Hydroxychloroquine And Azithromycin As A Treatment Of Covid-19: Electrocardiogram Variability

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Abstract

During the COVID-19 pandemic, the effectiveness of the combination of hydroxychloroquine and azithromycin is widely discussed. This treatment can cause many severe cardiac side effects that makes us discuss its utility. The aim of this study is to describe the cardiovascular effect of hydroxychloroquine and azithromycin by analyzing surface ECG in patients with COVID-19. This observational cohort study included Moroccan patients with COVID-19 diagnosis and were hospitalized in Cheikh Khalifa International University Hospital, Casablanca, Morocco between March 26 and April 20, 2020. Patients were treated with a combination of hydroxychloroquine and azithromycin over a period of at least ten days. We were interested in the effects of this combination on the electrocardiogram. A total of 118 eligible patients were enrolled in the study. QT interval prolongation was observed in 19% of patients under the treatment. Only 5 patients required discontinuation of treatment. The factors associated with QT prolongation are male gender (P value 0,043), age over 68 years (P value 0,09), cardiovascular comorbidity (P value 0,013), tisdale score $\geq$11 (P value < 0,001), and a severe form of COVID-19 (P value < 0,001). First degree atrioventricular block was observed in 2 patients. No serious rhythm or conduction disorders were observed in this study. QT prolongation is a real risk with the combination of hydroxychloroquine and azithromycin. In the current context, it is necessary to select patients at high risk of severe rhythm disturbances that require closer ECG monitoring. Treatment should be discontinued if there are alarming signs such as QTc prolongation beyond 550 ms and the development of ventricular extrasystole or torsade de pointe.

Keywords: Hydroxychloroquine, Azithromycin, COVID-19, Electrocardiogram, QT prolongation

1. Background

The first cases of the new coronavirus disease 2019 (COVID-19) were reported in December 2019 and since the pandemic has spread worldwide [1]. As of May 15, 2020, there were four million confirmed cases and 297,000 deaths worldwide [2].

In China, Chloroquine phosphate is the first drug used against COVID-19 in early clinical studies [3], it was added to the sixth edition of the Guide for the Interim Treatment of COVID-19 [4]. However, based on recent studies, its effectiveness has been claimed [5].

In Morocco, the Ministry of Health, in consultation with the scientific and technical committee of the national program to fight against coronaviruses,

decided on 23 March 2020 to adopt the therapeutic protocol based on hydroxychloroquine combined with azithromycin in the various hospitals of the kingdom. And since April 17 as prophylactic treatment in health professionals based on hydroxychloroquine [6].

This combination is currently at the heart of a vast controversy because of its effectiveness still discussed and these potential side effects especially cardiac [7].

Hydroxychloroquine and azithromycin are generally well tolerated medications used in clinical practice, but both can cause QT prolongation [8], their wide use in this epidemic may be hazardous especially in patients with cardiovascular comorbidity.

The aim of this observational study is to describe the electrical effects of the combination of hydroxychloroquine and azithromycin for the treatment of COVID-19 by analyzing the surface ECG and to identify high-risk patients requiring close monitoring or discontinuation of treatment.

2. Methods

2.1. Study design and participants

This observational cohort study included patients residing in Morocco with COVID-19 diagnosis and were hospitalized in Cheikh Khalifa International University Hospital, Casablanca, Morocco between March 26 and April 20, 2020.

Cheick Khalifa International University Hospital, Mohammed VI University of Health Sciences in Casablanca (Morocco) is one of the major authorized hospitals by government for COVID-19 patients. Our study was approved by Ethics Committee of the Mohammed VI University of Health Sciences in Casablanca.

2.2. Diagnosis and grading of COVID-19

All consecutive patients with COVID-19 confirmed by positive Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) results on respiratory specimens admitted to Cheick Khalifa International University Hospital and who were treated with hydroxychloroquine and azithromycin were included. Patients with contraindications to this combination were excluded from this study.

