DOI: *http://dx.doi.org/10.22122/arya.v18i0.2256* *Published by* *Vesnu Publications*

Factors associated with implantable cardioverter-defibrillator shocks in patients suffering from non-ischemic cardiomyopathy

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Original Article

Abstract

BACKGROUND: Although intra-cardiac shocks are a lifesaving approach in patients with systolic heart failure (HF), the probable effective factors related to shock occurrence are less frequently recognized. We designed this study to assess the factors associated with inappropriate or appropriate implantable cardioverter-defibrillator (ICD) shocks in patients with non-ischemic cardiomyopathy (NICM).

METHODS: Ninety-nine patients with NICM who implanted ICD were enrolled from March 2018 to September 2019 and followed up with a three-month interval for up to one year. Shock therapy was defined as either appropriate or inappropriate shock. The odds ratio (OR) of inappropriate shock occurrence was calculated with crude and different adjusted models.

RESULTS: The mean age of the population at baseline was 51.9 ± 15.4 years (men: 71%). Baseline data revealed that patients with inappropriate shocks had higher heart rates (HR), worse New York Heart Association (NYHA) class, and anti-tachycardia pacing (ATP) as well as higher percentages of amiodarone usage compared to groups with appropriate or no shock [HR: 96.8 ± 27.8 vs. 79.8 ± 12.1 vs. 76.2 ± 17.6 beats per minute (bpm), P = 0.014; NYHA class IV: 85.7% vs. 74.1% vs. 63.4%, P = 0.041; ATP: 37.5% vs. 29% vs. 5%, P = 0.010; amiodarone usage: 37.5% vs. 25.8% vs. 5%, P = 0.23, respectively]. Further multiple-adjusted OR did not reveal any significant independent association between the aforementioned variables and inappropriate shock incidence.

CONCLUSION: This study indicates no significant independent predisposing factor in the occurrence of inappropriate shocks among patients with NICM. Other studies are required in this regard.

Keywords: Defibrillators; Cardiomyopathy; Heart Failure

Date of submission: 30 Sep. 2020, ***Date of acceptance:*** 12 Dec. 2020

Introduction

Patients with heart failure (HF) are at increased risk of developing ventricular arrhythmias.[1] Implantable cardioverter-defibrillator (ICD) is an effective treatment recommended by both European and United States (US) guidelines as the first option to reduce the risk of sudden cardiac death and all-cause mortality in patients with either ischemic or non-ischemic HF. However, there is more evidence of ICD usage among patients suffering from ischemic heart disease (IHD).[2,3] Appropriate shocks would ideally occur because of ventricular arrhythmia. On the other hand, rapid supraventricular tachycardia (SVT), lead fracture, electromagnetic interference, and device malposition are predisposing factors for inappropriate shocks.[4] The term "shock paradox" is a chicken-and-egg question in the cardiology field. Previous studies have shown that appropriate or inappropriate ICD shocks are associated with higher mortality risk in the long term.[5-8]

Interestingly, intra-cardiac shocks during defibrillation threshold (DFT) testing lead to a significant reduction in the cardiac index only in patients with a reduced left ventricular ejection fraction (LVEF) of < 30%.[9]

How to cite this article: Rezaee M, Azhari A, Shafie D. **Factors associated with implantable cardioverter-defibrillator shocks in patients suffering from non-ischemic cardiomyopathy.** ARYA Atheroscler 2022; 18: 2256.

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It has been reported that approximately one-third of patients would receive a shock after 4-5 years of ICD implantation, and 16%-18% of them are inappropriate ones.[10,11] Anti-tachycardia pacing (ATP) treated ventricular tachyarrhythmia had no significant impact on mortality compared to patients without ventricular arrhythmia. In contrast, patients treated with intra-cardiac shock showed increased all-cause mortality compared to those without documented shock.[12]

Therefore, identifying associated factors with ICD shocks, especially inappropriate ones, might help better implement preventive interventions. For instance, in Woo et al.'s study, inappropriate ICD shock in patients with hypertrophic cardiomyopathy was significantly related to the age of fewer than 30 years at the time of ICD insertion and history of atrial fibrillation (AF).[13] The significance of increased heart rate (HR) on inappropriate shocks has been shown in a study indicating that the occurrence of this kind of shock was associated with the underuse of beta-blocker agents.[14] The association between younger age and inappropriate shock incidence might be explained with higher activity levels among these groups leading to increased HR.[15] Jagielski et al. suggested that age, serum sodium, potassium concentration, and primary indications for ICD insertion were the predictors of inappropriate ICD shock incidence.[15] Moreover, some previous studies have shown that AF independently increases the likelihood of both inappropriate and appropriate shocks in patients with ICDs.[15-18] Thus, a better understanding of the predisposing factors associated with ICD shocks seems essential.

