCCVH, which was subjected to some changes based on the availability of medications and other logistical issues. Available treatment options are shown in Table 1.

During treatment period, patients were followed-up as scheduled by the treatment protocol every 4 weeks, where they were examined, had laboratory investigations (hematologic panel, liver biochemical profile, and creatinine), and interviewed for the occurrence of adverse events. HCV PCR testing was performed at the end of treatment and repeated 12 weeks after cessation of therapy to test for the sustained virological response (SVR12).

Outcomes

The primary outcome of the current study was to determine and compare the efficacy of different treatment protocols in the management of chronic HCV. Primary efficacy assessment included SVR12 as defined by HCV PCR below lower limit of detection measured at 12 weeks after the end of

Table 1 Treatment regimens used for the studied patients

Interferon/sofosbuvir/ribavirin (IFN/SOF/RBV)	Weekly subcutaneous injection of pegylated IFN-α 180 µg, once-daily oral capsule of sofosbuvir (SOF) 400 mg, and oral weight-based ribavirin (RBV) (1000 mg daily in patients with a body weight of < 75 kg and 1200 mg daily with a body weight of ≥ 75 kg) in two divided doses, for 12 weeks
Paritaprevir/ombitasvir/ritonavir/ribavirin (PAR/OMP/RIT/RBV)	Once-daily two oral tablets of (75 mg of paritaprevir, 12.5 mg of ombitasvir and 50 mg of ritonavir) and oral weight-based ribavirin divided into two daily doses for 12 weeks
Sofosbuvir/daclatasvir (SOF/DCV)	Once-daily oral sofosbuvir 400 mg and oral daclatasvir 60 mg for 12 weeks
Sofosbuvir/daclatasvir/ribavirin (SOF/DCV/RBV)	Once-daily oral sofosbuvir 400 mg, oral daclatasvir 60 mg, and oral weight-based ribavirin for 12 weeks
Sofosbuvir/ledipasvir/ribavirin (SOF/LED/RBV)	Once-daily oral fixed combination of ledipasvir/sofosbuvir (90 mg/400 mg) with weight-based ribavirin for 12 weeks
Sofosbuvir/ribavirin (SOF/RBV)	Once-daily oral sofosbuvir 400 mg with weight-based ribavirin divided into two doses for 24 weeks
Sofosbuvir/simeprevir (SOF/SIM)	Once-daily oral sofosbuvir 400 mg and oral simeprevir 150 mg for 12 weeks
Sofosbuvir/simeprevir/daclatasvir/ribavirin (SOF/SIM/DCV/RBV)	Once-daily oral sofosbuvir 400 mg, oral simeprevir 150 mg, oral daclatasvir 60 mg, and oral weight-based ribavirin for 12 weeks

treatment. Secondary outcome was to identify possible predictors of response for each treatment protocol.

Statistical analysis

Data were expressed as number (percent) for categorical variables and as mean (± SD) or median (interquartile range) for continuous variables. Baseline data were compared per administered treatment as well as per treatment outcomes (SVR versus non-SVR). SVR rate was compared in study sub-groups (cirrhosis versus non-cirrhosis, treatment-naïve versus experienced). All quantitative parametric and non-parametric variables were analyzed using either Students' *t* test or Mann–Whitney test for comparison of two groups whenever appropriate. Chi square test was used for comparison of categorical variables. Univariate and multivariate adjusted logistic regression models were constructed to determine baseline predictors of SVR. Data were presented as odds ratios (OR) with 95% confidence intervals (95% CI). All statistical analyses were based on two-sided hypothesis tests with a significance level of $p < 0.05$.

