A decade of insertable cardiac monitors with remote monitoring in pediatric patients

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Abstract

Background: Remote monitoring-enabled insertable cardiac monitors (ICMs) are useful tools for arrhythmias and symptom management. This study sought to evaluate the outcome of ICM implantation in a large, heterogeneous cohort of pediatric and young adult patients.

Methods: Single centre, retrospective analysis of patients who underwent ICM implantation in 2010–2019. Patients were analysed according to age, symptoms, arrhythmias and underlying heart disease.

Results: A total of 200 consecutive patients (58% male), aged 11.5 ± 5.8 years at ICM implantation, were included. Follow-up was 31 ± 18 months. Electrophysiologic study (EPS) was initially performed in 123 patients and was negative in 85%. Patients had no heart disease (57.5%), congenital heart defects (21%), channelopathies (14.5%), cardiomyopathies/heart tumors (8%). The commonest symptoms were syncope/presyncope (45.5%) and palpitations (12.5%). A defined diagnosis was made in 63% of patients (positive diagnosis in 25%, negative in 38%) after 8 (2–19) months of monitoring. EPS results and the presence/absence of an arrhythmia before ICM implantation had no impact on the diagnostic yield. Symptomatic patients as well as patients without structural heart disease showed higher diagnostic yield. Patients with a positive diagnosis underwent pacemaker/implantable cardioverter-defibrillator implantation (13%), pharmacological treatment (10.5%), or catheter ablation (1.5%).

Conclusions: In a large cohort of 200 children and young adults, ICMs with remote monitoring showed a high diagnostic yield (63%), especially in symptomatic patients and in patients without structural heart disease.

Keywords: Insertable cardiac monitors; Remote monitoring; Syncope; Pediatric age; Congenital heart defects; Inherited arrhythmia

1. Introduction

An insertable cardiac monitor (ICM), or implantable loop recorder, is a device implanted in the chest subcutaneous tissues. It can be activated either automatically or by the patient/family member to store the electrocardiogram (ECG) recorded during an event [1]. The latest generation devices enable remote monitoring and facilitate early diagnosis by allowing daily automatic and patient-activated transmissions [2].

ICMs can play an important role in the detection of rare arrhythmias and in the diagnostic workup of syncope [3] and palpitations [4].

This study sought to evaluate the outcome of ICM implantation in a large, heterogeneous cohort of pediatric and young adult patients.

2. Methods

All consecutive patients who underwent ICM implantation between January 2010 and December 2019 were included in the study.

This study complies with the Declaration of Helsinki and was approved by the local ethics committee. Informed consent was obtained from all patients or their guardians.

All patients underwent ICM implantation after a comprehensive non-invasive evaluation [5,6] including clinical visit, standard 12-lead ECG, Holter monitoring, exercise test, external loop recorder and imaging studies as appropriate. Additionally, an electrophysiologic study (EPS) was often performed in patients with suspected tachyarrhythmias or when the evaluation of the sinus node and atrioventricular node-His bundle conduction was required [7]. In patients <15 kg of weight, transesophageal EPS was performed by applying the same protocol when only atrial pacing was needed.

2.1 Procedure

The implant procedure has previously been reported in detail [8] and is described below briefly. Most procedures were performed under general anesthesia or deep sedation, except for older adolescents and in adults, who underwent local anesthesia. The implantation site was guided by surface mapping to determine ECG signal quality and R-wave sensing. Pediatric ECG patches were placed at a 4 cm dis-
tance (the width of device electrodes) on the patient skin in the desired ICM location and connected to a Medtronic Pac- ing System Analyzer. The implantation site was considered adequate when recorded signals had the following characteris-
tics: R wave >0.3 mV, R wave amplitude at least twice the amplitude of P and T waves. A 1 cm cut was made in the skin and the device was inserted over the muscular fascia using the provided insertion tool. Antibiotic prophylaxis (cefuroxime) was given at the beginning of the procedure. Patients were discharged the day after implantation according to Institutional protocols.

In-hospital follow-up was scheduled every 6–12 months.

2.2 Device programming

Device programming was personalized according to symptoms or type of heart disease and patients were re-
programmed from out-of-box factory settings if needed. In general, bradycardia detection was set at 30 bpm (4 beats), pauses at 3.0 s, and tachycardia at 180–200 bpm (8–12 beats) in older children and adolescents. In younger children (<6 years), the upper rate limit was 210–220 bpm (12–24 beats) and the lower rate limit was 40 bpm. In general, in adults with congenital heart defects (CHD) the limits were 150–180 bpm for tachycardia and 30 bpm for bradycardia.