The usefulness of ICD insertion in patients with non-ischemic cardiomyopathy (NICM) is less frequently investigated. Khan et al. performed a systematic review to evaluate the probable efficacy of ICD implementation on sudden cardiac death occurrence among patients with NICM. They suggested that ICD significantly decreased all-cause death.[19] Although their findings favor decreasing mortality in NICM patients with ICD, a thorough study in terms of possible factors in shock occurrence in these kinds of patients is still required.

This article sought to investigate the potential effective factors associated with inappropriate or appropriate ICD shocks in patients with NICM.

Materials and Methods

The present research was a prospective study that was conducted on patients with previously implanted ICD in one of the governmental cardiac centers (Shahid Chamran Heart Center) in Isfahan, Iran. Between March 2018 and September 2019, 112 previously proved NICM patients with implanted ICDs and decreased LVEF (< 40%) were selected and followed every three months for up to one year. The minimum age for subject inclusion was defined as 18 years. We also recruited the patients with shock regardless of the numbers, and the last occurred shock for each patient was considered each patient's shock status. Unwillingness to participate in the project and the presence of an ischemic etiology of HF were defined as exclusion criteria. At the baseline, all participants were fully explained about the the aim of study by the principal investigator, and the probable questions were thoroughly answered. This study was performed according to the Declaration of Helsinki principles, and its protocol was approved by the Institutional Review Board of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1397.124). The main endpoint was shock-therapy, defined as either appropriate or inappropriate shock. Diagnosis of appropriate shock was made based on the investigator's decision according to the analysis of intracardiac electrograms and the shock itself. In the occurrence of the shock, the admitted patient was entirely evaluated in terms of para-clinic and laboratory data irrespective of the shock type, and individualized management was done accordingly. Moreover, device analysis was performed by an electrophysiologist, and proper device adjustments were done for the prevention of future attacks.

At baseline, all participants were asked about their demographic characteristics, including age and gender. The data about chronic diseases, including hypertension (HTN), kidney diseases, diabetes mellitus (DM), AF, thyroid diseases, liver diseases, and valvular dysfunction were also gathered. During physical examination at the baseline, HR [beats per minute (bpm)] and blood pressure indices including systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured. The blood pressure was taken three times with a one-minute interval, and the means were reported as each patient's blood pressure. Patients were also asked about the medications usage, including the following: angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers, furosemide, amiodarone, mineralocorticoid-receptor antagonists (MCRAs), and oral anticoagulation agents. Moreover, sodium, potassium, magnesium, calcium, albumin, glomerular filtration rate (GFR) levels, and New York Heart Association (NYHA) class were assessed at baseline. In terms of shock occurrence, SBP, DBP, HR, ejection fraction (EF), and electrolyte profile (sodium, potassium, magnesium, and calcium) plus albumin as well as device-related characteristics including QT interval, QRS duration, electrophysiological study, ATP, and cardiac resynchronization therapy with defibrillator (CRT-D) frequency were also investigated.

Statistical analysis: The results are presented as mean ± standard deviation (SD) or number (percentage) for continuous and categorical variables, respectively. In order to assess the normality of data, we used the Shapiro-Wilk test. For examining the differences between shock types and pre-defined variables, chi-square test (Fisher's exact test, if needed), Student's t-test, or analysis of variance (ANOVA) were utilized, as appropriate. The odds ratio (OR) of inappropriate shock occurrence was calculated with crude and adjusted models. Age and sex were adjusted in model 1. We also adjusted all potential confounders in the final model, including HR, NYHA, ATP, potassium, magnesium, and amiodarone usage, except for the desired variable in each previously defined group. We used the SPSS software (version 22.0, IBM Corporation, Armonk, NY, USA) for data analysis. The results were considered statistically significant when P-values were < 0.05.

