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Original Article CARDIOLOGY

Relation of multicenter automatic defibrillator implantation trial implantable cardioverter-defibrillator score with long-term cardiovascular events in patients with implantable cardioverter-defibrillator

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ABSTRACT

OBJECTIVE: To test the hypothesis that multicenter automatic defibrillator implantation trial (MADIT) - implantable cardioverter-defibrillator (ICD) scores predict replacement requirement and appropriate shock in a mixed population including both primary and secondary prevention and long-term adverse cardiovascular events.

METHODS: The study has a retrospective design. Patients who were implanted with ICD in the cardiology clinic of Atatürk University Faculty of Medicine between 2000 and 2013 were included in the study. For this purpose, 1394 patients who were implanted with a device in our clinic were reviewed. Then, those who were implanted with permanent pacemaker (n=1005), cardiac resynchronization treatment (CRT) (n=45) and CRT-ICD (n=198) were excluded.

RESULTS: A total of 146 patients (98 males, 67.1%) with a mean age of 61.1 (±14.8) years were recruited. The median follow-up time was 21.5 months (mean 30.6±25.9 months; minimum 4 months, and maximum 120 months). The median MADIT-ICD scores in the patients were 2. MADIT-ICD scores were categorized as low in 15.1%, intermediate in 57.5%, and high score in 27.4% of patients. Accordingly, MADIT-ICD scores (1.29 [1.00–1.68], p=0.050), hemoglobin (0.86 [0.75–0.99], p=0.047), and left ventricular ejection fraction (EF) (0.97 [0.94–0.99], p=0.023) were determined as independent predictors of major adverse cardiovascular events in the long-term follow-up of ICD-implanted population.

CONCLUSION: In this study, we showed that there was an independent association of long-term adverse cardiovascular events with MADIT-ICD score, hemoglobin, and EF in patients implanted with ICD.

Keywords: Cardiovascular events; implantable cardioverter defibrillator; reduces mortality.

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Implantable cardioverter-defibrillator (ICD) treatment reduces mortality due to cardiovascular events in patients with high-risk cardiovascular disease, ischemic heart disease, cardiomyopathy, congestive heart failure, and new-onset ventricular arrhythmia [1]. ICD treatment results in approximately 20% reduction in total mortality rate in primary and secondary prevention, and approximately 50% reduction in mortality due to arrhythmia after myocardial infarction (MI) [2, 3]. On the other hand, it does not provide symptomatic relief; however; possible mortality due to adverse arrhythmic events is reduced. Therefore, to provide optimal medical care to patients with ICD and to reduce health-care costs, it is important that the risk factors associated with morbidity and mortality are identified [2]. However, we are still unable to identify such patients effectively.

The multicenter automatic defibrillator implantation trial (MADIT) II showed that primary ICD therapy improves survival in patients with a prior MI and advanced left ventricular dysfunction. Furthermore, Goldenberg et al. [4] have recently developed a simple risk score for assessment of ICD efficacy, and all-cause mortality in the MADIT-II population. This score categorizes patients in low, moderate, and high-risk groups based on clinical and laboratory parameters such as age, atrial fibrillation (AF), QRS duration, functional capacity, and urea levels.

MADIT-ICD score was developed in a primary prevention population, and its correlation with all-cause mortality was investigated. Its correlation in secondary prevention patients, or its association with end-points other than all cause-mortality such as replacement requirement, or with appropriate shock have not been studied yet. For that reason, in the present study, we investigated the association between MADIT-ICD scores of patients with ICD implanted for either primary or secondary prevention, and end-points other than all-cause mortality such as replacement requirement, and with major adverse cardiovascular events (MACE) in the long term such as appropriate shock.

MATERIALS AND METHODS

Study population

The study has a retrospective design. Patients who were implanted with ICD in the cardiology clinic of Atatürk University Faculty of Medicine between 2000 and 2013 were included in the study. For this purpose, 1394 patients who were implanted with a device in our clinic were reviewed. Then, those who were implanted with permanent pacemaker (n=1005), cardiac resynchronization treatment (CRT) (n=45) and CRT-ICD (n=198) were excluded. As a result, the study included 146 patients who were implanted with only ICD. MACE that occurred in these patients during the long-term follow-up were identified, and their association with MADIT-ICD scores was evaluated. The study was approved by the local ethics committee.

