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ORIGINAL RESEARCH

Clinical and paraclinical characteristics of young patients with myocardial infarction from Northeast of Romania

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Abstract

The aim of this study was to evaluate the clinical and paraclinical features in young patients (18–40 years) with acute myocardial infarction (AMI) in the Northeast of Romania. We have considered all patients admitted between the 1st of January 2017 through the 31st of December 2019 at a tertiary care Cardiology Institute with the primary discharge diagnosis of AMI. These patients have been split into 2 groups depending on their age: the first group consisting of patients with an age equal to or lower than 40 years old and the second group consisting of patients with an age greater than 40 years old. After this, we have randomly selected a representative sample from each of the two groups. A total of 99 patients were ultimately enrolled in the study: 42 in the first group and 57 in the second group. Data collected included age, gender, medical history, laboratory tests, echocardiography parameters, coronarography study results, and case outcome. Most young patients with myocardial infarction were male, more likely to smoke (69% vs 35.1%, $p = 0.001$), and with a positive family history of cardiovascular diseases (35.7% vs 1.8%, $p < 0.001$) in comparison to their older counterparts. Also, they had fewer comorbidities, such as diabetes mellitus, hypertension, or a positive history of stroke or atrial fibrillation. Mean ejection fraction was significantly higher in young patients (43.4 ± 10.65 vs 37.16 ± 10.77, $p = 0.005$) and both tricuspid and mitral valve regurgitations were less severe. Coronary lesions were more severe in the older patients ($p = 0.009$), usually with more coronary arteries involved. No significant difference was recorded in the number of hospitalization days or in the case outcome. Acute myocardial infarction in young patients typically occurs more in men who smoke, those who are more than 30 years old, and those who have a positive family history of cardiovascular diseases. Echocardiographic parameters seem to be better than in the case of older patients and the coronary involvement is usually less severe.

Keywords

Myocardial infarction; Young adults; Cardiovascular risk factors; Mortality

1. Introduction

Cardiovascular and cerebrovascular diseases are a leading cause of death and lifelong disability worldwide, therefore, the need for effective prevention and management strategies is warranted [1]. Moreover, cardiovascular diseases (CVD) tend to affect older populations disproportionally [2]. It is well known by now that aging plays a critical role in cardiovascular diseases [3]. Older people tend to have more classic cardiovascular risk factors and also, cardiovascular diseases tend to be more prevalent [4]. Considering this, there are only few data regarding the features of myocardial infarction in younger populations and the specific factors involved.

The definition of a young person with an AMI is not well established. Studies tend to vary when it comes to the inclusion age, some go as low as 40 [5, 6] while others go as high as 55 years of age [7]. Therefore, we believe that choosing a lower cutoff age would give us more insight into the issue and the profile of the patients that we are dealing with.

Acute myocardial infarction in young individuals is an important clinical entity for both the clinician and the patient. In western countries, as the incidence of AMI in young people continues to increase, more and more young people will be affected. In general, younger patients with AMI tend to have a better prognosis than older patients; they tend to have a lower incidence of major adverse cardiac events (MACE) at 30 days and in the long term [8]. However, if compared with an

age-matched population, the long-term prognosis of younger people with AMI tends to be much worse [9].

This study aims to investigate the clinical-paraclinical particularities in a cohort of young people with myocardial infarction and compare them with an older control group.

2. Methods

2.1 Study population

All patients admitted between the 1st of January 2017 through the 31st of December 2019 at the Cardiovascular Diseases Institute "Prof. Dr. George I. M. Georgescu", Iasi, Romania with the primary discharge diagnosis of acute myocardial infarction were eligible for admission. This population has further been split into 2 groups based on age. The first group included patients with an age equal to or lower than 40 years old with an AMI diagnosis. The second group included patients with an age greater than 40 years old with an AMI diagnosis. From each of these 2 groups we have randomly selected a representative sample consisting of 42 young patients with AMI and 57 older patients with AMI. Data was collected manually from the clinical observation sheets. The research is in accordance with the Helsinki Declaration of 1975, revised in 2010.

