ORIGINAL ARTICLE

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Contribution of PET imaging to mortality risk stratification in candidates to lead extraction for pacemaker or defibrillator infection: a prospective single center study

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Abstract

Purpose ^{18}F-FDG PET/CT is an emerging technique for diagnosis of cardiac implantable electronic devices infection (CIEDI). Despite the improvements in transvenous lead extraction (TLE), long-term survival in patients with CIEDI is poor. The aim of the present study was to evaluate whether the extension of CIEDI at ^{18}F-FDG PET/CT can improve prediction of survival after TLE.

Methods Prospective, monocentric observational study enrolling consecutive candidates to TLE for a diagnosis of CIEDI. ^{18}F-FDG PET/CT was performed in all patients prior TLE.

Results There were 105 consecutive patients with confirmed CIEDI enrolled. An increased ^{18}F-FDG uptake was limited to cardiac implantable electrical device (CIED) pocket in 56 patients, 40 patients had a systemic involvement. We had nine negative PET in patients undergoing prolonged antimicrobial therapy (22.5 ± 14.0 days vs. 8.6 ± 13.0 days; $p = 0.005$). Implementation of ^{18}F-FDG PET/CT in modified Duke Criteria lead to reclassification of 23.8% of the patients. After a mean follow-up of 25.0 ± 9.0 months, 31 patients died (29.5%). Patients with CIED pocket involvement at ^{18}F-FDG PET/CT presented a better survival independently of presence/absence of systemic involvement (HR 0.493, 95%CI 0.240–0.984; $p = 0.048$). After integration of ^{18}F-FDG PET/CT data, absence of overt/hidden pocket involvement in CIEDI and a (glomerular filtration rate) GFR < 60 ml/min were the only independent predictors of mortality at long term.

Conclusions Patient with CIEDI and a **Cold Closed Pocket** (i.e., a CIED pocket without skin erosion/perforation nor increased capitation at ^{18}F-FDG PET/CT) present worse long-term survival. Patient management can benefit by systematic adoption of pre-TLE ^{18}F-FDG PET/CT through improved identification of CIED related endocarditis (CIEDIE) and hidden involvement of CIED pocket.

Keywords CIED · Survival · 18F-FDG PET · Duke criteria · Endocarditis

Introduction

The technical progress in cardiovascular implantable electrical devices (CIED) occurred in the last decades, and the expansion of indications for implantation led to a significant increase in the number and complexity of implanted devices for heart rhythm and heart failure management [1]. Consequently, CIED complications rapidly increased, in particular CIED infection (CIEDI), an issue characterized by a dramatic prognostic impact [2]. In case of CIEDI, complete hardware removal with transvenous lead extraction (TLE) is mandatory as soon as possible [3]. However, despite the improvement in TLE safety and efficacy the medium-to-long term outcomes of patients with CIEDI is poor, even after a successful TLE [4]. Several predictors of mortality have been

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proposed, in particular extension of CIEDI, but prospective long-term studies are lacking [2]. Combined fluorodesoxyglucose marked by fluorine-18 (^{18}F-FDG) positron emission tomography (PET) and computed tomography (CT) is an emerging technique for diagnosis of infectious diseases [5] which was shown to be useful in identifying the presence of systemic involvement of CIEDI [6, 7]. The aim of this single center, prospective study was to explore the role of ^{18}F-FDG PET/CT scan to improve prediction of long-term survival in candidates to TLE for CIEDI. In particular we focused on the difference between local and systemic involvement of CIEDI.

Methods

Study population

We started a prospective, single center registry including all consecutive patients referred for TLE at our tertiary university hospital; regional referral for TLE (>90% of the extracted patients are referred from other Centers of the Emilia-Romagna Region). All patients, >18 years old, referred for TLE to our center were considered for the enrollment in the registry after approval of the local ethical committee on human research (approved by the EC of the University Hospital S.Orsola-Malpighi the 11 Dec 2012, number 264/2012/O/Oss, Bologna Italy). For the specific aim of the present study, we included in the analysis only the patients satisfying the following criteria:

– Undergoing TLE for CIEDI according to current guidelines [8];
– Presence of a definite diagnosis of CIEDI based on clinical, laboratoristic, cultural and imaging data but without the need of PET/CT scan. Both local (signs and symptoms of infection limited to generator pocket) and systemic CIEDI were accepted. All diagnosis of CIEDI and indication for TLE have been re-evaluated at our Center by an expert team comprising a cardiologist, an echocardiography specialist, a microbiologist and an electrophysiologist [7];
– The patient, appropriately informed of the purpose of the study, signed the informed consent.

Notably, since March 2013 in our center, we perform ^{18}F-FDG PET/CT not only as a support in working out the diagnosis of CIEDI but also in all patients with a formal diagnosis of CIEDI to help post-TLE management (i.e., planning re-implantation strategy and the duration of antibiotic treatment). All data from the enrolled patients were anonymized and stored in a dedicated electronic database. We recorded data about patients' characteristics (sex, baseline clinical parameters and existing comorbidity, drugs in use, CIEDI

characteristics and cultures), CIED devices and implantation features, ^{18}F-FDG PET/CT scans data and TLE procedure data and complications. We excluded from our study all patients referred for TLE who could not undergo PET/CT scanning for any reason.