Atrial tachycardia/fibrillation detection was generally programmed off.

In patients with catecholaminergic polymorphic ven-
tricular tachycardia (CPVT), tachycardia detection was set at 30% over the maximum sinus rate without arrhythmias at exercise test.

All patients received the “Medtronic CareLink” re-
move monitoring system.

2.3 Diagnostic criteria

A positive diagnosis was made when symptomatic tachy- or brady-arrhythmias or relevant asymptomatic ar-
rhythmias were detected. Relevant asymptomatic arrhyth-
rias included: advanced/complete atrio-ventricular block (AVB), ventricular pause >3 s, rapid (>180 bpm) pro-
longed/sustained paroxysmal supraventricular (SVT) or ventricular tachycardia (VT) [3].

A negative diagnosis was defined as no rhythm abnor-
malities during symptoms.

When a positive diagnosis was made, the patient un-
derwent in-hospital clinical assessment and therapy. In case of a negative arrhythmic diagnosis, patients and families were reassured by phone.

2.4 Statistical analysis

Categorical data were expressed by counts and per-
centages. Continuous data were expressed by mean and standard deviation if normally distributed, or by me-
dian and interquartile range (25th–75th percentile) if non-
normally distributed. Normality was tested with the

Kolmogorov-Smirnov test. Patients were divided into sub-
groups according to symptoms (syncope/presyncope; syn-
cope/presyncope and palpitations; palpitations; no symp-
toms; other symptoms) and age (infants and small children [aged 1–5 years], children [6–11 years], adolescents [12–18 years], adults [>18 years]). Syncope and presyncope were also analysed separately. The definitions of syncope and presyncope followed current guideline criteria [3].

Patients were also divided according to arrhythmias and heart disease known prior to ICM implantation. Long QT syndrome (LQTS), Brugada syndrome, VT, SVT, ad-
anced/3rd degree AVB, and sinus node dysfunction (SND) were considered as severe arrhythmias; premature ventricu-
lar complex (PVC), 1st and 2nd degree Mobitz 1 AVB, and ventricular preexcitation as not severe. For statistical pur-
pose, SND and sinus pauses were considered in the same
group. Patients’ parameters were compared according to age category, symptoms, heart disease, arrhythmias, using Chi squared test or Fisher exact test for categorical variables and Student’s t-test or ANOVA for continuous variables. A

p-value < 0.05 was considered statistically significant.

Statistical analysis was performed using STATA 14.1 software (Stata Corp., College Station, TX, USA).

3. Results

3.1 Demographics

The study included 200 patients (Table 1). There were 33 patients aged 1–5 years, 69 patients aged 6–11 years, 73 patients aged 12–18 years, and 25 adult patients with CHD, aged 21.6 ± 3.7 years.

3.2 Electrophysiologic study

The EPS was performed in 123 patients before ICM im-
plantation (14 transesophageal and 109 intracavitary EPS). In the majority of cases (85%), EPS was negative. In the remaining 15%, EPS showed inducibility of non-
sustained atrial flutter (4 patients) or fibrillation (2 patients), non-sustained VT (4 patients), non-sustained SVT (5 pa-
tients), prolonged sinus node recovery time (2 patients) and prolonged H-V interval (1 patient). However, these find-
ings were considered non-specific and/or did not lead to a definite diagnosis or treatment. For example, patients with prolonged sinus node recovery time and H-V interval were correctly identified, but there was no clear indication for pacemaker implantation. Thus, in patients with non-
specific findings (positive EPS), the ICM was implanted for further monitoring and ultimate diagnosis.

