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Effect of Direct Acting Antivirals on Cardiovascular Performance in Patients with Chronic Hepatitis C Virus Infection

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Abstract

Background: Hepatitis C virus (HCV) is a major health problem in Egypt. Direct-acting antivirals (DAA) have markedly improved the treatment of HCV. However data regarding cardiovascular performance and safety are limited. The aim of our work was to assess cardiovascular performance and cardiac safety of direct acting antiviral agents in patients with chronic hepatitis C virus infection.

Results: Our study was a prospective cohort involving 64 HCV patients treated with DAA for 3 weeks. All patients performed surface electrocardiogram (ECG), stress ECG test and trans-thoracic echocardiography before and after treatment. The end point of this study was the development of major adverse cardiovascular event (MACE).12% of the studied patients showed improved cardiovascular performance after successful treatment of HCV with DAA. Predictors of improved cardiovascular performance included lower baseline alanine aminotransferase, lower baseline resting heart rate and higher maximum heart rate during exercise post treatment. DAA had no significant effect on resting ECG or transthoracic-echocardiographic parameters. No major adverse cardiovascular event or complication occurred during or 3 month after treatment.
None of the enrolled patients developed any signs of ischemia.

Conclusion: Direct acting antiviral agents were associated with an improvement in cardiovascular performance and exercise related symptoms. DAA proved its cardiac safety in patients with chronic hepatitis C virus infection receiving DAA

Keywords: HCV, Direct Acting, Antiviral, Cardiac Safety, cardiovascular performance, stress electrocardiogram.

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- **Background:**

Hepatitis C Virus (HCV) infection is considered one of the most important health problems worldwide, approximately affecting 185 million patients. Globally, it was found that liver cirrhosis and hepatocellular carcinoma were attributed to HCV in 27% and 25% of cases respectively. Egypt has one of the highest prevalence of HCV worldwide [1].

Although HCV is considered major contributor to different liver diseases, it also has extra-hepatic affection on the cardiovascular, kidney, lymph nodes, bone marrow, thyroid, and other organs[2].

HCV infection and cardiovascular affection are common conditions observed in a large proportion of the general population. Therefore, it is difficult to establish whether a simple association exists between the two conditions or other pathogenic mechanisms directly or indirectly link chronic HCV infection to cardiovascular disorders[3].

Direct-acting antivirals (DAA) have markedly improved the treatment of HCV, with a series of DAA combinations available for treatment[4].Recently few warnings and expert opinions were concerned about cardiovascular safety regarding: Drug interaction as amiodarone leading to severe bradycardia and sudden cardiac death [5].

2. Methods:

The study was a prospective cohort study including 64Egyptian patients with chronic HCV infectionrandomly selected from those who attended Ain Shams Viral Hepatitis and Research Unit to receive DAA according to the national protocol of management of HCV during the time of the study. Surface ECG, echocardiography, stress ECG and MACE assessment were used to assess cardiac safety of DAA. Cardiovascular performance was assessed by stress ECG and symptoms related exercise test. Patients were further subdivided into 2 groups:

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- Patients were considered improved if they did not complete exercise stress ECG at baseline and were able to complete exercise test after HCV treatment. (Complete= patient achieving ≥ 85% of maximum age predicted heart rate).

- Patients were considered Non-improved if they did not complete exercise ECG at baseline and were not able to complete exercise ECG after HCV treatment (Not complete=patient achieving <85% of maximum age predicted heart rate).

Inclusion criteria: HCV RNA positive & Patient Age ≥18 years with no contraindication to DAA.

Exclusion criteria: Previous cardiovascular abnormality, abnormal ECG, stress test and echocardiography, disability preventing them from exercise testing, condition impairing functional capacity, patients on negative chronotropic medications, patients not compliant to DAAs, patients with decompensated liver cirrhosis, co-infection with HIV or hepatitis B virus or autoimmune hepatitis, or relapse.