According to the World Health Organization [1], patients can be divided into four types as mild, moderate, severe and critical types. Patients in severe type should meet one of the three criteria: respiratory distress and respiratory rate higher than

Abbreviation	
ACEI	angiotensin-converting enzyme inhibitors
AF	atrial fibrillation
ARB	angiotensin receptor blockers
AVB	atrioventricular block
COVID-19	Corona Virus Infectious Disease 2019
ECG	electrocardiogram
PCI	percutaneous coronary intervention
QTm	the measured QT interval
QTc	the corrected QT interval
RT-PCR	real-time reverse transcriptase polymerase chain reaction
TdP	torsades de pointes
VES	ventricular extrasystole

30 times per minute; fingertip blood oxygen saturation less than 93% at rest; partial arterial oxygen pressure (PaO2)/fraction of inspiration oxygen (FiO2) less than 300 mmHg. Patients with one of the three conditions are considered as critical type: respiratory failure, requiring mechanical ventilation; shock; multiple organ failure, requiring intensive care management.

In this work, we divided the patients in two groups: non-severe group (mild and moderate types) and severe group (severe and critical types).

2.3. Treatment of COVID-19

From March 26 to April 20, the hospital received 118 patients with confirmed COVID-19 infection. 118 patients received the treatment established by the Ministry of Health: combination of hydroxychloroquine at a dosage of 200 mgX2/day and azithromycin 500 mg on the first day then 250 mgX2 per day for 10 days. All patients had a cardiovascular consultation with ECG prior to treatment and were under clinical, electrical, biological monitoring.

2.4. Data collection

The clinical data of patients were collected from electronic medical records, including demographics, clinical symptoms and signs, co-existing conditions, imaging findings, laboratory results, treatment and clinical outcomes.

A 12-lead ECG is recorded on graph paper, with a standard calibration of the ECG signal, 1 mV = 10 mm and the speed of unwinding of the graph paper of 25 mm/s.

ECG analysis is done manually by two cardiologists who are part of this study (AE, SA). All ECG parameters were analyzed: P-wave measurement, PR interval, QRS, QT interval, T-wave with the

appearance of conduction and rhythm disturbance, and repolarization disorder.

QT intervals were measured manually from lead II or V5 or V6 (the longest value being used) of 12-lead ECGs from beginning of the earliest onset of the QRS complex to the end of the T wave. The end of the T wave was determined by extending a tangent from steepest portion of the downslope of the T wave until it crossed the T-P segment. During normal sinus rhythm, QT and RR intervals were averaged over three consecutive complexes. During atrial fibrillation, QT and RR intervals were averaged over all complexes on the 6 s rhythm strips [9−11].

QT intervals were corrected for heart rate using Bazett method and Fridericia: Bazett's formula is used for heart rates between 60 and 85 bpm, in case of heart rates < 60 bpm or > 85 bpm, Fridericia's formula is used [10,11].

$$\text{Bazett's formula: QTcB(ms)} = QTm\ (\text{ms}) \Big/ \sqrt[2]{RR(s)}$$

$$\text{Fridericia'sformula:QTcFri(ms)} = QTm(\text{ms}) \Big/ \sqrt[3]{RR(s)}$$

QTm: measured QT.

The value of normal QTc is variable according to age and gender. A normal QTc interval is < 440 ms in prepuberty, <430 ms in post pubertal males, and <450 ms in post pubertal females [10−12].

In patients with wide QRS(>120 ms), due to underlying intraventricular conduction defects or paced rhythm, we use the following formula to estimate QTc interval: wide QRS adjusted QTc = QTc - (QRS duration - 100 ms) [11,12].

ECGs were recorded in all patients before drug administration and repeated on the second, the fourth, and the sixth day, as well as after treatment. For patients with abnormalities, ECGs were performed at shorter intervals.

We measured the Tisdale score which is a score the risk of QTc prolongation of drug combinations in all patients. This score is based on clinical, biological and electrical data [13] (Table 1). If the score is > 11/21, there is a high risk of drug-associated QT prolongation.

2.5. Statistical analysis

After visually inspecting data, descriptive statistics was carried out. Continuous data were expressed as mean ± standard deviation and categorical parameters were computed as percentages, where appropriate. Based on the normality of data distribution, Student's t-test or the Mann−Whitney U test and chi-squared test were conducted to compare parameters between COVID-19 positive and negative individuals. Figures with p-values equal to or less than 0.05 were considered statistically significant. Statistical analyses were carried out by means of the commercial software "Statistical Package for Social Sciences" (SPSS for Windows, version 24.0, IBM Corp., Armonk, NY, USA).

3. Results

3.1. Demographic and clinical characteristic

Our cohort included 52 female patients (44%), and 66 male patients (55,9%). The average age was 46 years, with 10 patients under 18 years of age, and extremes from 6 years to 86 years.