Results

This study included 864 chronic HCV genotype-4 patients ≥ 65 years; mean age was 67.7 ± 2.8 years; 35.9% were males, 90.6% were naïve to treatment, and 25% were cirrhotics (99.3% CTP A and 0.7% CTP B). Ascites was diagnosed only in 6 patients (0.7%). Mean BMI of studied patients was 30 ± 6 kg/m^2, only 5.8% of patients were smokers, 30% were diabetics and 35% had hypertension. 79.1% of patients completed their treatment in 12 weeks while the rest of them took 24 weeks to finish their treatment course. Normal ECG findings were reported in 84.4% of patients. Detailed demographic, baseline laboratory and radiological characteristics of studied patients are represented in Table 2.

Different treatment regimens were used according to the applied protocol and available medications. The used regimens were interferon/sofosbuvir/ribavirin (IFN/SOF/RBV) (55 patients), paritaprevir/ombitasvir/ritonavir/ribavirin (PAR/OMP/RIT/RBV) (34 patients), sofosbuvir/daclatasvir (SOF/DCV) (238 patients), sofosbuvir/daclatasvir/ribavirin (SOF/DCV/RBV) (234 patients), sofosbuvir/ledipasvir/ribavirin (SOF/LED/RBV) (12 patients), sofosbuvir/ribavirin (SOF/RBV) (138 patients), sofosbuvir/simeprevir (SOF/SIM) (150 patients), and sofosbuvir/simeprevir/daclatasvir/ribavirin (SOF/SIM/DCV/RBV) (3 patients). The attained SVR 12 rates were 98%, 100%, 100%, 100%, 100%, 94.2%, 99.3%, and 100% respectively, while the overall SVR 12 was achieved in 854 patients (98.9%). Details of the numbers and SVR in each treatment protocol are shown in Fig. 1. No serious adverse events, treatment discontinuations, or drop outs were reported in the studied patients. There was a statistically significant relation between SVR achievement and the status of cirrhosis where SVR was more significantly detected in the non-cirrhotic group, while there was no significant relation between attaining SVR and previous treatment status (Table 3).

Regarding the pretreatment predictors of favourable response, we found that Alfa fetoprotein, serum albumin, bilirubin, platelet count, portal vein diameter, liver stiffness and FIB4 showed significant relations with the achievement of SVR. The detailed relations between various laboratory and radiological parameters, and SVR are shown in Table 4.

Table 2 Baseline demographic, clinical, laboratory and radiological characteristics of studied patients

Age	
Mean ± SD	67.7 ± 2.8
Range	65–81
Gender	
Male	310 (35.9%)
Female	554 (64.1%)
Variables (mean ± SD)	
Height (m)	1.6 ± 0.1
Weight (kg)	79 ± 14.8
BMI (kg/m^2)	30 ± 6
Tobacco consumption	50 (5.8%)
Comorbidities	
Diabetes	260 (30.1%)
Hypertension	306 (35.4%)
Quantitative PCR	1,724,207.4 ± 5,103,899.7 IU/L
ALT	51.8 ± 32.6 IU/L
AST	61.2 ± 39.3 IU/L
AFP	13.4 ± 21.6 IU/L
Median	10.3
Creatinine	0.9 ± 0.5 mg/dL
Albumin	3.8 ± 0.5 g/dL
Random glucose	110.3 ± 31.5 mg/dL
TSH	1.9 ± 1.3 mIU/L
Total bilirubin	0.8 ± 0.4 mg/dL
Indirect bilirubin	0.5 ± 0.3 mg/dL
Hb	13.2 ± 1.6 g/L
WBC	6.0 ± 2.1 × 10^3 mm^3
Platelets	172.9 ± 65.6 × 10^3 mm^3
INR	1.1 ± 0.2
Variables (mean ± SD)	
PV diameter	11.8 ± 2.3 mm
FIB-4 calculation	4.2 ± 3.8
Baseline liver stiffness by Fibro-Scan	19.2 ± 12.9
Variables [no. (%)]	
Baseline ECG	
Normal	730 (84.4)
Abnormal	134 (15.6)
Baseline ascites	
No	858 (99.3)
Yes	6 (0.7)
Baseline CTP score	
A	858 (99.3)
B	6 (0.7)

