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Preliminary data from the retrospective and prospective observational studies on NSTEMI patient management in Moldova

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Abstract

Background: The outcomes of NSTEMI patients are known to be worse than those of STEMI patients and depend on guideline-directed management. The higher the rate of adherence to guideline recommendations the better the prognosis and outcomes of usually high-risk NSTEMI patients. The best efforts should be made to rapidly and correctly diagnose and manage this condition in order to achieve the best results.
Material and methods: An observational retrospective study was conducted in 3 PCI centers in Chisinau, Moldova, that included all patients hospitalized with NSTEMI through 2019. Another observational prospective study was conducted in the same 3 PCI centers with the consecutive inclusion of all NSTEMI patients in 2020-2021 and established follow-up dates.
Results: Extensive preliminary data from both studies based on 215 patients is presented and compared to that of the FAST-MI registry in France, as an example of care in a developed country.
Conclusions: Preliminary data has contoured a picture of NSTEMI patients management in Chisinau and has already detected major drawbacks to be corrected. The follow-up data will provide more insights on patient outcomes and correlations between management, short-term and long-term outcomes, whereas different biomarkers will be tested for diagnostic and prognostic values. Similar studies are needed in regional hospitals in order to assess the situation in these areas and search for improvement solutions.
Key words: myocardial infarction, NSTEMI, ACS, observational study, STEMI.

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Introduction

The recent decline in cardiovascular mortality in developed countries has been attributed to aggressive primary prevention as well as to the progress made in the treatment of established CVD. A large number of registries has been conducted over time to assess whether clinical practice guidelines have translated in better outcomes for patients with myocardial infarction in daily practice [1]. Observational studies are meant to illuminate the medical reality in a situation where clinicians are usually quite inert at integrating changes proposed by new guidelines into their daily routine. Often, it is somewhat complicated for them to recognize in the sophisticated design of clinical randomized trials that are held in ideally controlled conditions and have strict inclusion criteria, their own population of patients in a setting where all that matters are not the theoretically correct treatment but the one that has already been administered and the results of this treatment. Observational registries in the area of myocardial infarction have over a 100-year history [2]. Among the most well-known in Europe are the SWEDEHEART registry in Sweden and the FAST-MI in France. Currently the NSTEMI Registry of the EORP, a multicenter prospective observational study that started in 2019 is still enrolling patients. The Republic of Moldova is also participating with 4 centers having already included NSTEMI patients. The aim of the study is to elucidate the gaps in the management of NSTEMI patients in different countries compared to the standard of care stated in the current clinical practice guidelines and to report its results to the ESC [3]. At the same time the department of Interventional Cardiology of the Institute of Cardiology in Chisinau has initiated two observational studies (one retrospective and one prospective) with the participation of 3 hospitals that have catheterization labs on-site as a part of the scientific project "Evaluation of instrumental and biochemical markers in management of patients with acute myocardial infarction without ST segment elevation, and assessment of coronary microvascular dysfunction degree".

The data of the patients hospitalized in these hospitals (Institute of Cardiology, Novamed polyvalent hospital and Sfanta Treime municipal hospital) during 2019 with a final diagnosis of NSTEMI has already been analyzed, while ongoing is the prospective study that started in 2020. The study's aim is similar to that of the European registry – to locally assess the gaps in the management of NSTEMI patients in the PCI centers in Chisinau compared to the standard of care. After the analysis of the obtained data and also in accordance with the new ESC guidelines for the management of patients with ACS presenting without persistent ST elevation a local national guideline will be elaborated adapted to local health care conditions. It is universally known that the higher the level of adherence to guideline recommended care in NSTEMI patients the better the short- and long-term outcomes. Therefore, raising the level of this adherence will result in a better prognosis for these patients [4]. In theory we all know what we are supposed to do and how we should treat specific conditions, but in real life-settings different obstacles and clinical challenges make the choices we make for the patient's benefit much more complicated and harder to comply with what the guideline tells us to do.

General information

A retrospective observational study was conducted including all patients diagnosed with NSTEMI in 2019 in 3 participating hospitals with 24/7 on-site PCI. At the same time a prospective observational study that included consecutively all patients with NSTEMI started in the same hospitals in 2020 and is still ongoing, being considered a sequel of the retrospective one. We present the preliminary data from both studies, the fulfillment of objectives 3 to 7 is expected to happen in 2021-2022.