75 (63%) patients had no particular medical history, 33 (27,9%) patients were hypertensive, 17 (14,4%) patients were diabetic, 8 (6,7%) patients had ischemic heart disease. Three patients had atrial fibrillation (AF): one patient had permanent AF on beta blocker and anticoagulation and two patients had paroxysmal AF on an antiarrhythmic drug (flecainide) and on anticoagulation (Table 2).

According to the clinical presentation of COVID-19 infection, 79 (66%) patients had a non-severe form and 39 (33%) patients had a severe form, requiring hospitalization in an intensive care unit. 55 (46%) patients were completely asymptomatic, and 24 (20%) patients complained of moderate symptoms like agnosia and anosmia. 41 (34%) patients had fever and 39 (33%) patients had a dry cough. No direct cardiac damage related to COVID-19 was reported in our study.

3.2. Electrocardiogram

We analyzed and compared the ECG performed before and after the initiation of treatment (after 2, 4 and 6 days).

Table 1. Risk Score For Drug-Associated QTc Prolongation: The Tisdale score [13]. ≤ 6 predicts low risk, 7−10 medium risk, and ≥11 high risk of drug-associated QT prolongation.

Risk Factors	Points
Age ≥68 y	1
Female sex	1
Loop diuretic	1
Serum K+ ≤3.5 mEq/L	2
Admission QTc ≥450 ms	2
Acute MI	2
If one QTc-prolonging drug	3
If ≥ 2 QTc-prolonging drugs	6
Sepsis	3
Heart failure	3
Maximum Risk Score	21

Table 2. Baseline characteristics of the 118 patients.

VARIABLE	TOTAL
Female	52 (44,06%)
Male	66 (55,93%)
Age, mean	46 years
Cardiovascular Risk Factors	
Hypertension	33 (27,96%)
Diabetes type I/II	17 (14,40%)
Smoking	15 (12,71%)
Dyslipidemia	30 (25,42%)
Overweight	12 (10,16%)
Known cardiovascular disease	
Ischemic heart disease	8 (6,77%)
Coronary bypass surgery	1 (0,84%)
Valvulopathy	4 (3,38%)
Congestive heart failure	1 (0, 84%)
atrial fibrillation	3 (2,54%)
Non-Cardiovascular Medical History	
Asthma/Allergy	8 (6,77%)
Hyper or hypothyroidism	4 (3,38%)
Depression/anxiety	4 (3,38%)
Kidney failure	1 (0,84%)
Neoplasm	2 (1,69%)
Vascular cerebral accident	2 (1,69%)
Alcohol	2 (1,69%)
Drug therapy	
beta-blockers	8 (6,77%)
ACEI/ARB	28 (23,72%)
calcium Inhibitor	14 (11,86%)
statin	12 (10,16%)
flecainide	2 (1,69%)
amiodarone	1 (0,84%)
Diuretic	6 (5,06%)
Platelet antiaggregant	15 (12,71%)
Antidepressant	3 (2,54%)
Sedative/hypnotics/anxiolytic/anti-psychotics	2 (1,69%)
Salbutamol	7 (5,93%)
COVID-related symptoms	
Cough	39 (33,05%)
Fever	41 (34,74%)
Asthenia	13 (11,01%)
Headache	6 (5,08%)
Digestive signs: diarrheal, vomiting	7 (5,93%)
Anosmia	14 (11,86%)
Agnosia	16 (13,55%)
Chest pain	22 (18,64%)
Dyspnea	22 (18,64%)
Palpitation	11 (9,32%)
Unconsciousness	0 (0%)
Asymptomatic	20 (16,94%)
COVID-19 severity	
Non-severe group	79 (66,94%)
Patient admitted on reanimation	39 (33,05%)
Death	9 (7,62%)

The results are presented in the Table 3.

a. The PR interval

Two patients presented with an extension of the PR interval. No atrioventricular conduction disorder was found.

Table 3. ECG parameter variability before and after treatment.

	ECG before treatment[a]	ECG after treatment[a]	p-value[b]
P wave (ms)	82,25 ± 15,7	84,59 ± 15,2	0,091
PR (ms)	150,11 ± 26,3	153,64 ± 28,9	0,036
QRS duration (ms)	85,72 ± 17,2	88,53 ± 18,4	0,013
Corrected QT (ms)	427,33 ± 39,2	443,70 ± 44,4	$<10^{-4}$
T wave (ms)	427,33 ± 39,2	443,70 ± 44,4	$<10^{-4}$

[a] Data indicated as mean ± SD.
[b] Paired samples t-tests for within-group comparisons of ECG changes before and after treatment.

b. The QT interval

The prolonged corrected QT is defined as >460 ms in prepuberty, > 450 ms in post pubertal males and >470 ms in post pubertal females [12].