Results

Of the total study population, 99 (88.3%) completed the entire follow-up duration, and 13 patients came out of the study due to different reasons, including an unwillingness to continue the follow-up due to personal beliefs or migration from the city. The flow diagram of the study is shown in figure 1.

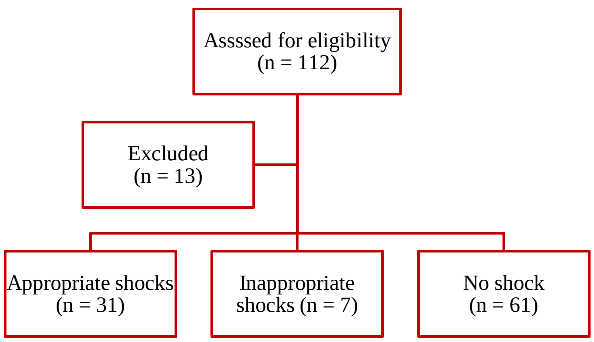

Figure 1. Flow diagram of the study population

The mean age of the population at baseline was 51.9 ± 15.4 years. Men were the dominant gender (71%). 7% of patients had inappropriate shocks [AF: 3 (42.8%), atrial tachycardia: 1 (14.3%), sinus tachycardia: 2 (28.6%), and myopotential: 1 (14.3%)]. The frequency of appropriate shocks was the following: ventricular tachycardia (VT): 23 (74.2%) and ventricular fibrillation (VF): 8 (25.8%). The baseline characteristics of the study population are shown in table 1. Patients who experienced inappropriate and appropriate shocks had significantly higher HR means than those receiving no shock (94.7 ± 29.3 vs. 77.9 ± 12.5 vs. 76.4 ± 17.6 bpm, respectively, P = 0.037) during the baseline assessment. In terms of drug consumption, subjects with experience of inappropriate shocks consumed amiodarone more frequently than the appropriate and no shock groups (37.5% vs. 25.8% vs. 5%, respectively, P = 0.023).

Other drugs were uniformly distributed among groups. Patients who experienced inappropriate shocks had a worse NYHA functional class than the other two groups (P = 0.041). There was no significant relation in terms of chronic diseases or laboratory data, including sodium, albumin, potassium, magnesium, and calcium according to different shock types.

Table 2 presents the para-clinic and laboratory characteristics of those participants who experienced shocks during the follow-up duration. Patients with inappropriate shocks had significantly higher HRs than those who experienced appropriate ones (96.8 ± 30.0 vs. 79.8 ± 12.0 bpm, P = 0.018). There was no remarkable difference between other para-clinic or laboratory data between groups.

Table 3 shows multiple-adjusted OR of inappropriate shock occurrence based on NYHA functional class, ATP, HR, and amiodarone usage. After adjusting all potential confounders, we found that our pre-defined variables were not significantly associated with inappropriate shocks among study populations.

Discussion

In the present study, NICM patients with implanted ICDs were assessed to identify potential factors associated with ICD shocks. Our findings revealed that 31.3% of patients experienced appropriate shocks, and 7% experienced inappropriate shocks. Our findings revealed no significant predisposing factor for the occurrence of inappropriate shocks among patients suffering from NICM.

Table 1. Baseline characteristics of the study population according to shock types