All patients were subjected to thorough history taking and clinical examination. Resting 12 leads surface electrocardiogram: heart rate, rhythm, ST segment deviation, arrhythmia, corrected QT interval (QTc) was measured according to Bazett's formula. Trans-thoracic echocardiographic assessment: LV end diastolic diameter (LVEDD) and LV end systolic diameter (LVESD), left ventricular ejection fraction (LVEF),left ventricular mass index (LVMI),left atrial (LA) diameter, valvular assessment, wall motion abnormalities assessment& right ventricular systolic pressure and diastolic function. Stress electrocardiogram testing: maximum heart rate, exercise time, metabolic equivalent, maximum age predicted heart rate, ST segment deviation, arrhythmia, symptoms developed during exercise and patients were further divided into non- improved and improved according to cardiovascular stress performance. Major adverse cardiovascular events (MACE) were followed up in all patients after 3 month of successful treatment. Hepatological assessment including: alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine (Cr), serum albumin (Alb), serum bilirubin (Bil),complete blood count (CBC), glycated hemoglobin

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(HBA1c), international normalized ratio (INR), polymerase chain reaction (PCR) hepatitis C, alkaline phosphatase, alpha feto-proteins using ELISA technique. Abdominal ultrasound (US) screening for: hepatomegaly, cirrhosis, splenomegaly, and ascites. Fib-4 score was calculated using a panel of routine blood tests (ALT, AST, platelet count and age).

Direct acting antiviral (DAA) agent choice was according to treatment protocols in Ain Shams Viral Hepatitis Unit including: sofosbuvir, daclatasvir, ribavirin, ombitasvir, paritaprevir according to clinical situation.

Statistical Analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Science (Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, New York: IBM Corp.). The quantitative data with parametric distribution were presented as mean, standard deviations and ranges while with non parametric distribution were presented as median with inter-quartile range (IQR). Also qualitative variables were presented as number and percentages.

The comparison between groups regarding qualitative data was done by using *Chi-square test* and/or *Fisher exact test* and/or *McNemar's test* with the continuity of Chi squared when the expected count in any cell found less than 5.

The comparison between two independent groups with quantitative data and parametric distribution was done by using *Independent t-test*

The comparison between two independent groups with quantitative data and non-parametric distribution was done by using *Mann-Whitney test.*

The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following:

- P-value > 0.05: Non significant (NS)
- P-value < 0.05: Significant (S)
- P-value < 0.01: Highly significant (HS)

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Results:

Regarding demographic characteristics in our study, 61% were males, mean age was 45years, 13% were diabetic, 11% were hypertensive, 13% were smokers, with a mean BMI of 28.1 Kg/m². (Table 1)

Table (1) Demographic data of studied population

Demographic		**No. = 64**
Age (years)	Mean ± SD Range	45.39 ± 11.56 21 – 68
Gender	Females Males	25 (39.1%) 39 (60.9%)
Weight (Kilograms)	Mean ± SD Range	79.53 ± 8.84 59 – 112
Height (Cm)	Mean ± SD Range	168.73 ± 9.02 140 – 184
Body surface area (m^2)	Mean ± SD Range	1.91 ± 0.13 1.61 – 2.17

Patients' baseline laboratory results were: ALT had a median of 1 fold, AST had a median of 0.9 fold, mean serum albumin level was 4.2gm/dl, mean hemoglobin count was 13.9gm/L, mean serum creatinine was 0.9 mg/dL.

Liver ultrasound performed showed a normal liver pattern in 50% in patients, abnormal liver pattern or hepatomegaly in 45% of patients, cirrhotic pattern among 5% of study group. SOF/DAC used in 70% of cases and SOF/DAC/RBV in 23% of cases.