^{18}F-FDG PET/CT scanning

All patients underwent ^{18}F-FDG PET/CT scan at our Unit for Nuclear Medicine. The methods were previously reported [7, 9]. In brief, all patients underwent a 1 day of high-fat and low-carbohydrate diet followed by a > 12 h fasting period and administration of standard dose of ^{18}F-FDG (370 MBq) 60 min before image acquisition. A low-dose combined CT scan was acquired in order to perform PET images correction for attenuation and anatomical reconstruction. ^{18}F-FDG PET/CT was examined by two expert nuclear physicians, who assessed both attenuation-corrected as well as non–attenuation-corrected images in order to recognize artifacts related to the correction of attenuation in proximity of an object of high density (e.g., metal of CIED). ^{18}F-FDG PET/CT was considered positive for CIED infection in the presence of abnormally elevated ^{18}F-FDG uptake involving CIED pocket or leads.

According to ^{18}F-FDG PET/CT scan results, patients were divided in two groups (systemic and not systemic CIEDI), depending on the pattern of radioactive tracer increased uptake. A ^{18}F-FDG uptake pattern indicative of leads involvement (after entering in the venous system) and/or presence of septic embolism or cardiac valves involvement was considered a positive PET/CT exam for systemic CIEDI, while ^{18}F-FDG PET/CT showing an increased uptake of ^{18}F-FDG limited to CIED generator pocket was classified as not systemic. Patients with a negative ^{18}F-FDG PET/CT scan were also considered affected by CIEDI without systemic involvement at PET/CT scan. Notably, per inclusion criteria for the analysis, the diagnosis of infection was already posed before performing ^{18}F-FDG PET/CT. Excluding these patients could include a bias in favor of PET/CT scan, and the study group unanimously decided to include these patients as previously stated.

Assessment of CIED-related endocarditis

All patients underwent a standardized clinical care pathway at our center, as previously reported [7, 10]. In brief, it included a detailed medical history, clinical examination, routine blood tests (including inflammatory markers), wound swabs, and multiple blood cultures (≥3 sets). All patients were investigated with both transthoracic and transesophageal echocardiography (by operators unaware of this study), before and early after TLE (within 24 h) to assess left/right ventricular structure and function, possible valvular involvement, pericardial

effusion, and other relevant findings. A post-TLE tubular, mobile mass, following the previous lead intracardiac route in the right-sided heart chambers, not related to valvular infective endocarditis (IE) and subvalvular tricuspid apparatus, was defined as a "ghost" [10].

An assessment of the presence of CIED related endocarditis (CIEDIE) was performed for all patients, before and after administration of ^{18}F-FDG PET/CT scan, providing two different classifications. At first, the diagnosis of CIEDIE was formulated by a multidisciplinary team (electrophysiologist, echocardiography specialist and microbiologist) according to modified Duke criteria [11]. According to Duke criteria, an echocardiogram was adopted as the standard imaging tecnique for this first classification (Duke-Standard). For the purpose of the present study, after this initial classification, every case was re-assessed including the results of ^{18}F-FDG PET/CT (with the intervention of an expert nuclear physician, included in the multidisciplinary team) to provide a second, post-PET, classification (Duke-PET).

Management of CIEDI and follow-up

All patients referred for TLE underwent antimicrobial therapy after the specimen of at least three samples of blood culture. An infective diseases specialist physician was consulted for all patients, and antibiotic therapy was individualized in agreement with the cardiologist after blood culture results. After TLE, lead tips, generator and pocket swab were sent to a laboratory for culturing. TLE procedure was performed by well-trained electrophysiologists in a high volume referral center, according to current recommendations [3]. A cardiac surgeon backup was present for every procedure, and a hybrid operating room was employed for all TLE since December 2015. Patients with recent CIED implantation (<12 months) and without major comorbidities underwent TLE under conscious sedation, while general anesthesia was adopted for all other patients. A temporary pacemaker was positioned in pacing-dependent patients during the procedure (when an epicardial re-implantation did not precede TLE). After the first step of generator removal the transvenous leads were removed by simple manual traction when feasible. In case of traction resistant leads, a mechanical sheath extraction or laser powered excimer sheath (SLS II, Spectranetics, Colorado Spring, CO, USA) was performed. A revision of CIED indication was observed in every patient undergoing TLE, and reimplantation was done only when necessary (as in the case of pacemaker-dependent patients). When feasible, an extravascular approach for CIED reimplantation was preferred. Every patient was followed after discharge by in-office evaluation at 6 and 12 months and subsequently annually. Moreover, a phone interview was performed every 6 months. A closer follow-up was adopted for compromised patients or subjects who did not have CIED re-implantation. Data collected during follow-up period include clinical course, re-hospitalizations, CIED re-implantation.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation if they presented a normal distribution at the Kurtosis and Kolmogorov–Smirnov tests and as median and interquartile ranges if a normal distribution was not evident. In accordance, significance of between-group differences was assessed with two tailed Student's t test, or with equivalent non-parametric tests, when appropriate. Discrete variables were expressed as frequencies and percentages, and significance of different distribution was determined by the Chi-squared or Fisher's exact test (as appropriate) for binary variables, and the Mann-Whitney test for ordinal variables. Kaplan–Meier survival curves were constructed for the estimation of unadjusted survival distributions from death for any cause. The log-rank test was adopted to assess between-group survival and stepwise forward Cox proportional hazards regression analysis was performed to determine characteristics that were related to the outcome; covariates with p values less than 0.05 in the log rank test were entered in the multivariate model. Hazards risks (HR) were reported with 95% confidence intervals (95%CI). Statistical calculations and survival plots were prepared with SPSS Version 23.0.0 (Statistical Package for Social Sciences Inc.), with significance set at $p < 0.05$.