After hydroxychloroquine and azithromycin combination treatment, 23 (19,49%) patients experienced QT prolongation. 18 patients (15.2%) increased their QTc by more than 40 ms (Fig. 1). QT prolongation occurs more in men, and in patients over 68 years of age. Hypokalemia was presented in only one patient with QTc prolongation.

In patients with prolonged QTc, Cardiovascular comorbidity (hypertension, diabetic, heart diseases) was present in 34%, the Tisdale score was ≥ to 7 in all patients. It was ≥11 in 5 patients.

69.5% of patients with QT prolongation were in severe COVID-19 infection, 4 of whom died as a result of the infection. The characteristics of patients with QTc prolongation are presented in Table 4.

The mean time to onset of these electrical signs was 2 days after the start of treatment.

Treatment was discontinued in 5 patients who had a prolonged QTc beyond 550 ms, with the appearance of ventricular extrasystole (VES) in two of them. No torsades de pointes (TdP) or severe rhythm disorders occurred.

c. Rhythm disorder

Four patients had ventricular extrasystole: Two patients had left delayed monomorphic VES without QTc prolongation, both patients are being followed for ischemic heart disease under treatment.

The other two patients had isolated monomorphic VES without bigeminism or trigeminism, their QTc increased from 525 ms to 546 ms for the first patient, and from 508 ms to 560 ms for the second patient, there was no dyskalemia. The combination of hydroxychloroquine and azithromycin was stopped.

A patient who had a paroxysmal AF under flecainide and anticoagulant was admitted initially in sinus rhythm. He had a long QT (540 ms) on the
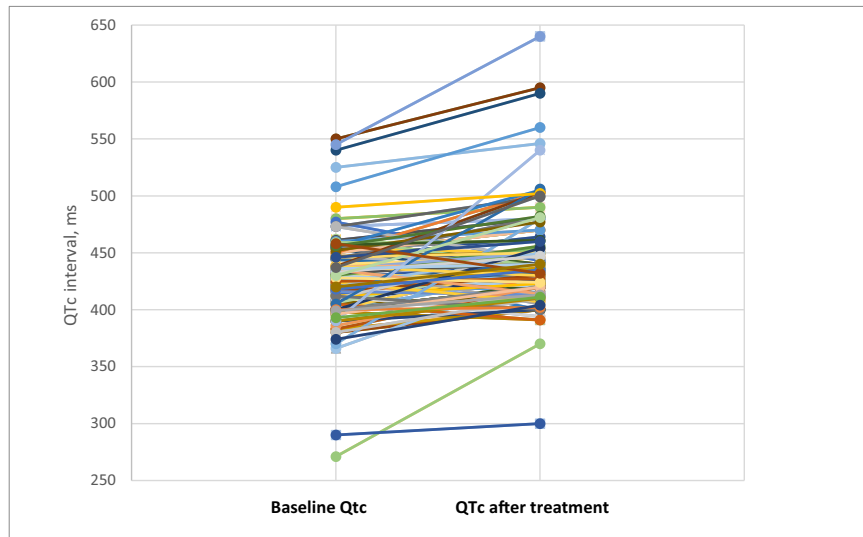
Fig. 1. Individual changes in corrected QT (QTc) interval.

second day of with recurrence AF despite being on flecainide. The combination of hydroxychloroquine and azithromycin was stopped. The patient returned to a sinus rhythm and to a normal QT space.

A patient with permanent AF on betablocker and anticoagulant therapy had a reduction in AF and returned to sinus rhythm without QT prolongation.

d. Repolarization disorder:

T-wave elongation was observed in 30%. U wave exaggeration was observed in 19% of patients.

e. Morphological abnormality

P-wave elongation was observed in 5%.
No electrical signs of left ventricular hypertrophy were observed after treatment. (Cornell and Sokolow indexes increased by 1%)

The heart axis hasn't changed.

4. Discussion

Hydroxychloroquine have a long-standing history in the prevention and treatment of malaria and the treatment of chronic inflammatory diseases including systemic lupus erythematosus and rheumatoid arthritis. And for its antiviral action, it is used in the treatment of COVID-19 [14,15].