Study objectives

1. Collection of extensive descriptive data on patients with NSTEMI hospitalized in PCI centers of Chisinau.

2. Assessment of management strategy tendencies in everyday practice in these centers.

3. Assessment of gaps in diagnosing and management of NSTEMI patients as well as the level of adherence to the ESC guidelines for the management of NSTE-ACS.

4. Evaluation of MACE rate and structure (mortality, non-fatal-MI, stroke, unstable angina) in patients with NSTEMI compared to STEMI patients after a 12-th month follow-up period.

5. Determination of any correlation and its type between management strategies and outcomes, both short-term and long-term.

6. Determination of the diagnostic and prognostic role of diverse biomarkers in addition to those mentioned in the guidelines for NSTEMI patients.

7. Comparison of the obtained results with the data from the NSTEMI Registry of the EURObservational Research Programme 2019 when published.

Material and methods

Study design

1. An observational retrospective study was conducted in 3 PCI centers in Chisinau, Moldova, that included all patients hospitalized with NSTEMI through 2019. All the data has been analyzed, with a partial patient follow-up.

2. An observational prospective study was conducted in the same 3 PCI centers with the consecutive inclusion of all NSTEMI patients in 2020-2021, follow-up dates established for 30 days, 6 months and 12 months.

Inclusion criteria

1 Patients of 18 years of age and older.

2. Patients with an established NSTEMI diagnosis according to the Universal definition of Myocardial Infarction, without persistent elevation of ST segment, type 1 MI [3].

Organizational moments

For the retrospective study all charts of patients diagnosed with NSTEMI during 2019 in the above mentioned hospitals were selected, excluding those that did not correspond to the inclusion criteria. The prospective study started in 2020 and is currently enrolling consecutively all patients with NSTEMI, that are daily selected from all acute coronary syndromes patients in every hospital.

Data collection

A special questionnaire was elaborated based upon the one from NSTEMI Registry of the EURObservational Research Programme 2019 and adapted to local conditions, consisting of 178 questions. Aside from demographic information, cardiovascular and non-cardiovascular disease history was collected (neurological, renal, pulmonary and oncological), patients' risk factors (smoking status, hypercholesterolemia, diabetes mellitus, obesity, family history of cardiovascular disease, arterial hypertension). Clinical data while in hospital included symptoms at admission and complications during the hospital stay. Investigations data included LVEF, a set of biochemical parameters and other laboratory findings. The therapeutic and interventional management of patients and their timing were also a part of the questionnaire. The established patient follow-up dates were 30 days, 6 months and 12 months. It is important to mention that the management of patients did not include any mandatory actions, being 100% at the physician's discretion. During statistical analysis the mean values and their errors have been calculated, as well as the frequencies of descriptive parameters in percent, valid percent and absolute values.

Patient follow-up

Patients are contacted through telephone at 1, 6 and 12 months, being interrogated about hospital admissions to a cardiology or neurology ward, causes of these admissions and disease complications.

Results

At the moment of this report being written a total of 215 patients that met the inclusion criteria were enrolled into both stu-dies, 83 out them in the Institute of Cardiology,

76 in Sfanta Treime hospital and 64 in Novamed Polivalent hospital. 30 patient charts from the Institute of Cardiology and 2 charts from Novamed Polivalent hospital with a diagnosis of I214 (non-Q myocardial infarction) did not fit into the inclusion criteria, therefore were excluded from the study.

Baseline patient characteristics

The mean age of patients was 66 years (s=10.406), 40.5% (n=87) being females and 59.5% (n= 128) – males. The most common risk factor was arterial hypertension present in 93.9% (n=200) of cases, followed by hypercholesterolemia in 68.1% (n=141) of patients, diabetes mellitus in 37.4% (n=79) and obesity in 27.3% (n=48). The least common risk factor was current smoking found in only 22.7% (n=40) of cases. These data resemble the French cohort of patients from the FAST-MI registry, although arterial hypertension being found only in 63% of cases with NSTEMI. A little less NSTEMI patients in France have hypercholesterolemia – 50% vs. 68.1% in our studies. The current MI episode was the first CV event for 74% (n=159) of patients in Moldova vs. 68% of patients with NSTEMI in France. Cardiovascular disease history included chronic heart failure in 60.8% (n=129) of patients, old MI in 23.7% (n=51) and atrial fibrillation in 18.7% (n=40). 10.7% (n=23) had a previous stroke and 7.9% (n=17) had PAD. Only 4.2% (n=9) of patients had a CABG performed at some point of their lives. The most frequent non-cardiac comorbidity was chronic kidney disease found in 17.8% (n=38) of patients. 13.1% (n=28) were diagnosed with COPD in the past and only 1.6% (n=3) had active cancer [1].