MADIT–ICD score

MADIT-ICD scores are calculated with consideration of 5 clinical parameters (blood urea nitrogen [BUN] >26 mg/dl, functional capacity >2, presence of AF, age >70, and QRS >120 m s). Each positive parameter is given 1 point. A total of 0 point indicates the low score, 1–2 points indicate intermediate score, and ≥3 points indicate high score [5].

Clinical evaluation and definitions

Patient files were reviewed with regard to clinical and biochemical parameters and device properties. Diabetes mellitus was defined as fasting blood glucose level measured at least twice as >126 mg/dL, hemoglobin A1c level measured as >6.5%, or use of an antidiabetic medication [5]. HT was defined as blood pressure measured at least twice as >140/90 mmHg, or use of antihypertensive medication [6]. Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate (GFR) <60 ml kg/min. Estimated GFR was calculated based on the Cockcroft-Gault formula. In addition, the previous history of percutan interventions, coronary by-pass, and cerebrovascular events was noted. Heart rate, QRS duration, and presence of AF were determined from the electrocardiograms performed at the time of admission. For all patients, the results of complete blood count and biochemical tests sent at the time of admission were recorded. Left ventricular ejection fraction (EF) measured with biplane Simpson in echocardiography examination at the time of admission was recorded. ICD indications ischemic and non-ischemic cardiomyopathy (CMP), hypertrophic CMP, arrhythmogenic right ventricular dysplasia, primary electrical disturbances, type of prevention (primary or secondary prevention), and type of ICD (VVI, DDD) were recorded.

End points

Patient files were reviewed to identify adverse cardiovascular events. A combined end-point was established

from all-cause mortality, replacement requirement, and incidence of appropriate shock (MACE: Major adverse cardiovascular events).

Statistical analysis

Normally distributed numerical variables were expressed as mean±standard deviation; non-normally distributed variables were expressed as median (minimum-maximum); whereas categorical variables were expressed as a percentage. To test the distribution characteristic of numerical variables, the Kolmogorov–Smirnov test was used. To determine the differences regarding numerical variables between the groups, Students t-test or Mann–Whitney U-test was used. To determine the differences regarding categorical variables between the groups, Chi-square test was used. Using Kaplan–Meier survival analysis, mortality, replacement requirement, the incidence of appropriate shock, and MACE were analyzed according to the groups of MADIT-ICD scores in the whole population. Difference between these groups was analyzed with Log-rank test. Those variables that were found to be significant in the univariate analysis of groups with or without MACE development were included in Cox regression analysis ($p<0.05$). Age, BUN, and functional capacity were found to be significant in univariate analysis; however, since these are items of the MADIT-ICD scores, they were not included in the Cox regression analysis. In statistical analyses, $p<0.05$ was accepted as significant. All statistical analyses were performed using SPSS (version 20) statistical package software.

RESULTS

The study included 146 patients who were implanted with ICD (mean age was 61.1±14.8 years, and 67.1% of the patients were male). Basic clinical and biochemical parameters of the patient population are summarized in Table 1. The median MADIT-ICD scores in the patient population were 2. MADIT-ICD scores were categorized as low in 15.1%, moderate in 57.5%, and high score in 27.4% of patients (Fig. 1).

The median follow-up time was 21.5 months (mean 30.6±25.9 months; minimum 4 months, and maximum 120 months). During the follow-up, 45.2% of the patients (n=66) developed MACE. Among these, all-cause mortality was detected in 21.2% (n=31), appropriate shock was detected in 25.3% (n=37), and replacement requirement was detected in 17.8% (n=26) of the pa-