The toxic effects of hydroxychloroquine are well detailed and described in the literature. Cardiac toxicity of hydroxychloroquine is uncommon, it can be either a rhythm disorder with prolonged QTc and risk of sudden death, or conduction disorder, or cardiomyopathy. These toxic effects depend on the duration of exposure and cumulative dose, so there may be acute toxicity from high doses or toxicity from chronic exposure [16].

Table 4. Characteristics of patients with QTc prolongation.

	QTc normal (n = 95)	Prolonged QTc (n = 23)	P value
Gender:			0,043
Female	47 (49,47%)	6 (26,08%)	
Male	48 (50,52%)	17 (73,91%)	
Age> 68	11 (11,57%)	7 (30,43%)	0,014
kalemia			0,82
hypokalemia	2 (2,10%)	1 (4,34%)	
hyperkalemia	3 (3,15%)	1 (4,34%)	
Cardiovascular comorbidity	7 (7,36%)	8 (34,78%)	0,013
Tisdale risk score			<0,001
≤6	77 (81,05%)	9 (39,13%)	
Between 7 and 10	16 (16,84%)	9 (39,13%)	
≥11	2 (2,10%)	5 (21,73%)	
Initial QTc≥ 500 ms	1 (1,05%)	5 (21,73%)	<0,001
Severe form of COVID-19	17 (17,89%)	16 (69,56%)	<0,001

In the context of COVID-19, the wide prescription of hydroxychloroquine is not safe: hydroxychloroquine is prescribed at high doses for a shortened duration in combination with azithromycin, also known for its proarrhythmic properties, and this in patients who may have comorbidities, or a severe infectious form [17].

QTc prolongation du to hydroxychloroquine are the consequence of the quinidine-like membrane stabilizing action, type IA according to the Vaughan and Williams classification. It is mainly due to the blocking of the sodium channels of the cardiac cell [18].

QT prolongation was observed in 19% of patients, which is slightly higher to what has been reported in patients with COVID-19 receiving hydroxychloroquine in a U.S. study (11.0%) or a Brazilian study (15%) [19,20].

QTc prolongation is dose-dependent, Borba et al. conducted clinical trial testing two doses of chloroquine in patients with COVID-19. They planned to include 440 patients but stopped after 81 patients were enrolled due to excessive QTc prolongation and a higher mortality in the high-dose group (patients receiving 1200 mg daily for 10 days) compared to the low-dose group (in which patients received 450 mg daily for 4 days after an initial dose of 900 mg on the first day) [20]. QTc prolongation was observed in 11% of patients on low dose, and in 18.9% of patients on high dose. However, in this study they used chloroquine diphosphate which is more toxic than hydroxychloroquine, and patients received in addition to chloroquine diphosphate, azithromycin, ceftriaxone, and Oseltamivir who also have been implicated in QTc prolongation and proarrhythmic events. The COVID-19 forms were more severe.

In our study, severe and critical forms of COVID-19 are less frequent, with a slightly lower mortality rate.

The factors associated with QTc prolongation were: age >68 years, male gender, cardiovascular comorbidity, Tisdale score ≥11, and a severe form of COVID-19.

QTc prolongation is more frequent in men (odds ratio 2.8; P value 0,043), it is similar to what has been described in Chorin study [19]. In the clinical trial by Borda et al. [20], frequency was similar between men and women. Apart from COVID-19, Tisdale reported a more frequent risk of QTc prolongation in women [13].

Age over 68 years is a factor associated with QTc prolongation as reported in several studies (P value 0,014). Cardiotoxicity may be enhanced by older age, pre-existing cardiac disease and renal insufficiency.

In our series, diabetes alone is not a predisposing factor for QTc prolongation. However, the combination of comorbidities such as hypertension, diabetes, heart diseases and kidney failure are predisposing factors. Conversion enzyme inhibitors and calcium channel blockers have not shown a causal relationship with electrical abnormalities. Dyskalemia is not a predisposing factor for QTc prolongation in our study unlike what was reported by Tisdale et al. [13].