2.2 Data collection

The data collected included: basic demographic information: age, gender, place of residency; admission complaints: thoracic pain, pain radiation, dyspnea, sweating; medical history: history of AMI, atrial fibrillation, history of stroke or of chest pain or home medication; and cardiovascular risk factors: smoking status, hypertension, diabetes mellitus, dyslipidemia, family history of AMI at an early age; systolic and diastolic blood pressure, heart rate and Killip class at admission; laboratory parameters: complete blood count, lipid profiles and cholesterol, myocardial cytolysis enzymes, liver cytolysis enzymes, inflammation markers, glycemia and renal markers; echocardiography parameters: mean ejection fraction, wall kinetic abnormalities and valvular regurgitation; and coronarography data: number of coronary lesions and artery involvement. All the data was collected from the general observation files of the patients. The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

2.3 Statistics

Statistical analysis was performed using IBM Statistical Package for the Social Science version 26.0. Data was labelled as either nominal or quantitative. The sample was assessed for normal distribution. Student's *t*-test was used to compare continuous variables, which were presented as mean and standard deviation. Categorical variables were presented as absolute numbers, percentages, and risk ratio with 95% confidence interval and compared by Chi-square test. All statistical tests used were two-sided, and we considered $p < 0.05$ as statistically significant.

3. Results

3.1 Baseline characteristics

A total of 99 patients were included in the study: 42 patients with an age equal to or lower than 40 (group 1) and 57 patients with an age greater than 40 (group 2). Both study groups included mostly males (88.1% vs 73.7%, $p = 0.131$) with a mean age of 35.38 $\pm$ 4.39 years in the first group and 66.86 $\pm$ 11.89 years in the second group. Notably, although we included patients with an age between 18 and 40 years, most young people with myocardial infarction tended to have an age closer to the upper limit of the age range. There was no statistically significant difference regarding the time from symptom onset to ambulance call, but patients with older age had an increased prehospital delay, probably because of their atypical symptoms. Also, the periods between emergency department referral and dispatch, were very close between the two groups. Regarding the mode of presentation, all patients from our study were brought to the hospital by ambulance. Most patients were diagnosed with ST-segment elevation myocardial infarction (STEMI) (82.5% vs 78.6%, $p = 0.628$) (Table 1).

3.2 Clinical exam

Some cardiovascular risk factors tend to be more specific for a certain group. A family history of acute myocardial infarction at a young age (35.7% vs 1.8%, $p < 0.001$) and smoking (69% vs 35.1%, $p = 0.001$) tend to be more frequent in the younger patients, while hypertension (31% vs 61.4%, $p = 0.003$) and diabetes mellitus (2.4% vs 26.4%, $p = 0.002$) are more commonly found in the second group of patients. No difference was observed regarding obesity (47.6% vs 36.8%, $p = 0.282$) or dyslipidemia (40.8% vs 26.4%, $p = 0.606$) (Table 1).

Older patients tend to have more comorbidities, such as atrial fibrillation (0% vs 14%, $p = 0.011$), a history of stroke (0% vs 14%, $p = 0.011$), chest pain (4.8% vs 19.3%, $p = 0.034$), and are more likely to have home medication (16.7% vs 63.2%). There was no statistically significant difference regarding the history of myocardial infarction between the 2 groups (7.1% vs 19.3%, $p = 0.155$).

Regarding the admission complaints, the main symptom was anterior thoracic pain (95.2% vs 93%, $p = 0.969$) with or without typical pain radiation (35.7% vs 15.8%, $p = 0.022$), followed by dyspnea (11.9% vs 5.3%, $p = 0.231$) and sweating (4.8% vs 8.8%, $p = 0.442$).

There was no difference between the groups' admission mean systolic blood pressure (137.55 $\pm$ 17.96 vs 132.70 $\pm$ 24.71, $p = 0.288$) or heart rate (85.83 $\pm$ 15.75 vs 81.77 $\pm$ 16.46, $p = 0.288$). However, there was a significant difference in diastolic blood pressure, with the younger patients having a higher mean diastolic blood pressure (87.62 $\pm$ 13.40 vs 77.85 $\pm$ 15.62, $p = 0.002$). Killip class at admission was also significantly lower in younger patients ($p = 0.004$) (Table 1).

3.3 Paraclinical tests

Most laboratory tests did not show significant differences between the two groups, although hemoglobin (14.95 $\pm$ 1.45

TABLE 1. Baseline characteristics of the patients included in the study.