BMI body mass index, *PCR* polymerase chain reaction, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *AFP* alpha-feto-protein, *TSH* thyroid-stimulating hormone, *Hb* haemoglobin, *WBC* white blood cells, *INR* international normalized ratio, *PV* portal vein, *CTP* Child–Turcotte–Pugh

Discussion

HCV eradication minimizes the risk of progression to liver cirrhosis and its complications that might be life threatening, and accordingly will improve overall survival, quality of life and reduce mortality [4]. In the past, the standard regimen of Peg-IFN and RBV had age limitation due to its significant adverse events in old patients, necessitating dose reduction or discontinuation of medications [15]. Nevertheless, the overall SVR rate was less than 50% with standard Peg-IFN and RBV regimens [4, 5]. With the revolutionary introduction of DAAs in 2011, there was subsequent increase in SVR12 approaching more than 90% with satisfying safety profile [12, 13]. Current international treatment guidelines do not specify the age limit for treating old patients [16, 17], however, this was stated by some national guidelines as the case of Egypt until recently [6, 7].

In this study, we aimed to report the real-life efficacy and baseline predictors of response to different DAAs regimens in treatment of chronic HCV old patients in Egypt. The overall SVR was 98.8% and this goes with most of the published real-life data coming from Egypt with SVR exceeding 95%. There was a significant relation between the type of the used treatment and achieving SVR indicating that treatment regimen is a predictor for sustained response. All patients who received SOF/DCV with or without RBV achieved 100% SVR; similarly, SOF/LED/RBV, SOF/SIM/DCV/RBV and PAR/OMP/RIT/RBV achieved an equivalent optimum response. The majority of our patients (472/864) received SOF/DCV ± RBV, and this is expected as this combination is the most commonly used regimen in the Egyptian program [6, 7], because of its proved efficacy in genotype 4 patients, in addition to the availability and cheapness of these medications [8]. The least SVR was observed with the 24 weeks SOF/RBV arm being only 94.2%. The use of this regimen was limited to the initial period of the program where SOF was the only available DAAs in the Egyptian market with some available clinical trial reports confirming the efficacy of this regimen in genotype 4 HCV patients [18, 19]. The low response rates in real-life settings, in addition to the availability of other DAAs in the Egyptian program terminated the use of this regimen shortly [20].

The high SVR in our patients confirms the good response to therapy in old patients and exceeds the recently reported results by Sherigar and his colleagues who stated an SVR of 91–98% in SOF-based regimen [21]. These results are similar to the reported outcome of treatment in general populations [22–24].

In this study, the number of old patients treated with DAAs was larger than similar studies using the same age