Table 1. Basic clinical and laboratory features

Age, years (average±SD)	61.1±14.8
Sex (male, %)	67.1
Diabetes mellitus, %	16.4
Hypertension, %	49.3
Smoker, %	40.0
Chronic renal failure, %	6.2
Functional capacity, %	
NYHA-I	0.7
NYHA-II	23.3
NYHA-III	56.8
NYHA-IV	19.2
Cardiomyopathy, %	
Ischemia	65.1
Nonischemia	14.4
Hypertrophic	13.0
ARVD	3.4
Long QT	2.7
PCI history, %	15.8
CABG history, %	21.2
History of SVE, %	6.8
Left ventricle ejection fraction, %	38.6±12.6
Mitral Regurgitation, (extreme, %)	10.3
Systolic pulmonary blood pressure, (average±SD)	38.7±11.1
Atrial fibrillation, %	12.3
QRS duration, (average±SD)	99.7±22.8
Systolic blood pressure, (average±SD)	113±14
Diastolic blood pressure, (average±SD)	72±9.6
Heart rate, (average±SD)	83±11
ICD Implantation indication, %	
Primer protection	24.6
Seconder protection	75.4
Implanted ICD type, %	
VVI-ICD	65.1
DDD-ICD	34.9
URE, (mg/dl) (average±SD)	26.7±14.4
Creatinine, (mg/dl) (average±SD)	1.08±0.4
Sodium, (meq/l) (average±SD)	137±4.4
Potassium, (meq/l) (average±SD)	4.4±0.5
Troponin, (µg/l) (average±SD)	0.8±3.3
White blood cell, x 10^3 µL (average±SD)	9.7±3.1
Hemoglobin, (g/dl) (average±SD)	13.8±2.0
Platelet, x 10^3 µL (average±SD)	237±67

ARVD: Arrhythmogenic right ventricular dysplasia; ICD: Implantable cardioverter defibrillator; SD: Standard deviation.

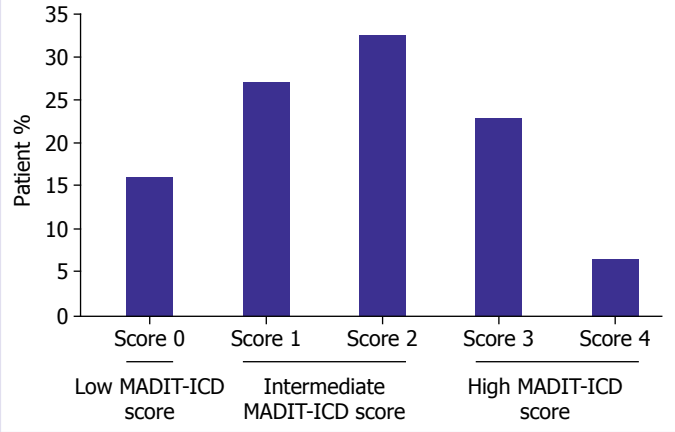

FIGURE 1. Distribution of multicenter automatic defibrillator implantation trial-implantable cardioverter-defibrillator scores in the patient population.

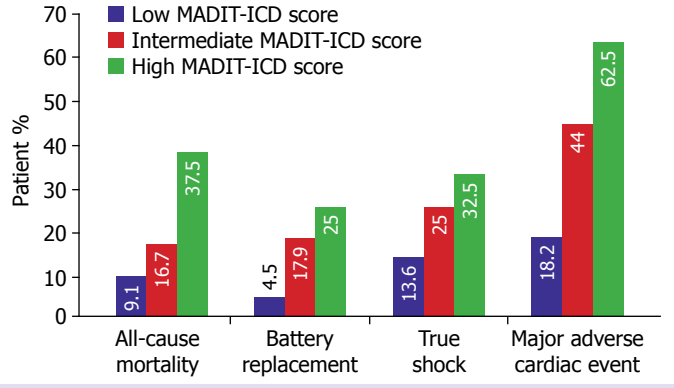

FIGURE 2. Incidences of mortality, replacement requirement, shock and major adverse cardiovascular events in the long-term follow-up according to the multicenter automatic defibrillator implantation trial-implantable cardioverter-defibrillator scores.

tients. Replacement indications were identified as the drained battery in 11 patients, pouch infection in 5 patients, infective endocarditis in 3 patients, trauma in 1 patient, and ICD malfunction in 1 patient.

After categorizing the patient population according to the MADIT-ICD scores as low, moderate, and high score groups, MACE development in the long-term follow-up was analyzed again in these groups (Table 2). Results of both Kaplan–Meier survival analysis and the Chi-square test showed that the incidence of MACE increased significantly as the severity of MADIT-ICD scores increased. Replacement requirement also increased with increasing MADIT-ICD score; however, there was a limited statistical association. The incidence of appropriate shock did not show association with MADIT-ICD scores. As a result, the increase observed in MACE as MADIT-ICD scores increased was driven by all-cause mortality (Figs. 2-4).