	Age ≤40 years (Group 1)	Age >40 years (Group 2)	*p* value
Mean age (years)	35.38 ± 4.39	66.86 ± 11.89	N/A
Male	88.1%	73.7%	0.131
Urban area	64.3%	47.4%	0.127
STEMI	82.5%	78.6%	0.628
Admission complaints			
Thoracic pain	95.2%	93%	0.969
Pain radiation	35.7%	15.8%	**0.022**
Dyspnea	11.9%	5.3%	0.231
Sweating	4.8%	8.8%	0.442
Medical history			
Old AMI	7.1%	19.3%	0.155
Atrial fibrillation	0%	14%	**0.011**
Stroke	0%	14%	**0.011**
History of chest pain	4.8%	19.3%	**0.034**
Home medication	16.7%	63.2%	<**0.0001**
Risk factors			
Diabetes mellitus	2.4%	26.4%	**0.002**
Dyslipidemia	40.8%	54.2%	0.606
Family history of AMI	35.7%	1.8%	<**0.0001**
Hypertension	31%	61.4%	**0.003**
Smoking	69%	35.10%	**0.001**
Obesity	47.6%	36.8%	0.282
Admission hemodynamics			
Mean SBP (mmHg)	137.55 ± 17.96	132.70 ± 24.71	0.288
Mean DBP (mmHg)	87.62 ± 13.40	77.85 ± 15.62	**0.002**
Mean HR (bpm)	85.83 ± 15.75	81.77 ± 16.46	0.288
Killip Class			
I	38	40	0.348
II	1	16	**0.004**
III	0	1	0.856
IV	2	0	0.768

Abbreviations: AMI, acute myocardial infarction; BPM, beats per minute; DBP, diastolic blood pressure; HR, heart rate (beats per minute); SBP, systolic blood pressure; STEMI, myocardial infarction with ST-segment elevation; Killip Class I, no evidence of heart failure; Killip Class II, findings consistent with mild to moderate heart failure; Killip Class III, overt pulmonary edema; Killip Class IV, cardiogenic shock.
The bold means that it is statistically significant.

vs 14.21 ± 1.67, $p = 0.022$) and uric acid (5.19 ± 1.53 vs 6.21 ± 2.21, $p = 0.043$) were significantly different (Table 2).

Mean ejection fraction was significantly better in the first group (43.4 ± 10.65 vs 37.16 ± 10.77, $p = 0.005$), even though the lowest value recorded was in a young patient. Mitral and tricuspid regurgitation were more common and more severe in older individuals. Also, interventricular septum dimensions were lower in the first group (Table 3).

Coronary lesions were significantly fewer in the young patients ($p = 0.009$) with a mean of 1.2 ± 0.872 lesions per person; multiple vessel disease was relatively uncommon. Intriguingly enough, in 7 young patients, no coronary lesions were found during the angiography study ($p = 0.007$) (Table 4).

3.4 Outcome

Most patients were discharged (80.95% vs 82.46%, $p = 0.848$) with a mean hospital stay of 4.61 ± 3.23 days for the first group and 5 ± 1.81 days for the second group. There were only 2 deaths recorded, both in the younger group (Table 5).

TABLE 2. Laboratory tests.

	Age ≤40 years (Group 1)	Age >40 years (Group 2)	*p* value
Fibrinogen (mg/dL)	466.61 ± 194.35	529 ± 165.6	0.093
Hemoglobin (mg/dL)	14.95 ± 1.45	14.21 ± 1.67	**0.022**
Leukocytes /mm^3	11834 ± 4041	10630 ± 2579	0.073
Thrombocytes /mm^3	252.95 ± 86.56	230.61 ± 60.07	0.137
Cholesterol mg/dL	202.21 ± 63.64	210.75 ± 56.19	0.512
HDL (U/L)	50.18 ± 32.34	48.54 ± 21.053	0.772
LDL (U/L)	131.88 ± 65.08	135.96 ± 51.99	0.747
Triglycerides mg/dL	141.55 ± 81.51	141.36 ± 69.98	0.991
GGT (U/L)	52.22 ± 39.88	42.76 ± 42.35	0.272
ALT (U/L)	138.29 ± 504.8	38.64 ± 25.48	0.143
AST (U/L)	175.21 ± 553.78	105.37 ± 104.53	0.354
LDH (U/L)	804.45 ± 1585.42	634.82 ± 438	0.443
CK-MB (U/L)	85.86 ± 106.94	82.30 ± 84.33	0.854
Glycemia mg/dL	125.03 ± 56.44	139.91 ± 62.46	0.232
Creatinine mg/dL	7.2 ± 28.96	1.15 ± 1.27	0.118
Urea mg/dL	30.90 ± 11.72	48.95 ± 28.03	0.118
Uric acid mg/dL	5.19 ± 1.53	6.21 ± 2.21	**0.043**
CRP (U/L)	31.47 ± 42.56	52.29 ± 59.26	0.083
cTNI (U/L)	5026 ± 8030	4203 ± 10,402	0.754