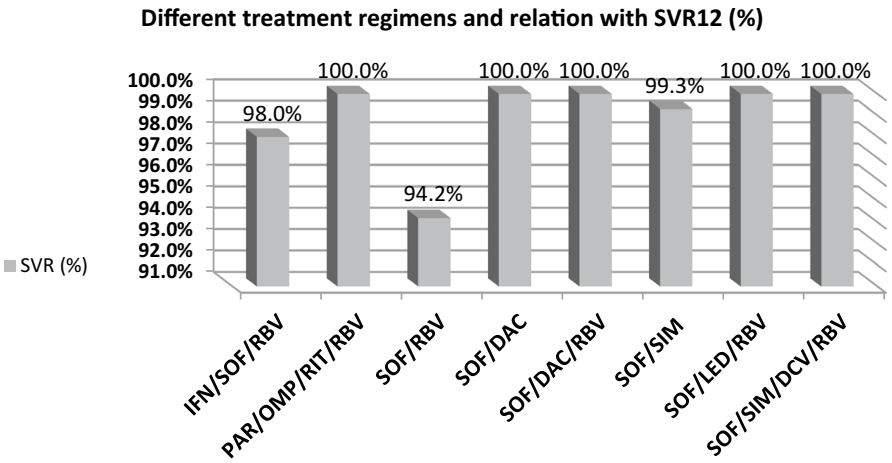

Fig. 1 Different treatment regimens and relation to SVR12. *SVR* sustained virological response, *IFN/SOF/RBV* interferon/sofosbuvir/ribavirin, *PAR/OMP/RIT/RBV* paritaprevir/ombitasvir/ritonavir/ribavirin, *SOF/RBV* sofosbuvir/ribavirin, *SOF/DAC* sofosbuvir/daclatasvir, *SOF/DAC/RBV* sofosbuvir/daclatasvir/ribavirin, *SOF/SIM* sofosbuvir/simeprevir, *SOF/LED/RBV* sofosbuvir/ledipasvir/ribavirin, *SOF/SIM/DCV/RBV* sofosbuvir/simeprevir/daclatasvir/ribavirin

Table 3 Relation between SVR and treatment experience, and presence or absence of cirrhosis

Studied patients ($n=864$)	Treatment outcome				Fischer exact test	*P* value	OR (CI 95%)
	SVR ($n=854$)		Non SVR ($n=10$)				
	No.	%	No.	%			
Treatment status							
Treatment-naïve ($n=783$)	774	90.6	9	90	0.02	0.6	1.18 (9.6–0.1)
Treatment-experienced ($n=81$)	80	9.4	1	10			
Study subgroup							
Non-cirrhotic ($n=648$)	646	75.6	2	20	17.6	**0.001**	22.5 (181.5–2.8)
Cirrhotic ($n=216$)	208	24.4	8	80			

The bold value indicates statistically significant

cut-off [25, 26]. On the other hand, the number of cirrhotic patients in our study (25%) was lower than the Italian study which included 85% cirrhotic patients which could explain the lower response rates in this study compared to our patients [26]. The smaller number of cirrhotic patients in our cohort could be attributed to the absence of prioritization in Egyptian treatment program according to fibrosis stage [6].

High prevalence of comorbidities among old patients, with its consequences of high pill burden creates another problem related to possible drug–drug interactions [24]; therefore, adjustment of concurrent therapies is mandatory to avoid occurrence of such unpleasant event, especially with anti-hypertensive drugs necessitating either changing anti-hypertensive molecule or dosage. In our center, this was the main role of the clinical pharmacy unit which was responsible for reviewing the patient medications, search for drug–drug interactions, and modifies drugs accordingly. Similarly, the close monitoring of concurrent diseases especially arterial hypertension and diabetes mellitus (representing 35% and 30%, respectively, in the current study), constituted a significant clinical importance, and this necessitated specific monitoring and was confirmed in many similar studies [26, 27]. Patients with hypertension required a close follow up of blood pressure and heart rate, also, diabetic subjects required a special care, because fluctuation of glycemic control, including improvement [28] or episodic hypoglycemia [29], which have been recently observed in patients receiving DAAs. These issues outline the complexity of old patients and their management, especially the use of antiviral therapy.

The meticulous monitoring and prompt management of these important issues (drug–drug interactions, adherence, and adverse events) in our patients had a great influence on the outcome, which was generally successful, confirming the excellent efficacy of DAAs in this "special population". One of the main strengths of this report is the absence of treatment discontinuation, stoppage or drop outs. The tight follow-up system in our units with the use of a call system and patient recall services helped a lot in the data completeness in our center. Issuing the patient a voucher for a free-of-charge PCR testing to be used after 12 weeks of treatment end, was also a great motive for patients to be more adherent to follow-up.