3.3 Symptoms/Arrhythmias/Heart diseases

Symptoms and arrhythmias leading to ICM implantation are shown in Table 1. The characteristics of the 38 patients with AVB are reported in Table 2. Patients with complete AVB underwent ICM implantation to record heart rate, and to exclude pauses and ventricular arrhythmias. Four of the five patients with complete AVB showed ven-
Table 1. Demographic and pre-implantation data (n = 200).

| Characteristics         | Male sex  | Female sex | Age, years | Weight, kg | Height, cm |
|-------------------------|-----------|------------|------------|------------|------------|
|                         | 117 (58.5)| 83 (41.5)  | 11.5 ± 5.8 | 45 ± 21    | 144 ± 26   |

Heart disease

| No heart disease        | 115 (57.5) |
| Congenital heart defects* | 42 (21)    |
| Channelopathy*          | 29 (14.5)  |
| Cardiomyopathy*, cardiac tumour | 16 (8)     |

Arrhythmias

| Atrio-ventricular block | 38 (19) |
| Sinus node dysfunction, pauses | 17 (8.5) |
| Supraventricular tachycardia | 23 (11.5) |
| Ventricular tachycardia | 23 (11.5) |
| Premature ventricular complex | 19 (9.5) |
| Long QT syndrome | 13 (6.5) |
| Ventricular preexcitation | 9 (4.5) |
| Brugada syndrome | 6 (3) |
| No arrhythmia | 52 (26) |

Symptoms

| Syncope/presyncope | 91 (45.5) |
| Palpitations | 25 (12.5) |
| Syncope/presyncope + palpitations | 43 (21.5) |
| No symptoms | 33 (16.5) |
| Other | 8 (4) |

Values are given as n (%) or mean ± standard deviation. *One patient had both cardiomyopathy and long QT syndrome, another one had both cardiomyopathy and congenital heart defect. Other symptoms include dyspnoea and asthenia/fatigue.

Intraventricular pauses >three-fold the cycle length of the underlying rhythm and severe bradycardia during junctional escape rhythm and underwent pacemaker implantation (see below). Asymptomatic patients (16.5%) underwent ICM implantation because of known arrhythmias or heart disease requiring monitoring (e.g., channelopathy). Heart diseases are shown in Tables 1 and 3.

3.4 Implantation procedure

The devices implanted were Medtronic Reveal XT 9529™ (n = 17, implanted in the years 2010–2013), and Medtronic Reveal LINQ LNQ11™ (n = 183, the new miniaturized ICM implanted between 2013 and 2019).

The devices were implanted in the subcutaneous precordial (198 cases) or axillary (2 small children) pocket (Fig. 1).

Sensing at implantation was 1.3 ± 0.8 mV (range 0.4–5.4 mV).

Table 2. Patients with atrio-ventricular block.

| Arrhythmia                  | No. | Symptoms | ICM diagnosis |
|----------------------------|-----|----------|---------------|
| Low-degree AVB             |     |          |               |
| 1st degree                 | 7   | 11       | 77% (negative diagnosis 62%) |
| 2nd degree Mobitz 1         | 6   | 13       | 64% (positive diagnosis 44%) |
| Advanced (2:1, 3:1)         | 7   | 13       | 64% (positive diagnosis 44%) |
| Paroxysmal 3rd degree       | 13  |          |               |
| Complete 3rd degree         | 5   | 13       |               |
| Total                      | 38  | 24       |               |

AVB, atrio-ventricular block; ICM, insertable cardiac monitor.

3.5 Follow-up

Follow-up extended to February 2020, and its overall duration was 31 ± 18 months [median 31 (15–42) months].

After reaching the end of battery life, ICMs were reimplanted in 32 patients to continue monitoring, because of undefined diagnosis. In this subgroup, total follow-up was 58 ± 10 months.

Complications (pocket erosion) were recorded in 6 patients (3%) with a median age of 11 (3–24) years and a me-
Table 3. Heart diseases.

| Heart disease                                               | No. |
|-------------------------------------------------------------|-----|
| Congenital heart defects                                   | 42  |
| Tetralogy of Fallot                                         | 15  |
| Atrial septal defect                                       | 5   |
| Double outlet right ventricle                              | 4   |
| Status post-Fontan/Glenn palliation                        | 3   |
| Transposition of the great arteries, status post-arterial switch | 3   |
| Transposition of the great arteries, status post-atrial switch | 1   |
| Mitral valve defects                                       | 3   |
| Anomalous pulmonary venous return                          | 2   |
| Congenitally corrected transposition of the great arteries  | 2   |
| Ebstein’s anomaly of the tricuspid valve                   | 2   |
| Aortic coarctation                                          | 1   |
| Truncus arteriosus                                         | 1   |
| Channelopathies                                            | 29  |
| Long QT syndrome                                           | 13* |
| Brugada syndrome                                           | 6   |
| Suspected Brugada syndrome                                 | 4   |
| Catecholaminergic polymorphic ventricular tachycardia       | 6   |
| Cardiomyopathies, myocarditis, heart tumours               | 16  |
| Hypertrophic cardiomyopathy                                | 5*  |
| Arrhythmogenic cardiomyopathy                              | 3   |
| Dilated cardiomyopathy                                     | 1   |
| Restrictive cardiomyopathy                                 | 1   |
| Myocarditis                                                 | 2   |
| Rhabdomyoma                                                 | 3   |
| Fibroma                                                     | 1   |
| Total                                                       | 87  |

*One patient had both cardiomyopathy and congenital heart defect.