The most frequent class of medication taken by patients before the current episode was ACE-inhibitors and AR-blockers, reported in 66.4% (n=140) of cases, followed by aspirin administered by 61.1% (n=129) of patients, beta-blockers in 49.2% (n=104) and diuretics in 25.8% (n=54) of cases. Unfortunately, statins were only taken by 10.8% (n=23) of patients before the episode, most of which – 7.5% - in small doses. In contrast, statins were on the list of 37% of patients before the NSTEMI episode in France, whilst the rate of aspirin intake is substantially lower than in Moldova – 33% – in accordance with a quite reserved recent aspirin prescription tactics in primary prevention [1, 5].

Table 1

Baseline, demographic data, risk factors, cardiovascular and non-cardiac history

Population with NSTEMI studied (n=215)	
Demographic data	
Institute of Cardiology	83
Novamed Polivalent Hospital	64
Sfânta Treime Hospital	76
Age, years	66.09, S=10.406
Women	40.5% (87)
Men	59.5% (128)
Body mass index	27.9731 S=4.63648
Risk factors	
Arterial hypertension	93.9% (200)
Hypercholesterolemia	68.1% (141)
Diabetes mellitus	37.4% (79)
Current smoking	22.7% (40)
Family history of CVD	17.7% (38)
Obesity	27.3% (48)
CVD history	
Fist CV event	74%, (159)
Old MI	23.7% (51)
History of CABG	4.2% (9)
Chronic heart failure	60.8% (129)
Atrial fibrillation	18.7% (40)
Previous stroke	10.7% (23)
PAD	7.9% (17)
Non-cardiac comorbidities	
Chronic kidney disease	17.8% (38)
COPD	13.1% (28)
Active cancer	1.6% (3)

Table 2

Pre-episode medication

Medication	Population with NSTEMI studied (n=215)
ASA	61.1% (129)
P2Y12 Inhibitor	11% (23)
Statins	10.8% (23)
Statins: low doses	7.5% (16)
Statins: standard doses	3.3% (7)
Beta-blockers	49.2% (104)
ACEI and ARB	66.4% (140)
Aldosterone antagonists	15.6% (33)
Diuretics	25.8% (54)
Oral anticoagulants	5.6% (12)
Antidiabetic drugs	30.9% (66)
DAPT	11% (23)
ARNI	0
PPI	1.4% (3)
Ivabradine	0
H2 receptor antagonists	0.9% (2)

The most characteristic complaint of NSTEMI patients upon admission was typical chest pain present in 94.4% (n=203) of cases, frequently accompanied by shortness of breath in 82.8% (n=178) of patients, as well as increased fatigability in 78.6% (n=169). Fewer patients presented with palpitations – 40.9% (n=88), nausea and vomiting in 16.3% (n=35) of cases. Most of the patients were brought with a Killip class of I and II – 40.9% (n=88) and 40.5% (n=87) of cases respectively. The mean heart rate at admission was 82.51 (s=20.923) per minute. The mean systolic blood pressure upon admission was 140.64 (s=28.455) mm Hg, whereas the mean GRACE score was 84.689 (s=55.95) points. It is quite important to mention that no scores were calculated initially in any of the charts presented, all of the calculations being made after the charts were analyzed during data

collection for the study. The quite low GRACE scores compared to those reported in the FAST-MI study for NSTEMI patients (139 ± 37) probably need to be revaluated. In only 61% (n=130) of cases the diagnosis on admission was actually NSTEMI, followed by unstable/aggravated angina in 17.4% (n=37). Unfortunately, high sensitivity troponin was used on admission in only 21 % (n=47), the mean value for it being 347.5289 (s=687.40176) [1]. The most common ECG presentations are listed in the table below.