All patients had normal sinus rhythm, mean resting heart rate of 88 BPM. Mean corrected QT interval (QTc) was 406ms. 9%of patients had prolonged QTc. Electrocardiogramcomparison was not significant in comparison between baseline and post treatment among our study population. (Table 2)

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Table (2): Electrocardiogram comparison between pre-treatment and after treatment

Baseline ECG	Pre-treatment	Post-treatment	Test value	P-value	Sig.
Resting HR	88.78 ± 10.52	87.75 ± 9.79	0.906	0.368	NS
ST Normal	59(92.2%)	60(93.8%)	0.120	0.729	NS
ST deviation	5(7.8%)	4(6.3%)			
QTc	407.41 ± 35.71	402.26 ± 57.97	0.700	0.486	NS
QTcNormal	58(90.6%)	62(96.90%)	1.411	0.235	NS
QTc prolonged	6(9.4%)	2(3.10%)			

Baseline echocardiography study showed a mean left ventricular ejection fraction (LVEF) was 67%, mean left ventricular end diastolic diameter (LVEDD) and mean left ventricular end systolic diameter (LVESD) was 48mm and 30mm respectively. In our study, 54% had normal diastolic function, meanwhile 45% had grade 1 diastolic dysfunction. Echocardiographic comparison was not significant in comparison between baseline and post treatment among our study population. (Table 3)

Table (3): Comparison between pre-treatment and post treatment regarding echocardiographic data

Echocardiography	Pre-treatment	Post treatment	Test value	P-value	Sig.
	No. = 64	No. = 64			
Left ventricular ejection fraction (%)	66.83 ± 5.21	66.99 ± 4.19	-0.264	0.792	NS
Fraction shortening (%)	37.06 ± 4.19	37.57 ± 4.10	-0.829	0.410	NS
Left ventricular end diastolic diameter (mm)	47.52 ± 4.71	47.23 ± 4.42	0.641	0.524	NS
Left ventricular end systolic diameter (mm)	29.69 ± 3.77	29.47 ±3.62	0.682	0.498	NS
Left ventricular mass index (m^2)	73.78 ± 17.97	74.87 ± 17.51	0.469	0.641	NS

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Left atrium diameter (mm)	34.69 ± 3.72	34.17 ± 3.72	1.199	0.235	NS
Diastolic dysfunction Normal Diastolic dysfunction grade I	 35 (54.7%) 29 (45.3%)	 35 (54.7%) 29 (45.3%)	 0.000	 1.000	 NS

Regarding baseline stress electrocardiogram (stress ECG):77% of patients completed stress test by achieving 85% of maximum age predicted heart rate. 14% of patients had premature ventricular contractions during exercise and rest. 47% of patients had symptoms during exercise ECG: fatigue (16%), leg discomfort (11%), chest discomfort (8%), dyspnea (8%), palpitation (5%). 12.5% of studied population showed improvement in cardiovascular profile after HCV clearance. Improvement of symptoms accompanied during exercise ECG: fatigue, chest discomfort, dyspnea was significant in comparison between before and after treatment. (Table 4)

Table (4): Comparison between pre-treatment and post treatment stress electrocardiogram

		Pre-treatment	**Post-treatment**	**Test value**	**P-value**	**Sig.**
Max HR	Mean±SD	163.66 ± 19.15	166.78 17.77	-1.669	0.100	NS
TIME	Mean±SD	9.87 ± 2.95	9.82 2.90	0.233	0.817	NS
%MAPHR	Mean±SD	93.03 ± 11.49	95.34± 10.05	2.118	0.038	S
Mets	Mean±SD	11.92 ± 3.31	12.00 3.16	-0.279	0.781	NS
Rhythm	Sinus	64 (100.0%)	64 (100.0%)	-	-	-
ST deviation	Normal Abnormal	58 (90.6%) 6 (9.4%)	63 (98.4%) 1 (1.6%)	3.778	0.052	NS
Arrhythmia	Normal PVC	55 (85.9%) 9 (14.1%)	59 (92.2%) 5 (7.8%)	1.283	0.257	NS
Complete Stress Test	No Yes	15 (23.4%) 49 (76.6%)	7 (10.2%) 57 (89.8%)	6.125	0.0133	S
Leg Discomfort	No Yes	57 (89.1%) 7 (10.9%)	61 (95.3%) 3 (4.7%)	1.736	0.188	NS
Fatigue	No Yes	54 (84.4%) 10 (15.6%)	61 (95.3%) 3 (4.7%)	4.195	0.041	S
Chest discomfort	No	59 (92.2%)	64 (100.0%)	5.203	0.023	S