There was a significant difference between the groups with and without MACE development in terms of age, hypertension, ischemic CMP, CKD, functional capacity, left ventricular EF, systolic pulmonary artery pressure (PAP), BUN, creatinine, hemoglobin, and MADIT-ICD scores. The other examined variable did not a significant difference between the two groups (Table 3).

To identify the independent predictors of MACE, Cox proportional-Hazard analysis was employed. As univariate analysis showed MADIT-ICD scores, systolic PAP, hemoglobin, creatinine, and left ventricular EF as significant, these variables were included in the Cox-regression analysis. Accordingly, MADIT-ICD scores (1.29 [1.00–1.68], p=0.050), hemoglobin (0.86 [0.75–0.99], p=0.047), and left ventricular EF (0.97 [0.94–0.99], p=0.023) were determined as independent predictors of MACE in the long-term follow-up of ICD-implanted population (Table 4).

TABLE 2. Adverse cardiac events according to the MADIT-ICD score groups

Variables (%)	Low MADIT-ICD score (n=22)	Middle MADIT-ICD score (n=84)	High MADIT-ICD score (n=40)	p*	p**
Death due to all causes	9.1	16.7	37.5	0.001	0.004
Replace need	4.5	17.9	25	0.716	0.051
Shock	13.6	25	32.5	0.153	0.107
Major unwanted cardiac sum of events	18.2	44	62.5	0.002	0.001

*The p-value found by the log-rank test for the MADIT-ICD score subgroups; **The p value found by the X2 test for the MADIT-ICD score subgroups.

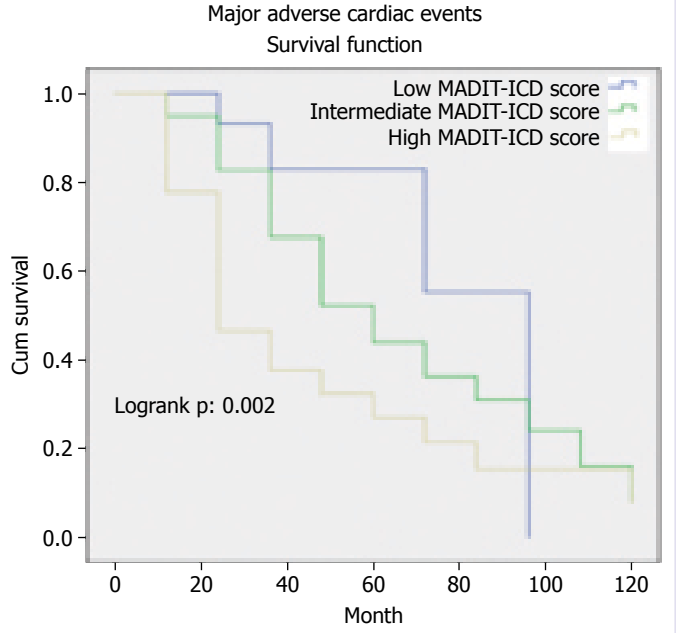

Figure 3. Kaplan–Meier survival curve for major adverse cardiovascular events (left) and mortality (right) according to the multicenter automatic defibrillator implantation trial-implantable cardioverter-defibrillator score groups in the whole population.

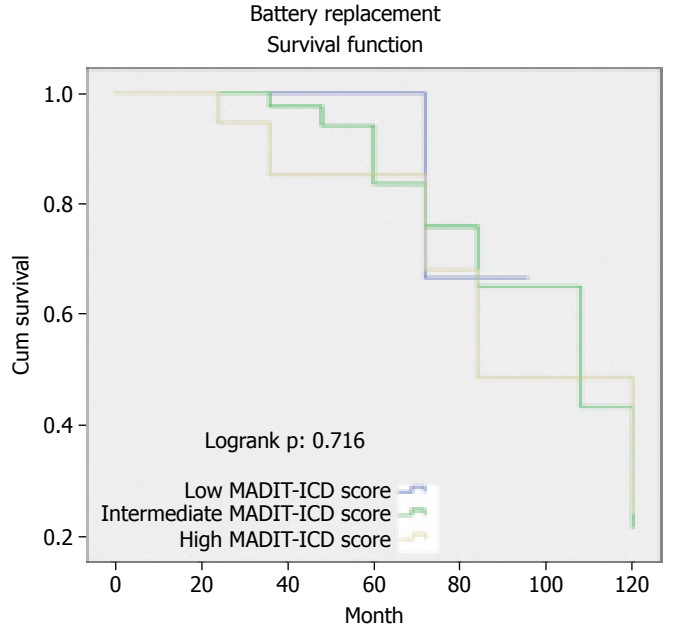

Figure 4. Kaplan–Meier survival curve for replacement requirement (left) and incidence of appropriate shock (right) according to the multicenter automatic defibrillator implantation trial-implantable cardioverter-defibrillator score groups in the whole population.