Table 3

Current episode, clinical and laboratory findings

Symptoms upon admission	Population with NSTEMI studied (n=215)
Typical angina	94.4% (203)
Dyspnea	82.8% (178)
Fatigability	78.6% (169)
Palpitations	40.9% (88)
Asymptomatic	1.9% (4)
Nausea/vomiting	16.3% (35)
Atypical chest pain	2.8% (6)
Cardiac arrest/syncope	2.8% (6)
Killip class on admission	
I	40.9% (88)
II	40.5% (87)
III	14% (30)
IV	4.7% (10)
Localization of the infarction	
Anterior	26.5% (57)
Inferior	15.8% (34)
Other	46.1% (99)
Diagnosis on admission	
STEMI	6.6% (14)
NSTEMI	61% (130)
Unstable/de novo angina	7% (15)
Unstable/aggravated angina	17.4 % (37)
Unstable/peri-infarct angina	2.3% (5)
Other	5.6 % (12)
ECG at presentation	
Sinus rhythm	86.5% (186)
Atrial fibrillation	13.5% (29)
LBBB	5.1% (11)
RBBB	6.5% (14)
Heart rate on admission	82.51 (s=20.923)
Systolic blood pressure	140.65 (s=28.455)
Diastolic blood pressure	83.13 (s=14.542)
GRACE score	84.689 (s=55.95)
TIMI score	5.72 (s=6.703)
CRUSADE score	35.34 (s=16.221)
Creatinine	112.7507 (s=85.3008)
Hemoglobin	130.877 (s=20.4493)
LDL-c	3.2963 (s=1.0902)
HDL-c	1.2626 (s=0.35145)
Triglycerides	1.8306 (s=0.95976)
High sensitivity troponin	347.5289 (s=687.40176)

Sadly, the time-lapse from the first symptoms to hospital admission is extremely high – the mean of it being almost 12 hours, whereas in France it is of only 155 minutes in NSTEMI patients and 90 minutes for STEMI. Most of the patients were admitted to an intensive care unit – 61.4% (n=132), another 38.6% (n=83) ended up in a cardiology ward. 84.7% (n=182) of the patients got a coronary angiography at some point during their hospital stay, in France this indicator being at 95% of NSTEMI patients. 96.6% (n=172) of patients had a radial puncture, surprisingly almost 10% more than in the FAST-MI registry. The mean time from admission to cath lab in Chisinau was about 26 hours, the majority – 73.1% (n=133) being in the first 24 hours of hospital stay. Percutaneous angioplasties were performed in 63.7% (n=137) of those who got catheterized, most of which happened in the same session as the initial coronary angiography. Drug eluting stents were implanted in 89.6% (n=121) of cases, demonstrating almost the same results as in France [1]. After admission DAPT was given to 82.4% (n=169) of patients, to 85.7% (n=144) of which in the first 24 hours. Among the 3 participating centers only the Institute of Cardiology has cardiac surgery on-site, therefore just two patients from the whole study had a CABG performed during their hospital stay, representing 0.9% of all cases.

Table 4

Management on admission and during hospital stay

Population with NSTEMI studied (n=215)	
Time from pain start to admission (hours)	11.9884 (s=24.8055)
Time from admission to coronary angiography (hours)	25.7115 (s=46.17695)
DAPT on admission	82.4% (169)
DAPT<24 hours from admission	85.7% (144)
DAPT 24-48 hours from admission	6.5% (11)
DAPT >48 hours from admission	7.7% (13)
Place of admission	
Intensive care unit	61.4% (132)
Cardiology ward	38.6% (83)
Admission method	
Ambulance	75.8% (163)
Outpatient clinic transfer	8.4% (18)
Transfer from another hospital	14.4% (31)
Other	1.4% (3)
Interventional treatment	
Coronary angiography	84.7% (182)
Coronary angiography <24 hours	73.1% (133)
Coronary angiography >24 hours	26.9% (49)
Conservative management	15.3% (33)
PCI	63.7% (137)
PCI in the same session of CA	95.5% (131)
PCI <2 hours from admission	26.7% (36)
PCI <24 hours from admission	51.1% (69)
PCI <48 hours from admission	6.7% (9)
PCI >48 hours from admission	15.6% (21)

Type of stent	
DES	89.6% (121)
BMS	0.7% (1)
Balloon angioplasty	8.9% (12)
Vascular access	
Radial	96.6% (172)
Femoral	2.8% (5)
Other	0.6% (1)
Planned CABG in another hospitalization	2.8 % (6)
CABG during hospital stay	0.9% (2)

The treatment while in the hospital included statin administration, however in just 79% (n=169) of cases, close to the 78% in France [1]. Standard statin doses were given to 59.8% (n=126) of patients. 81.3% (n=148) received LMWH, unfractionated heparin being administered in only 4.4% (n=8) of cases.