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	Yes	5 (7.8%)	0 (0.0%)			
Dyspnea	No Yes	59 (92.2%) 5 (7.8%)	64 (100.0%) 0 (0.0%)	5.203	0.023	S
Palpitation	No Yes	61 (95.3%) 3 (4.7%)	62 (96.9%) 2 (3.1%)	0.208	0.648	NS

Improvement in cardiovascular stress profile was correlated to: lower baseline liver function tests in the form of alanine aminotransferase, baseline heart rate, and higher maximum heart rate in post treatment stress test.(Tables 5,6 and 7)

None of our patients suffered from ischemic attacks during stress exercise ECG.None of our patients suffered from major adverse cardiovascular events (MACE) during treatment and for three month after treatment.

Table (5): Comparison between non-improved and improved group laboratory results

		non-Improved No.7	**Improved No.8**	**Test value**	**P-value**	**Sig.**
ALT fold	Median (IQR) Range	2.70 (1.4 - 3.78) 0.84 – 4.47	0.74 (0.49 - 1.17) 0.3 – 2.23	-2.546	0.011	S
AST fold	Median (IQR) Range	1.75 (1.06 - 2.21) 0.88 – 3.55	0.81 (0.65 - 1.41) 0.46 – 2.88	-1.852	0.064	NS
AFP fold	Median (IQR) Range	.45 (0.33 - 1.49) 0.16 – 1.5	0.33 (0.27 - 0.43) 0.19 – 1.21	-1.274	0.203	NS
Albumin	Mean ± SD Range	4.36 ± 0.42 3.9 – 4.9	3.79 ± 0.57 3–4.4	2.189	0.047	S
Total bilirubin	Mean ± SD Range	0.60 ± 0.24 0.2 – 0.9	0.61 ± 0.48 0.2 – 1.7	-0.062	0.951	NS
Serum creatinine	Mean ± SD Range	0.81 ± 0.09 0.7 – 0.9	0.97 ± 0.44 0.5 – 1.79	-0.922	0.373	NS
INR	Mean ± SD Range	1.12 ± 0.10 0.97 – 1.26	1.20 ± 0.37 0.69 – 1.98	-0.511	0.618	NS
Platelet	Mean ± SD Range	271.00 ± 51.93 194 – 350	206.00 ± 69.28 49 – 277	2.030	0.063	NS
HbA1c* (%)	Mean ± SD Range	7.01 ± 3.42 5.3 – 14.7	6.35 ± 1.46 5–9.3	0.501	0.625	NS

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Table (6): Comparison between non-improved and improved group pre-treatment electrocardiogram

		non-Improved	Improved	Test value	P-value	Sig.
		No. = 7	No.= 8			
Resting heart rate	Mean ± SD	95.29 ± 7.11	82.50 ±5.40	3.954	0.002	HS
	Range	83 – 106	76–92			
Corrected QT	Mean ± SD	413.20 ± 29.47	413.11 ± 29.91	0.006	0.995	NS
	Range	352.33 – 445.78	360.15 – 467.62			
QTC interpretation	Normal	7 (100.0%)	7 (87.5%)	0.938	0.333	NS
	Prolonged	0 (0.0%)	1 (12.5%)			

Table (7): Comparison between non-improved and improved group post treatment stress electrocardiogram

		non-Improved	Improved	Test value	P-Value	Sig.
		No.%	No.%			
Maximum heart rate	Mean ± SD	143.71 ± 11.43	163.43 ± 17.67	-2.479	0.029	S
	Range	126 – 165	139 – 192			
Exercise time	Mean ± SD	8.09 ± 2.38	10.19 ± 3.27	-1.378	0.193	NS
	Range	5 – 11.4	5.7 – 14.5			
Maximum age predicted heart rate	Mean ± SD	79.22 ± 4.48	91.81 ± 9.15	-3.301	0.006	HS
	Range	72.41 – 84.62	85.28 – 110.34			
Metabolic equivalent	Mean ± SD	9.67 ± 2.82	12.33 ± 4.03	-1.428	0.179	NS
	Range	4.8 – 12.9	5.6 – 17.3			

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Discussion:

HCV infection is considered one of the most important health problems worldwide, approximately affecting 185 million patients. Egypt has one of the highest prevalence of HCV worldwide [1]**.**HCV and cardiovascular affection are common conditions observed in a large proportion of the general population. Therefore, it is difficult to establish whether a simple association exists between the two conditions or other pathogenic mechanisms directly or indirectly link chronic HCV infection to cardiovascular disorders[3]**.** Direct-acting antivirals (DAA) have markedly improved the treatment of HCV, with a series of DAA combinations available for treatment[4]**.**

None of our patients suffered from major adverse cardiovascular events (MACE) during treatment and for three month after treatment. In concordance with our study, Adinolfi et al demonstrated that HCV clearance by DAA significantly reduced annual incidence of cardiovascular events by 0.68%. Cardiovascular risks were reduced by 2-3.5 folds after HCV clearance. Multivariate analysis showed that HCV clearance was associated with independent CV event reduction independent from the degree of liver fibrosis. [6]

It is hypothesized that decreased adverse cardiovascular events after HCV elimination using DAA maybe related to better atherosclerosis, immunological and inflammatory response. HCV elimination using DAA induced an early and significant decrease in circulating inflammatory biomarkers.[7]

In our study we report 9% of HCV patients had prolonged corrected QT interval. The mechanism responsible for QT prolongation in HCV patients is unknown. However it has been suggested that electrolyte abnormalities, alteration in autonomic nervous system, myocardial ischemia may affect heart rate and electromechanical coupling. Additional factors as gonadal hormone metabolism that occur in advanced cirrhosis may contribute in QTc prolongation**.** Hagiwara et al performed periodic QTc assessment for HCV patients during DAA and revealed that 2 patients had significant prolongation in QTc during treatment. Although our results denote that corrected QT interval did not change significantly after treatment, however available literature represents disperse information. [8][9]

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In 2015 The FDA issued a warning about the potential effect of sofosbuvir on fatal arrhythmias in combination with amiodarone. Similar warning was released by Gilead Sciences suggesting that occurrence of fatal arrhythmias may be related to drug interactions through P glycoproteins in cardiac myocyte or through direct action in sinoatrial node or atrioventricular node [10].

However a large systematic review and meta-analysis of randomized clinical trials including 2346 patients showed that DAA were not associated with increased risks in cardiovascular outcomes including arrhythmias and bradycardia among sofosbuvir treated patients [11].

In our current study, echocardiographic parameters did not change in comparison between pre-treatment and post-treatment results. Although a study performed on 34 patients warned from possible cardiotoxicity (Left ventricular dysfunction by echocardiographic assessment) using HCV nucleotide polymerase inhibitor. [12]. However our results are in alignment with other studies demonstrating safety of DAA on echocardiographic parameters. [13][14]

Regarding stress electrocardiogram in our study, 12.5% of studied population had an improved cardiovascular performance after HCV clearance through completion of exercise ECG post treatment (demonstrated by their ability to achieve ≥85% of maximum age predicted heart rate). In addition to improvement of symptoms accompanied during exercise ECG. None of our patients suffered from signs of ischemia during stress exercise ECG. Improvement in cardiovascular performance was correlated to: lower baseline liver function tests in the form of alanine aminotransferase, lower baseline heart rate and higher maximum heart rate in post treatment stress test. Thus, denoting that early treatment of HCV in early phase of infection before occurrence of liver derangement and decompensation or systemic affection of cardiovascular profile would have a positive impact cardiovascular outcome and improved symptoms.

A recent cross sectional study aimed to evaluate functional capacity in HCV patients using 6 minute walk test (6MWT). The study included 3 groups: Group I: control, Group II: HCV without cirrhosis, Group III: HCV with cirrhosis. The study demonstrated significant difference in 6MWT in group III (131 meters) than group II (326meters) than group I (360

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meters). 6MWT was negatively correlated with alanine aspartate, bilirubin, alkaline phosphatase, creatinine and INR. The study concluded that six-minute walk test was a reliable indicator to measure the functional capacity for patients with chronic HCV. Thus ensuring early treatment of HCV before occurrence of cirrhosis would indicate an improved functional capacity[15].