Variables	Total (n = 99)	Shock types			P*
		Appropriate (n = 31)	Inappropriate (n = 7)	No shock (n = 61)	
Age (year)	51.9 ± 15.4	46.9 ± 12.8	53.7 ± 20.1	54.2 ± 15.8	0.094
Male gender	70 (71.0)	22 (71.0)	7 (100)	41 (67.0)	0.196
SBP (mmHg)	115.0 ± 20.4	112.7 ± 26.6	109.1 ± 33.8	116.6 ± 15.2	0.531
DBP (mmHg)	71.2 ± 15.3	74.8 ± 15.0	67.8 ± 20.7	70.1 ± 14.8	0.360
HR (bpm)	78.2 ± 17.9	77.9 ± 12.5	94.7 ± 29.3	76.4 ± 17.6	0.037
HR < 70 bpm	89 (89.9)	28 (90.3)	4 (57.1)	57 (93.4)	0.281
HR ≥ 70 bpm	10 (10.1)	3 (9.7)	3 (42.9)	4 (6.6)	
HTN	20 (20.0)	5 (16.1)	1 (12.5)	14 (23.3)	0.685
Kidney disease	3 (3.0)	1 (3.2)	1 (12.5)	1 (1.7)	0.889
DM	22 (22.0)	4 (12.9)	1 (12.5)	17 (28.3)	0.193
AF	18 (18.1)	5 (16.1)	1 (12.5)	12 (20.0)	0.360
Thyroid diseases	12 (12.1)	3 (9.7)	1 (12.5)	8 (13.3)	0.878
Liver diseases	1 (1.0)	1 (3.2)	0 (0)	0 (0)	0.330
Valvular dysfunction	5 (5.0)	2 (6.9)	0 (0)	3 (5.2)	0.842
ACEIs/ARBs	53 (67.9)	19 (76.0)	6 (75.0)	28 (62.2)	0.497
Beta-blockers	69 (70.0)	23 (74.2)	5 (62.5)	41 (68.3)	0.657
Furosemide	28 (28.2)	8 (32.0)	1 (12.5)	19 (42.2)	0.238
Amiodarone	14 (14.1)	8 (25.8)	3 (37.5)	3 (5.0)	0.023
MCRA	26 (26.2)	9 (36.0)	3 (37.5)	14 (31.1)	0.481
Oral anticoagulation	16 (16.1)	4 (12.9)	1 (12.5)	11 (18.3)	0.342
Sodium (mEq/l)	139.5 ± 3.7	138.2 ± 2.7	139.7 ± 5.2	140.0 ± 3.7	0.159
Albumin (g/dl)	3.9 ± 0.4	3.9 ± 0.3	4.0 ± 0.3	3.8 ± 0.5	0.370
Potassium (mEq/l)	4.4 ± 0.5	4.2 ± 0.5	4.6 ± 0.4	4.4 ± 0.4	0.061
Magnesium (mg/dl)	2.0 ± 0.2	1.8 ± 0.1	2.2 ± 0.4	1.9 ± 0.1	0.544
Calcium (mg/dl)	8.9 ± 1.1	9.4 ± 0.3	9.3 ± 0.6	9.1 ± 0.7	0.066
GFR	74.3 ± 26.3	76.4 ± 21.2	78.8 ± 23.3	72.6 ± 24.3	0.658
EF (%)	23.0 ± 5.3	25.4 ± 5.6	21.6 ± 4.9	22.0 ± 5.6	0.412
NYHA	6 (6.0)	1 (3.2)	0 (0)	5 (8.1)	0.041
Class I	24 (24.2)	3 (9.6)	1 (14.2)	20 (32.7)	
Class II	14 (14.1)	4 (12.9)	0 (0)	10 (16.3)	
Class III	55 (55.5)	23 (74.1)	6 (85.7)	26 (63.4)	
Class IV	6 (6.0)	1 (3.2)	0 (0)	5 (8.1)	

Data are presented as mean ± standard deviation (SD) or number and percentage
*P-value calculated by chi-square test, Fisher's exact test, or one-way analysis of variance (ANOVA)
SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate; HTN: Hypertension; DM: Diabetes mellitus; AF: Atrial fibrillation; ARBs: Angiotensin receptor blockers; MCRA: Mineralocorticoid-receptor antagonist; ACEIs: Angiotensin-converting enzyme inhibitors; GFR: Glomerular filtration rate; EF: Ejection fraction; NYHA: New York Heart Association

The rate of appropriate shock in patients with NICM in our study was 31.3%, which was higher than that reported in the study by Marinheiro et al. (21%)[20] and Kober et al. (11.5%).[21] The differences between appropriate and inappropriate shock prevalence might be explained by different detection zones' programming for the therapeutic shock delivery or insufficient intake of beta-blockers.[22]

We found that NYHA class IV was mostly observed among patients with inappropriate shocks, whereas most NYHA class I patients did not experience any shock. These findings were similar to other studies. Several studies reported that increased NYHA class was associated with inappropriate ICD shocks.[23-25] NYHA class IV or LVEF < 20% have been shown to be strongly associated with an increased risk of sudden cardiac death.[26-28] In a study of ICD shocks for primary prevention, HF with NYHA class III had been suggested as one of the predictors of mortality among the patients.[27]