Table 5

Medication during hospital stay

	Population with NSTEMI studied (n=215)
DAPT	82.4% (169)
Unfractionated heparin	4.4% (8)
LMWH	81.3% (148)
Fondaparinux	1.6% (3)
Statins	
Low dose	8.4% (18)
Standard dose	59.8% (126)
High intensity	11.7% (25)

The most frequent complication during hospital stay in NSTEMI patients was pulmonary edema reported in 16.3% (n=35) of cases, followed by cardiogenic shock in 13% (n=28) of patients. 9.3% (n=20) suffered from acute heart failure and 7.9% (n=17) had a cardiac arrest. In-stent thrombosis occurred in only 0.9% (n=2) out of those who received a stent. Hemorrhages emerged in 2.5% (n=5) of cases. The mean length of hospital stay was 7.55 (s=5.419) days, being similar to that in the FAST-MI registry (7.33 ± 9.0 days) [1].

Table 6

Complications during hospital stay, in-hospital mortality, mean length of hospital stay, place of discharge

Complications during hospital stay	**Population with NSTEMI studied (n=215)**
LVEF %	
>=50%	51.6% (111)
40-49%	29.8% (64)
<40%	7.4% (16)
<=35%	10.7% (23)
Cardiogenic shock	13% (28)
Recurrent MI	3.7% (8)
In-stent thrombosis	0.9% (2)
Cardiac arrest	7.9% (17)
Stroke	1.4% (3)
Hemorrhage	2.3% (5)
Death	8.4% (18)
Acute heart failure	9.3% (20)
Pulmonary edema	16.3% (35)
PE	1.9% (4)
VT/VF	9.3% (20)
Mechanical complication (myocardial rupture)	0.5% (1)
Mean length of hospital stay	7.55 (s=5.419)
Discharge	
Home	73.5% (158)
Rehab	15.8% (34)

At discharge among the prescribed medication ASA was in the top with 90.5% (n=180), beta-blockers prescribed to 89.9% (n=179) of patients, ACEI/ARB in 85.9% (n=170), clopidogrel in 82.3% (n=163) and statins in 61.2% (n=120), more than a half of those receiving standard statin doses. 10.7% (n=21) were given oral anticoagulation, PPI being given with DAPT in 37.8% (n=74) of cases [1].

Table 6

Medication at discharge

	Population with NSTEMI studied (n=215)
ASA	90.5% (180)
Clopidogrel	82.3% (163)
Statins	61.2% (120)
Statins low doses	13.8% (27)
Statins standard doses	35.7% (70)
High intensity statin doses	11.7% (23)
Beta-blockers	89.9% (179)
ACEI/ARB	85.9% (170)
Oral anticoagulation	10.7% (21)
Metformin	19.5% (39)
Insulin	9% (18)
PPI	37.8% (74)
Diuretics	39.3% (77)
H2-receptor antagonists	6.1% (12)

Discussion

The level of participation in the studies of the three centers is relatively high, the overall picture that has started to contour being quite representative, however we must not forget that the given situation only refers to the population from the capital and suburbia that have 4 PCI 24/7 hospitals available at their service. Respectively, the situation concerning ACS management, especially those without ST elevation, outside this area remains on the dark side and is probably substantially different i.e. a lot worse than the one we have studied.