DISCUSSION

In the present study, we found that MADIT-ICD scores were an independent predictor of all-cause mortality and MACE in the long-term follow-up of patients who were implanted with ICD for either primary or secondary prevention purpose. In addition, we showed that this scores could also be useful for predicting long-term events regarding left ventricular EF and hemoglobin levels.

Sudden cardiac arrest is encountered as the first sign in approximately 30% of patients presenting to

Table 3. Comparison of the major clinical and laboratory findings of MACEs with and without development

Variables	MACEs (-) (n=80)	MACEs (+) (n=66)	p
Age, years (average±SD)	58.0±15.7	64.8±12.6	0.005
Sex (male, %)	67.5	66.7	0.915
Diabetes mellitus, %	12.5	21.2	0.157
Hypertention, %	42.5	57.6	0.070
Smoker, %	41.3	38.5	0.733
Choronic renal failure, %	1.3	12.1	0.007
Fonctional capacity, %			
NYHA-I	1.3	0	0.009
NYHA-II	31.3	13.6	
NYHA-III	52.5	62.1	
NYHA-IV	15.0	24.2	
Ischemic cardiomyopathy, %	58.8	72.7	0.078
Other cardiomyopathy, %			
Nonischemic	12.5	16.7	0.048
Hypertrophic	17.5	7.6	
ARVD	6.3	0	
PCI history, %	15	16.7	0.783
CABG history, %	22.5	19.7	0.680
History of SVE, %	6.3	7.6	0.752
Left ventricle ejection fraction, %	40.9±13.7	35.8±10.7	0.013
Systolic pulmonary blood pressure, (average±SD)	36.8±11.4	41.1±10.4	0.020
Atrial fibrillation, %	10.0	15.2	0.346
QRS duration, (average±SD)	98.1±22.4	101±23	0.354
Systolic blood pressure, (average±SD)	113±14	112±14	0.747
Diastolik blood pressure, (average±SD)	72±10	71±9	0.527
Heart rate, (average±SD)	82.5±10.6	83.6±11.4	0.538
ICD implantation endication, %			
Primer protection	23.8	25.8	0.778
Sekonder protection	76.3	74.2	
Implanted ICD type, %			
VVI-ICD	66.3	63.6	0.742
DDD-ICD	33.8	36.4	
URE, (mg/dl) (average±SD)	24.5±11.6	29.3±16.9	0.041
creatinine, (mg/dl) (average±SD)	1.0±0.2	1.1±0.5	0.035
Sodium, (meq/l) (average±SD)	138±3.8	137±5	0.412
Potassium, (meq/l) (average±SD)	4.4±0.5	4.3±0.5	0.795
Troponin, (µg/l) (average±SD)	1.1±4.4	0.4±1.0	0.155
White blood cell, x 10^3 µL (average±SD)	9.8±3.1	9.5±3.0	0.195
Hemoglobin, (g/dl) (average±SD)	14.2±1.8	13.4±2.1	0.018
Platelet, x 10^3 µL (average±SD)	237±63	237±72	0.989
MADIT-ICD score (median)	1.5	2	0.001

ARVD: Arrhythmogenic right ventricular dysplasia; ICD: Implantable cardioverter defibrillator; SD: Standard deviation.

the hospital [7, 8]. The underlying cause is known to be malignant ventricular arrhythmias in 80–90% of such patients [9]. Nevertheless, only a minority of patients presenting with sudden cardiac arrest is responsive to resuscitation, and even in areas of best health conditions, the maximum reported response rate was 3% [10]. In all patient populations, the major malignant arrhythmias causing sudden cardiac death are known