The mean of HR in patients with inappropriate shocks was significantly higher compared to those with appropriate shocks or without shock. It has been announced that increased HR is a risk factor for cardiovascular death in patients with chronic HF treated with standard treatment.[29] Previous studies have also widely reported that in patients with IHD, cardiovascular mortality is significantly associated with increased HR.[29,30]

Table 2. Para-clinic and laboratory characteristics of the study population according to shock types

Variables	Total (n = 38)	Shock types		P*
		Appropriate (n = 31)	Inappropriate (n = 7)	
SBP (mmHg)	113.2 ± 28.3	113.9 ± 28.6	110.5 ± 29.3	0.783
DBP (mmHg)	74.3 ± 17.5	75.4 ± 17.1	69.2 ± 19.6	0.409
HR (bpm)	82.9 ± 17.5	79.8 ± 12.0	96.8 ± 30.0	0.018
HR < 70 bpm	7 (18.4)	5 (16.1)	2 (28.6)	0.443
HR ≥ 70 bpm	31 (81.6)	26 (83.9)	5 (71.4)	
Sodium (mEq/l)	138.3 ± 4.3	138.6 ± 4.1	137.2 ± 5.2	0.460
Albumin (g/dl)	3.9 ± 0.3	4.0 ± 0.3	3.8 ± 0.3	0.235
Potassium (mEq/l)	4.2 ± 0.6	4.1 ± 0.6	4.4 ± 0.3	0.321
Magnesium (mg/dl)	2.0 ± 0.1	2.0 ± 0.1	2.0 ± 0.1	0.814
Calcium (mg/dl)	8.9 ± 1.5	9.0 ± 0.4	8.0 ± 3.6	0.132
EF (%)	23.8 ± 5.7	23.5 ± 5.9	25.0 ± 5.0	0.553
QRS duration (ms)	92.6 ± 30.1	90.3 ± 28.8	102.8 ± 36.3	0.328
QT interval (ms)	409.8 ± 72.3	403.8 ± 77.6	436.5 ± 33.8	0.286
CRT-D	6 (16.2)	4 (13.3)	2 (28.6)	0.325
ATP	11 (28.9)	9 (29.0)	2 (28.6)	0.981

Data are presented as mean ± standard deviation (SD) or number and percentage
*P-value calculated by chi-square test or Student's t-test
SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate; EF: Ejection fraction; CRT-D: Cardiac resynchronization therapy with defibrillator; ATP: Anti-tachycardia pacing

Proper management of HR might result in significant improvement in terms of cardiac function. Controlled HR between 60-80 bpm at rest and 90-115 bpm during moderate exercise has been recommended for patients suffering from HF.[31] In our study, only 69% of patients consumed beta-blockers. This percentage was 69% and 85% in SCD-HeFT and DEFINITE studies, respectively.[11,32] The use of beta-blockers was low in our study and is far from the recommended guidelines. The use of medications that help control HR such as beta-blockers in patients with chronic HF can positively improve these patients' survival, and clinicians should pay attention to this topic.

Device therapy with ATP is a means to decrease the incidence of ICD-delivered shocks for consequent improvement of ICD function.[33] ICDs deliver two types of therapies for tachyarrhythmias, including low-voltage trains of ATP stimuli (pulses) and high-voltage cardioversion or defibrillation stimuli (shocks). Most monomorphic VT is reentrant in patients with structural heart diseases and thus, could be terminated by ATP. This method uses pacing stimuli to terminate reentrant tachycardia. The ATP stimulus must then propagate to the reentry circuit through relatively refractory myocardium and capture the myocardium in the VT circuit during an excitable gap in refractoriness state. To facilitate propagation in relatively refractory myocardium and ensure that at least one stimulus enters the excitable gap, ATP is delivered as a sequence or "train" of 3 to 10 stimuli at a faster rate than the VT, and ATP terminates VT by causing a bidirectional block.[34]

In a randomized trial on patients with both ischemic cardiomyopathy (ICM) and NICM who had implanted ICDs for either primary or secondary prevention, those treated with ATP compared to shock had an improvement in their mental and physical quality of life scores.[35] Another study reported that managing patient's ATP before defibrillation reduced the number of patients receiving a first all-cause shock within the first 12 months.[36] These findings revealed the positive effect of ATP on reducing delivered shocks and consequently improving the ICD function.