The baseline NSTEMI patient characteristics are close to those reported in the FAST-MI study, with some minor differences mentioned above. The enormous time from symptom onset to admission is very alarming, being almost

4 times greater than the same indicator in France. We could probably speculate that in the COVID-19 era the fear makes the uninstructed about chest pain danger and need to seek urgent medical care population wait at home without soliciting an ambulance until the pain is unbearable or some complications arise. The rate of actual NSTEMI diagnosis at hospital admission is 61%, it being probably a lot higher had the high sensitivity troponin been applied. The causes of its seldom use in the emergency department could be different. Often (historically here), this kind of lab work is not available due to test lack, the first contact physicians actually having to work with either a qualitative troponin or a simple quantitative test, that does not provide high sensitivity testing. In our study we tested the first blood collected from patients with a diagnosis of unstable angina in the emergency department with a high sensitivity troponin test and had many sufficiently positive results bringing the number of patients that could be early diagnosed with NSTEMI. Therefore, initial testin of all unstable anginas in the emergency department or even in the ambulance with a high sensitivity test would raise the number of early diagnosed NSTEMI [6-9]. The access to coronary angiography is surprisingly in a good way high, once the patient is admitted and diagnosed with NSTEMI, being almost 85%, which is still by 10% lower than in France [1]. The vascular access site is a radial access in 9 out of 10 patients, being in accordance with the current guidelines [10-11]. The vast majority of patients that undergo coronary angiography, most of them in the first 24 hours from admission, will also receive a stent in 95% of cases, a drug eluting stent in almost 90% of those [12-14]. There is still a lot of work to be done concerning the use and dosage of statins during hospital stay and after discharge. Clopidogrel remains the only $P2Y_{12}$ inhibitor available on the market, waiting for other recommended $P2Y_{12}$ inhibitors [15] to become available, DAPT being administered in more than 80% of cases. A large number of patients treated during COVID-19's charts are still in the process of analysis. We are awaiting a rise in mechanical MI complications and in-hospital mortality rate as a result of extremely late admission of NSTEMI (and even STEMI) patients. However, apart from in-stent thrombosis rates, the rest of in-hospital complications are still a lot more common than reported by French investigators [1]. The mean length of hospital stay is similar in both countries but we expect it to fall in the context of the pandemic, in the attempt to reduce the time of patient contact with the medical care system. The weak point of all hospitals is unfortunately the access to cardiac surgery that has only become available since 2020 in the Institute of Cardiology, all of the emergency surgeries performed before 2020 had to be arranged via a transfer to another hospital.

At this moment the first three objectives of the study are already contouring, ongoing is the prospective study of patient enrollment and the follow-up of patients from the retrospective part of the study, in order to determine the possible correlations between the management of patients and the short- and long-term outcomes. The collection of biologic material from the patients is aimed at multiple biomarker panels testing additional to those mentioned in the guidelines, exploring their role in patient diagnosis and their prognostic values. We are awaiting the results of the NSTEMI Registry of the EURObservational Research Programme 2019, which is still enrolling patients, but is going to provide extended data about NSTEMI patient management in different countries, not just developed ones, describing lacunas and creating possibilities of their correction on a way of a better health care and prognosis for NSTEMI patients.

Conclusions

Observational studies are a relatively simple and cheap tool for assessing real life situations in everyday medical practice and comparing them with the guideline recommended standard of care [16]. Preliminary data from the observational studies, one retrospective and one prospective have already revealed several drawbacks that need to be corrected while the prospective study continues. Some major drawbacks as the underuse of high-sensitivity troponin and the time lapse from symptom onset to admission need to be addressed as soon as possible, taking into account the possible aggravation of situation due to COVID-19 in 2020 where people with chest pain hesitate even more before soliciting an ambulance. While there are rather small differences in patient profile between Chisinau and data from a developed country like France, the differences in in-hospital complications might suggest we are going to see a similar trend in short- and long-term outcomes. As the next results become available the search for clinical mishandling and its possible solutions continues [1]. Hopefully, enough data is gathered and its analysis will allow us to publish a local clinical practice guideline for the management of patients presenting with ACS without ST segment elevation that will be based on the ESC guideline, but will take into account local possibilities. In order to provide extended information on the situation outside the capital and the suburbia, similar assessment is needed in the regional hospitals aiming at their integration into one system of acute coronary syndrome care in a small country like Moldova, eliminating time and distance discrimination and providing equal access with an adequate timing to PCI centers for patients from any small village. This means focusing on a serious update of the current available STEMI programme and transforming it into acute coronary syndrome programme.

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AP and MP conceptualized the project and drafted the first manuscript. MI and OD interpreted the data. VI, LC, and IP critically revised the manuscript. All authors revised and approved the final version of the manuscript.

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Conflict of Interests
No competing interests were disclosed.