Achieving SVR is not the sole treatment goal in old patients; other important issues should be taken into

Table 4 Relation between SVR and various baseline laboratory and radiological data

Variables	Treatment outcome		*U*	*P* value
	SVR (854)	Non SVR (10)		
	Mean ± SD	Mean ± SD		
Quantitative PCR	1,422,714.5 ± 2634	1,169,363.60 ± 113,955	**0.415**	0.678
ALT (IU/L)	51.18 ± 32.7	60.6 ± 23.98	**1.588**	0.112
AST (IU/L)	60.41 ± 39.1	90.74 ± 58.1	**1.684**	0.092
AFP (IU/L)	12.95 ± 19.5	20.6 ± 14.1	**2.215**	**0.027**
Median	7.0	16.5		
Range	0.6–192.8	1.5–49.0		
Creatinine (mg/dL)	0.91 ± 0.35	0.94 ± 0.22	**0.665**	0.506
Albumin (g/dL)	3.8 ± 0.5	3.3 ± 0.48	**2.70**	**0.007**
Glucose (mg/dL)	110.17 ± 31.9	103.4 ± 18.3	**0.256**	0.798
TSH	1.85 ± 1.23	2.83 ± 2.1	**1.134**	0.257
Total bilirubin (mg/dL)	0.83 ± 0.38	1.27 ± 0.644	**2.408**	**0.023**
Indirect bilirubin (mg/dL)	0.53 ± 0.27	0.55 ± 0.30	**0.263**	0.793
Hb (g/L)	13.2 ± 1.6	13.06 ± 1.99	**0.074**	0.941
WBC × 10^3/mm^3	5.99 ± 2.1	6.51 ± 3.56	**0.253**	0.800
ANC × 10^3/mm^3	3.14 ± 1.4	3.14 ± 1.5	**0.028**	0.978
Platelets × 10^3/mm^3	171.84 ± 66.8	114.30 ± 54.9	**3.56**	**0.001**
INR	1.14 ± 0.15	1.13 ± 0.18	**0.703**	0.482
HbA1c (%)	6.45 ± 1.13	6.5 ± 1.17	**0.143**	0.886
PV diameter (mm)	11.83 ± 2.23	14.33 ± 2.5	**1.792**	**0.035**
FIB-4 calculation	4.18 ± 3.9	10.5 ± 8.2	**2.913**	**0.004**
Liver stiffness	18.6 ± 12.8	34.30 ± 10.6	**2.800**	**0.005**

The bold values indicate statistically significant

consideration when evaluating the outcome of DAAs treatment in old patients. In fact, some studies documented a great benefit both on life expectancy and quality of life in old individuals treated with DAAs [30]. Special questionnaires were utilized in the assessment of self-reported outcomes showing a great improvement in individual perception of health [31]. Being a real life trial, the main interest of our study were related to the efficacy and tolerability of the medication in old patients, and hence, our records lacks the use of other assessments like functionality, nutrition or Quality of Life, and this could be one of the limitations of our study. Another limitation was the absence of more older patients (above 80 years) in our study despite having no age limits in recruitment as an exclusion criterion. In this context, the relatively low life expectancy in Egypt (68 years in males and 73 in females), could be a reason [32].

In conclusion, the real-life nature of the current study, in addition to the relatively large sample recruited from a single center, confirm the efficacy and safety of DAAs use in old patients 65 years old and more. Predictors of favourable response were higher serum albumin and platelet count, and lower Alfa fetoprotein, serum bilirubin, portal vein diameter, liver stiffness and FIB4.

Author contributions Guarantor of the article: ME. Specific author contributions: ME, ZA, RE, MA, ME and SMA SM designed the research; ME, ZA, MNW, NY and SE performed the research; MT, LA and SMA contributed analytic tools; ME, ZA, MT and SMA analyzed the data; ME, ZA and SMA wrote the paper. All authors approved the final version of the manuscript.

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Compliance with ethical standards

Conflict of interest None of the authors have any conflicts of interests or financial disclosures related to this work.

Ethical approval This research is approved by the Institutional Review Board for Human Subject Research at National Hepatology and Tropical Medicine Research Institute (Serial: 28-2015).

Informed consent A written informed consent was obtained from all enrolled participants before enrolment to the study.

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