Unlike DAA, Takase et aldemonstrated that interferon based therapy caused significant decrease in exercise tolerance time, maximum heart rate during exercise treadmill test in comparison between before and after treatment using treadmill test. Although none of the patients experienced exercise induced ischemia before or after interferon therapy. [16]

We find that there is a literature gap in comparing cardiovascular outcomes in chronic HCV patients using exercise stress ECG before and after treatment using DAA.

Muñoz-Hernández et al analyzed the impact of sustained virologic response on endothelial dysfunction and subclinical atherosclerosis in 114 HCV patients receiving DAA using laser Doppler flowmetry, ankle brachial index, lipid profile, oxidative stress factors, adhesion marker, vascular endothelial growth factor and platelet apoptosis microparticle. The study demonstrated improvement in patient with endothelial dysfunction by increased hyperemia after HCV clearance, improved ankle brachial index in addition to improvement in endothelial biomarkers. SimilarlyDi Minnoet al demonstrated similar improvement of endothelial function by flow mediated dilatation and post ischemic hyperemia after HCV clearance using DAA in 22 patients. The study showed improvement 3 month post treatment in comparison with pre-treatment results. Results were significant irrespective of presence of cardiovascular risk factors. These studies are in alignment with our work and may help to explain the potential benefit of HCV clearance on exercise capacity in chronic HCV patients receiving DAA. [17][18]

Study limitation:

- The results were obtained from a small sample size and from a single medical center.
- Other confounding factors were not analyzed such as urea level, estimation of volume status, hypertension grade.
- Limitation of the assessment on two occasions before starting treatment and 12 weeks after treatment.
- Lack of control arm to ensure that the positive effect on cardiovascular profile was only due to HCV eradication

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Conclusion:

Direct acting antiviral agents proved its cardiac safety in management of chronic HCV among Egyptian patients with chronic hepatitis C virus. Our study demonstrated improvement in cardiovascular profile and exercise symptom improvement after elimination of hepatitis C virus

Abbreviations:

HCV: hepatitis C virus.

DAA: Direct Acting Antiviral Agents.

ECG: Electrocardiogram.

PCR: Polymerase chain reaction.

6 MWT: 6 minute walk test.

LVEDD: left ventricular end diastolic diameter.

LVESD: left ventricular end systolic diameter.

LVEF: left ventricular ejection fraction

LA: left atrium

BPM: beat per minute.

QTc: Mean corrected QT interval

SOF: Sofosbuvir

DAC: Daclatasvir.

RBV: Ribavirin.

Hb: hemoglobin count.

ALT: alanine aminotransferase.

AST: aspartate transaminase.

Alb: serum albumin.

Cr: serum creatinine.

HR: heart rate

Max HR: maximum heart rate

MAPHR: maximum age predicted heart rate

Mets: Metablic equivalent

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Declarations:

- Ethics approval and consent to participate: This work was carried out in compliance with Ethical Standards. Ethical approval and informed consent: Written informed consent was obtained from all the participants of this study, which was performed in accordance with Declaration of Helsinki, and was approved by the Ethics Committee of Ain Shams Faculty of Medicine, Egypt (Federal Wide Assurance No:000017585)
- Consent for publication: This work was carried out in compliance with Ethical Standards. Ethical approval and informed consent: Written informed consent was obtained from all the participants of this study, which was performed in accordance with Declaration of Helsinki, and was approved by the Ethics Committee of Ain Shams Faculty of Medicine, Egypt (Federal Wide Assurance No:000017585)
- Availability of data and material: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.
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  Author 1: conceptualized and designed the protocol, collected the data, analyzed the data, created tables and figures, performed statistics and wrote the manuscript.

  Author 2: conceptualized and designed the protocol, collected the data, analyzed the data, created tables and figures, performed statistics and wrote the manuscript.

  Author 3: conceptualized and revised the protocol, revised statistics, revised and wrote the manuscript
  Author 4: revised the protocol, collected the data and wrote the manuscript

  Author 5: revised the protocol and wrote the manuscript

  Author 6: designed the protocol, collected and analyzed the data, wrote and revised the manuscript.

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