Median weight of 42 (17–62) kg at ICM implantation. Erosions occurred within the first 3 months after implantation. The ICM was explanted in all cases.

3.6 Outcome

An arrhythmia diagnosis was made in 126 patients (63%), and was positive in 50 patients (25%) and negative in 76 patients (38%). Time to diagnosis was 8 (2–19) months. A diagnosis was not made in the remaining 74 patients (37%). The events recorded were device-initiated in 54% of cases and patient-initiated in 46%.

Patients with an ICM diagnosis were older (12.2 ± 5.9 years) than those without a diagnosis (10.4 ± 5.5 years) (p = 0.036). However, there were no significant differences according to age subgroups.

In the 32 patients who underwent ICM replacement, the diagnostic yield was 44% (n = 14), with a positive diagnosis in 25% and a negative diagnosis in 19%.

3.7 Electrophysiologic study

The EPS results had no impact on the diagnostic yield (p = 0.6). Among the 105 patients with a negative EPS, ICM monitoring was not diagnostic in 35 cases (33%) and was diagnostic in the remaining 67%. Among the 18 patients with a positive EPS, ICM monitoring was not diagnostic in 7 cases (39%) and was diagnostic in the remaining 61%.

3.8 Symptoms

Patients with symptoms leading to ICM implantation showed significantly higher diagnostic yields (89%) than asymptomatic patients (29%; p = 0.0001).

A significantly higher diagnostic rate was detected for palpitations (76%) when compared to other symptoms (p = 0.0001) (Fig. 2). Whenever syncope was differentiated from presyncope, it showed a higher diagnostic rate than presyncope: syncope (70%), presyncope (46%), syncope associated with palpitations (80%), presyncope and palpitations (69%) (p = 0.0001).

3.9 Arrhythmias

The presence or absence of arrhythmias before ICM implantation (Table 1) was not significantly associated with a diagnosis defined by ICM, with a diagnostic yield of 61% vs 67% (p = 0.3).
Table 4. Outcome according to heart disease.

| Heart disease                        | No. patients | Diagnosis by ICM | No diagnosis by ICM |
|--------------------------------------|--------------|------------------|---------------------|
| No heart disease                     | 115          | 82 (71%)         | 33 (29%)            |
| Congenital heart defects             | 41           | 25 (61%)         | 16 (39%)            |
| Channelopathies                      | 28           | 13 (46%)         | 15 (54%)            |
| Cardiomyopathies/myocarditis         | 10           | 4 (40%)          | 6 (60%)             |
| Cardiomyopathy and channelopathy     | 1            | 0                | 1 (100%)            |
| Cardiomyopathy and congenital heart defect | 1    | 1 (100%)         | 0                   |
| Tumours                              | 4            | 1 (25%)          | 3 (75%)             |
| Total                                | 200          | 126 (63%)        | 74 (37%)            |

Significant differences \( (p = 0.008) \).

The analysis of arrhythmias already known at implantation showed that the diagnostic yield of ICMs was not significantly different: SVT (78%), SND (76%), AVB (63%), PVC (58%) and VT (39%) \( (p = 0.09) \). The diagnostic outcome in AVB patients is reported in Table 2.

3.10 Heart disease

The outcome according to heart disease is reported in Table 4 and showed a significant difference \( (p = 0.008) \). Patients without structural heart disease showed the highest diagnostic yield, followed by those with CHD.

Only one patient with LQTS showed sustained VT at ICM monitoring and was effectively treated by antiarrhythmic drugs.

No relevant arrhythmias were recorded among the 6 patients with Brugada syndrome and the 4 patients with suspected Brugada syndrome.

The 6 patients with CPVT showed non-relevant arrhythmias or symptoms during ICM monitoring and continued their pharmacologic therapy.