A severe COVID-19 infection form is associated with a high risk of QTc prolongation, which may be explained by sepsis with multivisceral failure. This has been reported in several studies [13,20].
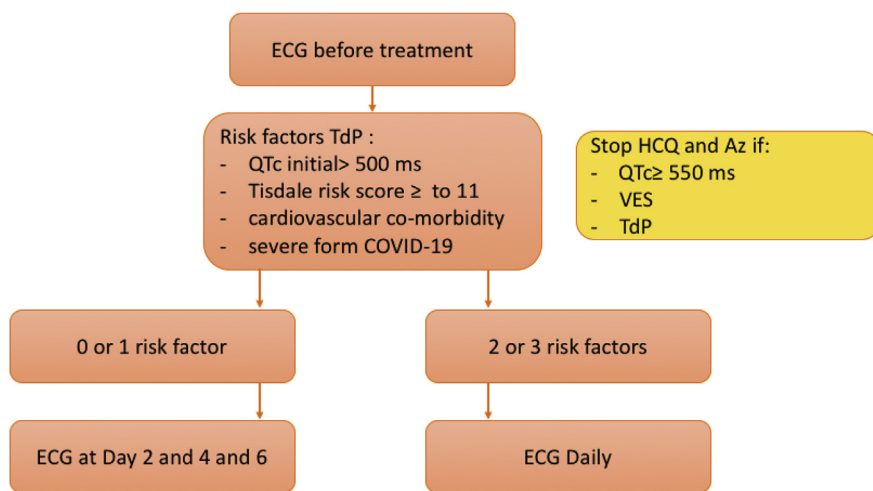

Fig. 2. Protocol proposing for electrical monitoring of patients with COVID-19. QTc: corrected QT, VES: ventricular extrasystole, TdP: torsades de pointes.

In the context of COVID-19, the addition of azithromycin to hydroxychloroquine is associated with greater QTc prolongation according to recently published studies [21,22].

QTc interval prolongation can be considered as a prognostic criterion for the inherent severity of COVID-19 infection, in addition to the need to discontinue first-line therapy [21].

Other electrical abnormalities described in the literature as severe conduction disorders have not been reported in our series [23]. We observed moderate P-wave elongation and QRS widening, and it is similar to what has been described in the long-term use of the treatment [24].

The Moroccan and American Society of Cardiology recommendation focus on baseline risk assessment, frequent QTc monitoring, and strict cutoffs for therapy cessation [6, 25].

Finally, the introduction of combined hydroxychloroquine and azithromycin therapy requires a rigorous follow-up of the patients, we propose the following protocol for monitoring patients with COVID-19 (Fig. 2).

5. Conclusions

The combination of hydroxychloroquine and azithromycin is not safe in the context of COVID-19. QTc prolongation is a real risk. Therefore, it is necessary to identify high-risk rhythmic patients in whom ECG monitoring should be performed very closely. Treatment should be discontinued if there are any alarming signs: QTc> 550 ms or appearance of VES, or TdP.

6. Limits

The main limitation of the study is the limited number of patients included. Viral cardiac involvement was not completely ruled out in all patients, extensive cardiac workup was performed only in symptomatic patients.

Author contribution

Conception and design of study: Amal El Ouarradi, Salma Abdeladim, Sara Oualim, Mohamed Sabry. Literature review: Amal El Ouarradi, Salma Abdeladim, Sara Oualim, El Arbi Bouaiti. Acquisition of data: Amal El Ouarradi, Rita Aniq Filali, Ilham Bensahi, Mahassine Elharass, Sara Hafid, El Arbi Bouaiti. Analysis and interpretation of data: Amal El Ouarradi, El Arbi Bouaiti, Abdelhamid Moustaghfir, Mohamed Sabry. Analysis and interpretation of data: Amal El Ouarradi, Abdelhamid Naitlhou, El Arbi Bouaiti. Research investigation and analysis: Amal El Ouarradi, Rita Aniq Filali, Ilham Bensahi, Mahassine Elharass, Hamza Tazi. Research investigation and analysis: Amal El Ouarradi, El Arbi Bouaiti, Abdelhamid Moustaghfir. Drafting of manuscript: Amal El Ouarradi, Salma Abdeladim, Rita Aniq Filali, Ilham Bensahi, Mahassine Elharass. Revising and editing the manuscript critically for important intellectual contents: Amal El Ouarradi, Salma Abdeladim, Sara Oualim, Sara Hafid, Hamza Tazi, Abdelhamid Naitlhou. Data preparation and presentation: Amal El Ouarradi, Sara Hafid, Hamza Tazi, El Arbi Bouaiti. Supervision of the research: Abdelhamid Naitlhou, El Arbi Bouaiti, Mohamed Sabry. Research coordination and management: Abdelhamid Moustaghfir.

Declaration of interests

All authors declare no competing interests.

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