Table 4. Cox regression analysis for predicting MACE

Variables	Univariate HR, %95 GA	Univariate p value	Multivariate HR, %95 GA	Multivariate p value
MADIT-ICD score	**1.35 (1.09–1.67)**	**0.001**	**1.29 (1.00–1.68)**	**0.050**
PBPs	1.01 (0.99–1.03)	0.020	1.00 (0.98–1.03)	0.654
Hemoglobin	0.86 (0.75–0.99)	0.018	0.86 (0.75–0.99)	0.047
Creatinine	1.36 (0.83–2.22)	0.035	0.75 (0.41–1.37)	0.358
LV-EF	0.97 (0.94–0.99)	0.013	0.97 (0.94–0.99)	0.023

to be ventricular tachycardia attacks that degenerate to ventricular fibrillation [11, 12]. Furthermore, it is a known fact that nearly half of these patients are lost within 2 years unless they are properly treated. Some previous studies reported similar mortality rates in comparison to ICD implantation and medical treatment and that some unwanted clinical conditions may develop due to the shocks; [13, 14] however, as a result of many clinical studies, it is currently a well-accepted view that ICD implantation for both primary and secondary prevention reduces mortality [15, 16].

As it is stated, it is accepted that ICD implantation reduces mortality in comparison to the medical treatment; however, there is controversy about patient selection. At present, it is not clearly known which patients will develop adverse events in the long-term following ICD implantation, or what its predictors are. MADIT-ICD scores are used commonly as an up-to-date scoring system related with this subject. It is known that it yields favorable results in predicting which patients in the primary prevention population will develop adverse events. MADIT-ICD scores were initially developed by Goldenberg et al. [4] They followed up patients who were implanted with ICD for primary prevention purpose for nearly 7 years. They divided patients into high, intermediate, and low-risk groups based on 5 pre-determined clinical risk factors. The results of the study showed that ICD implantation was beneficial in the low and intermediate risk groups; however, it did not have long-term benefit in the high-risk group (positive for at least three clinical parameters). In their study, Iwona et al. [17] accepted all-cause mortality as an endpoint in a population similar to that of MADIT study, and they showed that in addition to MADIT-ICD scores, some clinical parameters were also significant in predicting long-term mortality in a group of patients who were implanted with ICD for primary prevention purpose. Recently, Naksuk et al. [18] stated that in a more limited population that was similar to that of MADIT, MADIT scores were useful in predicting all-cause mortality; however, they suggested that this scoring did not have a predictive value for appropriate shock. Similarly, we also found that there was no association between appropriate shock and MADIT-ICD scores. In the present study, we investigated a patient population who were implanted with ICD for both primary and secondary prevention, but mostly secondary prevention; and we showed that MADIT-ICD scores were useful in predicting MACE in this population, and we also found that hemoglobin and EF also had an independent association with MACE as well.

For the 1st time in literature, we showed that MADIT-ICD scores were beneficial in predicting long-term mortality as well as clinical end-points such as replacement requirement and appropriate shock in a mixed population including both primary and secondary prevention. Our results indicate that a simple and convenient scoring system such as MADIT-ICD scores is beneficial in predicting adverse event development in the long-term in a high-risk population of patients who underwent ICD therapy. Therefore, we showed that utilization of this score in patients who underwent ICD treatment would aid in identifying high-risk patients. Such patients may receive a more intensive treatment to achieve clinical improvement.

Study limitations

The major limitations of the present study are that it was conducted in a single-center and did not have a prospective design. In addition, although all patients undergo-

ing ICD implantation in our clinic were included in the study, our patient number was limited, which was another limitation of this study. In addition, the original population in which MADIT-ICD scores were defined included only patients who underwent ICD implantation for primary prevention, and the defined end-point was all-cause mortality only, which present the main differences from our study.

Conclusion

In this study, we showed that there was an independent association of long-term adverse cardiovascular events with MADIT-ICD scores, hemoglobin, and EF in patients implanted with ICD. These parameters may be used in risk stratification of ICD-implanted patients to contribute in optimal care, improvement of life quality, and reduction of treatment costs in such patients.

Conflict of Interest: The authors declare no conflict of interest.

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Authorship Contributions: Concept – I.H.T., S.S.; Design – A.U., I.H.T.; Supervision – S.S., A.U.; Materials – H.D., A.U.; Data collection &/or processing – L.A., A.U., H.D.; Analysis and/or interpretation – I.H.T., A.U., S.S.; Writing – I.H.T., A.U.; Critical review – C.D., A.U.

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