3.11 Device/drug treatment

Pacemaker and implantable cardioverter-defibrillator implantation was performed in 22 and 4 patients, respectively. Cryoablation of slow pathway was performed in 3 patients. Drug treatment was started in 21 patients, using antiarrhythmic drugs in 10 patients and aminophylline in 11 patients with severe cardioinhibitory syncope.

4. Discussion

Since the new millennium, ICMs have been implanted in children and adolescents, with a diagnostic yield of 50–71% \( (9–13) \). ICMs have been found to be more diagnostic in symptomatic (94%) than asymptomatic patients (30%) \[13\]. However, a substantial number of symptoms remained unexplained \[12\]. Previous studies showed that complications (pocket erosion/infection) occurred in up to 7% of patients \[10–13\]. The longest median follow-up durations were 18–19 months \[10,11\].

Over the past decade, the new miniaturized ICMs have become available \[8,14\]. Placidi et al. \[8\] first described the results of this new devices implanted in very young and small children. In that study, overall diagnostic yield was 47% but pocket erosion/infections occurred in 9% of patients \[8\]. In 2019, Bezzerides et al. \[15\] described 133 patients with ICMs and found a diagnostic yield of 58%, with positive diagnoses in 40% and negative diagnoses in 60% during a median follow-up of 12 months. Complications occurred in 4.5% of patients. Overall, 22% of patients received device treatment, 12% medication change and 6% EPS/ablation \[15\].

To the best of our knowledge, the current study reports the results of the largest cohort of pediatric and young adult ICM patients with the longest median follow-up (31 vs. 18 months \[10\]). The data obtained showed an overall diagnostic yield of 63%, which was higher in symptomatic patients (89%), in patients without structural heart disease (71%) and in those with CHD (61%). These findings are consistent with those reported for the pediatric population, with an overall diagnostic yield of 63% (vs. 58–67%) \[9,12,15\], a diagnostic yield in symptomatic patients of 89% (vs. 90%) \[13\], and in those with syncope of 70% (vs. 72%) \[12\]. The diagnostic yield was higher for patients with palpitations (76% vs. 25–43%) \[12,15\]. This finding may be due to the longer follow-up.

Negative arrhythmic diagnoses were generally more frequent than positive diagnoses, that is, symptoms occurred without any arrhythmia registered. Interestingly, in patients who underwent ICM replacement for further monitoring, the diagnostic yield was lower and positive diagnoses were more frequent than negative arrhythmic diagnoses. The main symptoms were syncope and palpitations, which are common symptoms in children and adolescents. Cardiac syncope occurred in 5%, and undefined syncope in 3% of patients referred to a Pediatric Syncope Unit \[16\]. In the current study, symptomatic patients had a high diagnostic yield especially in the presence of palpitations. The diagnostic yield rose to 80% when patients had both syncope and palpitations. Conversely, presyncope showed a lower diagnostic yield. This result is new, not being reported in previous studies that included only few cases of near syncope \[9,12\].
Fig. 3. ICM findings: oversensing. (A) Sinus arrest. Oversensing of noise, registered as ventricular activity (ventricular sensing, VS and fibrillation sensing, FS, that concluded the automatic detection of the pause, underestimating its duration). (B) 3rd degree AVB with long RR pauses. Rare oversensing of P waves detected as ventricular sensing (VS).
Our previous data revealed a 100% diagnostic yield of ICM in children with palpitations and negative EPS [8]. Data from this study in a larger population followed up for a longer period confirmed that high diagnostic yield. A negative arrhythmic diagnosis was established in the majority of patients. A positive diagnosis was made in few patients and was mainly due to atrio-ventricular node reentry tachycardia, which should be considered in case of suspicious symptoms and when other examinations, including EPS, proved inconclusive [17].

The presence of arrhythmias leading to ICM implantation was not significantly associated with a higher diagnostic yield. However, bradyarrhythmias (AVB and SND/sinus pauses) and SVT showed the best results.

AVB was the main arrhythmia leading to implantation. Patients with high-degree AVB showed mainly positive diagnoses, most often leading to pacemaker implantation (Table 2). Patients with low-degree AVB showed mainly negative arrhythmic diagnoses, requiring no treatment. These findings show that a definite diagnosis and appropriate therapy could most often be established in patients with high-degree AVB, even if asymptomatic. In patients with low-degree AVB, in whom ICM was more often implanted than in high-degree AVB because of symptoms, negative diagnoses were frequent, thus excluding the need for therapy and allowing patient’s reassurance. This is the case of symptomatic patients (syncope/presyncope, etc.) in whom ECG recording showed 1st degree or Mobitz 2nd degree AVB, but also unexpected asymptomatic (for example, nocturnal) 2:1, 3:1 or paroxysmal complete AVB. In these cases, ICM monitoring often showed that symptoms were not correlated with arrhythmias and these higher-degree AVB episodes did not require pacemaker implantation [18]. Conversely, episodes of symptomatic intermittent high-degree AVB led to pacemaker implantation.