Combination usage of medical, interventional, or technical methods is a desirable goal for proper management. In our study, amiodarone was the only agent more frequently used among individuals with inappropriate shocks. This might be explained by the fact that those who received amiodarone were more likely to have an arrhythmia or had more arrhythmic attacks and consequently received amiodarone to reduce the shock occurrence; thus, the presence of amiodarone with higher arrhythmia frequency would not be classified as a sign of cause or effect. Moreover, this agent might alter the SVT and VT discrimination algorithms, effectively preventing inappropriate shocks. On the other hand, amiodarone effectively reduces ventricular response in arrhythmia from supraventricular location and ultimately might reduce the frequency of inappropriate shocks.

Table 3. The multiple-adjusted odds ratio (OR) of inappropriate shock incidence according to New York Heart Association (NYHA) class, anti-tachycardia pacing (ATP), heart rate (HR), and amiodarone usage

Models	NYHA		P	ATP		P	HR		P	Amiodarone		P
	Class I and II	Class III and IV		Negative	Positive		< 70 bpm	≥ 70 bpm		Negative	Positive	
Crude	1.00	0.88 (0.08-9.44)	0.922	1.00	0.97 (0.15-5.99)	0.981	1.00	0.48 (0.07-3.21)	0.450	1.00	1.15 (0.18-7.14)	0.881
Model 1*	1.00	1.27 (0.09-16.69)	0.851	1.00	0.59 (0.08-3.96)	0.589	1.00	0.38 (0.04-3.19)	0.373	1.00	0.64 (0.09-4.52)	0.660
Model 2**	1.00	1.30 (0.08-19.92)	0.850	1.00	0.34 (0.02-4.90)	0.429	1.00	0.72 (0.07-7.64)	0.827	1.00	0.77 (0.07-7.64)	0.827

*Adjusted for age and sex; **Adjusted for age, sex, heart rate (HR), New York Heart Association (NYHA) class, anti-tachycardia pacing (ATP), potassium, magnesium, and amiodarone usage

NYHA: New York Heart Association; ATP: Anti-tachycardia pacing; HR: Heart rate

However, low statistical power due to the sample size might limit evaluating the exact association between medication and shock therapy. A study was done to compare the antiarrhythmic properties of amiodarone and beta-blockers for ICD shock reduction. They finally found that amiodarone, in conjunction with beta-blockers, reduced the risk of both appropriate and inappropriate shocks versus the sole usages of beta-blockers.[37] Another study showed that amiodarone was significantly effective in reducing the rate of inappropriate shocks and was superior to beta-blockers.[38]

Although we found no relation in terms of serum potassium between patients with either appropriate or inappropriate shocks, abnormal potassium level is reported to be an important differential diagnosis in patients with structural heart diseases presenting after repeated ICD shocks.[39] Hypokalemia triggers arrhythmias in HF, which might be due to a lower arrhythmia threshold because of cardiac remodeling.[40] Therefore, an optimal medical regimen for controlling potassium levels in a normal range might result in a lower cardiac arrhythmia occurrence among these kinds of patients. The uniform distribution of potassium between groups in our study might be responsible for observed insignificant findings in terms of this electrolyte.

Conclusion

This study showed no remarkable contributing factor in the occurrence of inappropriate shocks among NICM patients with ICDs. Further studies are certainly warranted to evaluate the factors associated with inappropriate shocks in these patients.

Limitations: There are some limitations attributed to the current study. Our sample size was quite small, and the generalization of our outcomes should be cautiously done. Moreover, the data about the exact etiology of patients' NICM were not accessible for further analysis and interpretation.

Acknowledgments

The authors would like to appreciate Heart Failure Research Center. This article is theresult of a thesis of residency course with number 397454 in Isfahan University of Medical Sciences.

Conflict of Interests

Authors have no conflict of interests.

Authors' Contribution

MR contributed to conceptualization, visualization, data curation, and writing original draft. DS participated in conceptualization, visualization, writing the original draft, reviewing and editing, project administration, and supervision. AA contributed to conceptualization, visualization, writing, reviewing, and editing.

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