Abbreviations: HDL, high density lipoproteins; LDL, low density lipoproteins; GGT, gamma glutamyl transferase; AST, aspartate aminotransferase; ALT, alanin aminotrasferase; LDH, lactate dehydrogenase; CK-MB, creatine kinase-MB; CRP, C reactive protein; cTNI, cardiac troponin I.
The bold means that it is statistically significant.

4. Discussion

In this study, we investigated the clinical and paraclinical particularities of young people with myocardial infarction in a primary percutaneous coronary intervention (PCI) center from the North-East region of Romania. Most young people with myocardial infarction included were male. It is important to note that most young people with myocardial infarction tend to be concentrated towards the upper end of the age interval. This might be explained partially by the fact that cardiovascular diseases are chronic in nature and tend to develop in time, thus age should be considered as one of the most important cardiovascular risk factors [10]. Other studies investigating young patients with myocardial infarction (MI) reported similar findings in regard to the age distribution (34.8 ± 4.1 and 35 ± 4.9) and proportion of males (81% and 89.8%), therefore suggesting MI in young patients occurs primarily in men [11, 12].

Women tend to develop cardiovascular diseases on average 7–10 years later than males [13]. This discrepancy between males and females can be explained by the cardioprotective effects of estrogen, particularly in premenopausal women [14]. Estrogen is believed to increase angiogenesis and vasodilation, decrease reactive oxygen species (ROS), oxidative stress, and fibrosis, and limit cardiac remodeling and hypertrophy. A meta-analysis of 25 observational studies has shown a decreased cardiovascular risk in postmenopausal woman taking hormone replacement therapy, therefore suggesting the protective roles of estrogen [15]. Nevertheless, there are certain controversies regarding the timing of hormone replacement therapy and patient eligibility [16].

It is also important to note the environmental and genetic differences of certain populations. For instance, in India, coronary heart diseases are more common and more severe, tending to occur earlier in life than in a western population [17]. Certain gene polymorphisms more prevalent in Asian Indians have also been associated with an increased level of lipids in plasma, which is an independent risk factor for coronary heart disease (CHD) [18].

Most common symptoms at admission were anterior thoracic pain, followed by typical angina pain radiating into the neck, jaw, or left arm. It is important to note that an important differential diagnosis of myocardial infarction primarily in young patients is acute myocarditis due to similar clinical presentation, elevated biomarkers, and electrocardiogram (ECG) changes. One study shows that in the 18–29 age group the more likely cause for the cardiac injury is myocarditis, whereas AMI is more prevalent after 30 years of age [19].

Certain groups of patients, especially those with diabetes, are less likely to report typical chest pain with or without pain radiation. These groups of people are particularly susceptible to longer delays at admission [20]. In our study, the higher

TABLE 3. Echocardiography results.

	Age ≤40 years (Group 1)	Age >40 years (Group 2)	*p* value
Ejection fraction %	43.4 ± 10.65	37.16 ± 10.77	**0.005**
IVS (mm)	11.52 ± 2.56	12.87 ± 2.66	**0.013**
TAPSE (mm)	20.03 ± 5.83	19.86 ± 3.73	0.879
Kinetic abnormalities			
No kinetic abnormalities	7.0%	4.8%	0.642
Anterior wall	64.9%	69.0%	0.666
Inferior wall	68.4%	54.8%	0.165
Lateral wall	52.6%	34.1%	0.152
Global kinetic abnormalities	29.8%	14.3%	0.07
Mitral regurgitation			
No mitral regurgitation	45.23%	22.8%	<**0.001**
Grade 1	40.47%	33.3%	0.078
Grade 2	11.9%	38.59%	0.164
Grade 3	0%	3.5%	0.642
Grade 4	0%	1.75%	0.876
Tricuspid regurgitation			
No tricuspid regurgitation	73.81%	50.87%	**0.009**
Grade 1	19.04%	33.33%	0.064
Grade 2	4.76%	10.52%	0.084
Grade 3	0%	5.26%	0.164

IVS, interventricular septum; TAPSE, tricuspid annular plane systolic excursion.
The bold means that it is statistically significant.