The diagnostic performance was lower for PVCs and VT. In case of PVCs, this might occur because symptomatic patients with PVC had often similar symptoms not related to PVC, and monitoring did not show more severe arrhythmias. Furthermore, the Medtronic Reveal LINQ™ cannot automatically detect or count the PVC, but PVC episodes can be detected by patient-activated recording. On the contrary, in case of VT, ICM programming can justify the low diagnostic yield: if VT rate is lower than the tachycardia limit, asymptomatic episodes might be undetected. Conversely, if the tachycardia limit is too low, sinus tachycardia can saturate the ICM memory and the device might not record true tachycardias.

Sensing defects can occur as well. During asymptolic pauses, ventricular oversensing (muscular movements, noise artifacts) may cause underestimation of pause durations (Fig. 3). A pause episode is detected by the device when the interval between the last ventricular complex before and the first ventricular complex after the pause exceeds the planned interval. The device terminates a pause episode when it records 12 ventricular markers following its detection. However, if there are further pauses in an episode without 12 ventricular markers in between, the device will consider only the duration of the first pause. The further pauses can be detectable on ECG but are not included in the duration counter. For this reason, patients/parents were instructed not only to register the symptom but also to make a patient-activated transmission as soon as possible after an episode.

Among structural heart disease, CHD patients showed the highest diagnostic yield (61%), whereas those with cardiomyopathies the lowest. This finding seems quite consistent with that previously reported in pediatric and adult CHD patients (71%) [10] and higher than that found in adult CHD patients (41%) [19].

Conversely, channelopathies did not show a high diagnostic yield, as reported in adults [20]. Nowadays ICMs can be implanted in asymptomatic children with severe arrhythmias, including LQTS, CPVT, Brugada syndrome, or variants of unknown significance. This approach is new but justified by the small device dimensions and by the possibility of obtaining an early recognition of dangerous arrhythmias and rhythm monitoring during unclear symptoms. Therefore, this approach can guide management, and continuous cardiac monitoring may provide psychological protection to parents. However, it was shown that symptoms were not reliable surrogates for arrhythmia in children with inherited arrhythmia syndromes [21].

5. Limitations

This is a retrospective, single-centre study. Population selection might be biased by the fact that our institution is a third level centre and a Pediatric Syncope Unit, and acts as a referral centre for syncope/presyncope. This might result in higher proportions of patients with this symptom compared with a real-world scenario. Although the number of patients is quite large for a pediatric cohort, subgroup numbers may be too small for robust comparisons. Albeit some analyses were performed on the results of EPS and ICM monitoring, the study was not intended to compare or demonstrate a superiority of any of these procedures.

6. Conclusions

In a large pediatric population after long-term follow-up, ICMs showed a high diagnostic yield in the overall cohort, which was significantly higher in (1) symptomatic patients, mostly with palpitations, (2) patients without structural heart disease, and (3) patients with syncope rather than those with presyncope.

Patients with positive/negative diagnoses were significantly older than those without an arrhythmia diagnosis. However, there were no significant differences according to age subgroups.

Although most patients had negative EPS before implantation, ICMs were diagnostic in a high proportion of
patients. The diagnostic yield was higher in CHD patients than in patients with cardiomyopathies and channelopathies. Prolonged monitoring after ICM replacement did not increase the diagnostic yield.

Author contributions

MSS and FD—methodology; MSS, FD, LP, CDM, DR, IC, MCI, CP, IT, FAS, MC—validation; MSS and FD—visualization; MSS, FD, LP, CDM, DR, IC, MCI, CP, LR, IT, FAS, MC—formal analysis, investigation and data curation; MSS, FD, LP, CDM, DR, IC, MCI, CP, LR—writing - original draft preparation; MSS, FD, LP, CDM, DR, IC, MCI, CP, LR—writing - review and editing.

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review as part of the Ricerca Corrente RRC-2020-2366948.

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Conflict of interest

The authors declare no conflict of interest.

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