TABLE 4. Coronarography study results.

	Age ≤40 years (Group 1)	Age >40 years (Group 2)	*p* value
Number of coronary lesions			
No coronary lesion	8	1	0.164
One coronary lesion	21	24	0.654
Two coronary lesions	8	20	0.084
Three coronary lesions	4	10	**0.009**
Mean artery involvement	1.2 ± 0.872	1.71 ± 0.786	**0.003**
Artery involvement			
RCA	33.3%	49.1%	0.116
LCX	21.4%	40.4%	**0.047**
LAD	54.8%	64.9%	0.307
MINOCA	16.67%	1.75%	**0.007**

RCA, right coronary artery; LCX, left circumflex artery; LAD, left anterior descending artery; MINOCA, myocardial infarction with non-obstructed coronary arteries.
The bold means that it is statistically significant.

number of diabetic patients in the control group can explain the significant difference in pain radiation between the two groups.

In our study, younger patients were significantly less likely to have traditional risk factors, such as diabetes mellitus or hypertension. Recent studies confirm that younger patients tend to have fewer comorbidities than their older counterparts [21]. We found no significant difference between the groups in regards to dyslipidemia or obesity, therefore, lipid abnormalities seem to be more prevalent in the patients included in the study than in the general population [22].

Smoking was significantly more common in the younger patients and seems to be one of the most important cardiovascular risk factors in young adults [21]. Smoking is easy to recognize, and quitting can significantly improve the long-term prognosis

TABLE 5. Case finality.

	Age ≤40 years (Group 1)	Age >40 years (Group 2)	*p* value
Discharged	80.95%	82.46%	0.848
Transferred	14.29%	17.54%	0.663
Death	4.76%	0%	0.096
Hospitalization (days)	4.61 ± 3.23	5 ± 1.81	0.458

of both cardiovascular diseases and pulmonary diseases [23]. A positive family history for cardiovascular diseases is also more common in young patients, which is shown in other studies as well [24, 25]. This may represent a predisposition of the individual to developing early atherosclerosis and vascular diseases. Such patients would probably benefit from early interventions to limit their overall cardiovascular risk, which is higher.

There was no difference in the mean systolic blood pressure and heart rate at admission between the two groups. However, the older patients were significantly more likely to have home medication. Younger patients had a higher mean diastolic blood pressure compared to older patients and had a lower Killip class upon admission. Because younger people tend to have fewer comorbidities and overall a less advanced atherosclerotic disease, we expect them to have a lower risk of developing heart failure. Other studies support the idea that younger patients have a lower Killip class and therefore, a better in-hospital prognosis [7, 26, 27].

Older patients had a mean hemoglobin level lower than young patients. It is well known that older patients are more likely to develop anaemia [28, 29] which is associated with a poor clinical outcome [30]. Moreover, the etiologies of anaemia at an older age are complex and may involve several mechanisms, ranging from chronic kidney disease to bone marrow insufficiencies to chronic inflammatory processes [31].

Uric acid levels were higher in the older patients. It is well known that uric acid is associated with an increased risk of vascular diseases, stroke, hypertension, metabolic syndrome and renal disease [32, 33]. It is interesting to note that hyperuricemia is more strongly associated with cardiovascular events and hypertension in the young and in women, even though in this study older patients had overall higher levels [34].

Echocardiographic parameters in younger individuals were overall better. Mean ejection fraction was significantly higher in the young, and both mitral and tricuspid valvular regurgitation were less severe. Other studies support our results that younger patients have an overall better ejection fraction [35].

Young patients had significantly fewer coronary lesions than older patients, with multiple vessel diseases being relatively uncommon. It has been shown that patients with milder coronary involvement, particularly single vessel disease and a better ejection fraction have a better long-term prognosis [36].

Another interesting finding is that younger people tend to have more myocardial infarctions with non-obstructive coronary arteries. Other studies report that myocardial infarction with non-obstructive coronary arteries (MINOCA) is more common in young people and in females. It presents as a non-STEMI and patients have fewer traditional cardiovascular risk factors [37]. It is important to note that MINOCA is a syndrome that has many causes including coronary artery spasm, spontaneous coronary dissection, coronary microvascular spasm, or myocarditis [38]. Moreover, prognosis in MINOCA patients seems to be correlated with the mechanism, and although these patients do not have obstructed coronaries, the long-term prognosis in some studies seems to be like that of patients with single/double-vessel disease [39–41].

There was no significant difference between the groups in the mean hospitalization days or case finality. Although the only 2 patients that died were young, many studies report that the prognosis of young people both in-hospital and long term is more favorable than their older counterparts. Even so, if compared to age-matched controls, the prognosis is significantly worse with a much higher mortality.

A surprising find that is otherwise different from other studies in the literature is the presence of two deaths in the young group, and the absence of deaths during hospitalization in patients over 40 years of age. These two deaths occurred in a diabetic man and a woman without typical angina chest pain that were brought to our hospital late, at 24 and 48 hours after the onset of symptoms, in a very serious general condition and with severe left ventricular systolic dysfunction. The underestimation of risk in the young population, especially in women, because of their lower level of traditional cardiovascular risk factors, may explain the presence of the two deaths in the group of young patients. The inclusion of a relatively small number of patients in the study may explain the absence of deaths among patients over 40 years of age. Accordingly, we aim to expand our research and include more patients in the study, which will improve the power of the study and will be of immense help in arriving at the right diagnosis and treatment of myocardial infarction in young patients.

5. Study limitations

There are some limitations that should be acknowledged. Firstly, this is a retrospective study, and many inherent biases could influence the results. Secondly, the number of young patients included in the study is relatively small. This is due to the fact that AMI is relatively rare in young individuals. From the total patients with myocardial infarction considered for enrolment, less than 1% were less than 40 years of age. Thus, by choosing a lower cut-off age, we greatly reduced the number of patients eligible for enrolment.

Nonetheless, our results are generally in agreement with other authors. Due to the inclusion of patients of younger age and the wide amount of data collected, we believe our study paints a clearer picture of the type of patients that are susceptible to develop an AMI. This provides clinicians with

insight to identify patients at risk.

6. Conclusions

The results of our study show that young men are primarily affected, and the most common risk factors are currently smoking status and a family history of cardiovascular diseases at a young age. Also, they tend to have fewer comorbidities such as diabetes or hypertension, and are less likely to have home medication and have fewer cardiovascular events (stoke, atrial fibrillation, history of chest pain). Typical clinical presentation consists of patients with retrosternal chest pain being the most common symptom, typical radiating pain being more common than in older individuals, and Killip class tending to be lower at admission. Mean left ventricular ejection fraction is better than in older counterparts, and there are fewer coronary lesions with no difference in short-term prognosis.

Considering the increasing incidence of acute myocardial infarction in young people and also the more reserved long-term prognosis of these patients, prevention strategies must be adopted, and cardiovascular risk should be assessed even in young individuals that are not traditionally considered at risk.

AUTHOR CONTRIBUTIONS

ANC, LA contributed to the study conception and design. ANC, RA, AFB, CBM performed data collection. LA, RS, IDC, CS performed data analysis. The first draft of the manuscript was written by ANC and LA and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Data acquisition and analysis was performed in compliance with protocols approved by the Ethical Committee of the Cardiovascular Diseases Institute "Prof. Dr. George I. M. Georgescu", Iasi, Romania (ethical approval number 186/22.12.2016). Written informed consent was obtained from all participants included in the study. The research is in accordance with the Helsinki Declaration of 1975, as revised in 2010.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. Larisa Anghel, Cristian Stătescu and Radu Sascău are serving as the Guest editors of this journal. We declare that Larisa Anghel, Cristian Stătescu and Radu Sascău had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to OK.

DATA AVAILABILITY

The data used to support the findings of this study are available from the corresponding author upon request.

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