Results

Enrolled population

A total of 105 consecutive patients (81.0% males) aged 72.7 years, referred to our center for TLE to treat CIEDI, underwent ^{18}F-FDG PET/CT before TLE from 1 March 2013 to 31 May 2016. In the same study period only three patients did not undergo PET/CT scan, because of logistic reasons, while one patient was not included since he refused consent to participation in the study. In 57.1% of the enrolled patients, the device involved in CIEDI was a defibrillator (ICD), while 22.9% carried a CIED with resynchronization capability (CRT). The average indwelling time of the oldest lead was 98.5 ± 83.6 months (range 3.0–363.4 months). Among enrolled patients 60.0% presented an "open" CIED pocket (i.e., draining sinus or partial/total externalization of CIED), with positive blood cultures in 40.0% (of whom 22.9% were positive for *S. aureus* species), and 27.6% had documentation of lead endocarditis at transthoracic/transesophageal echocardiography.

^{18}F-FDG PET/CT results and CIEDIE diagnosis

The ^{18}F-FDG PET/CT scan showed a local extension of CIEDI in 56 patients, while 40 patients had systemic involvement, associated with septic embolism in 12. An adequate cardiac ^{18}F-FDG uptake suppression was obtained in 98/105 patients (in 6/7 of the remaining patients a second PET/CT scan was performed because of this issue, if the other presenting a local infection without any other sign of systemic involvement, it was deemed not clinically relevant). The resulting patterns of CIED infection localization after ^{18}F-FDG PET/CT scan are represented in Fig. 1. Table 1 shows the characteristics of the enrolled population according to presence/absence of systemic involvement shown by ^{18}F-FDG PET/CT. Unsurprisingly, patients with systemic involvement more frequently presented also positive blood cultures and pre-TLE vegetations, while an open CIED pocket was less frequent. Notably, in nine patients, despite the clinical evidence of CIEDI, the results of ^{18}F-FDG PET/CT excluded any significant involvement of the CIED system, either local or systemic. Eight patients of this subgroup had reported at least one episode of temperature > 38 °C, all had documentation of positive blood cultures and presence of lead masses was found in seven. These patients differed from the remaining cohort in antibiotic therapy before ^{18}F-FDG PET/CT that was: (1) more frequently used (100% vs. 64.6% of

the patients; $p = 0.03$), (2) for a longer period (22.5 ± 14.0 days vs. 8.6 ± 13.0 days; $p = 0.005$) and (3) usually targeted to positive blood cultures (88.9% vs. 40.3%; $p = 0.006$). Regarding CIED infective endocarditis (CIEDIE) assessment, Fig. 2 shows patient stratification based on modified Duke Criteria before and after performance of ^{18}F-FDG PET/CT. In brief, 25/105 (23.8%) patients were re-classified with 11 new cases of confirmed CIEDIE (with a relative increase of 44.0%). Finally, the PET/CT scan of the 42 patients with a closed CIED pocket showed: only systemic involvement in 16, involvement limited to the pocket in 11, seven both systemic and pocket involvement, and eight patients presented a negative PET/CT scan.

TLE outcomes and long-term follow-up

TLE was performed in all the patients, requiring powered sheaths in 64/105 without any relation with ^{18}F-FDG PET/CT results. Complete radiological success was obtained in all but five leads, 3/5 with partial radiological success (two procedures interrupted for major complications). After hardware removal, post-extraction "ghosts" were present in 15/105 patients. Clinical success was achieved in 103/105 patients, with two subjects experiencing a major complication secondary to a vascular tear promptly repaired by the cardiac surgeon who also completed lead extraction with epicardial re-implantation. Three patients developed post-TLE pocket

Fig. 1 Different patterns of CIED infection at ^{18}F-FDG PET/CT. **a** infection involves both CIED pocket and catheters (including pulmonary septic embolism, yellow arrow). **b** Increased ^{18}F-FDG uptake limited to CIED leads. **c** involvement only of the pocket. **d** ^{18}F-FDG PET/CT is negative, despite clinical/instrumental signs of infection (e.g., lead-related vegetations at echocardiogram, white arrow); vegetation in the upper right atrium is circled in red. Legend: LA = left atrium; RA = right atrium
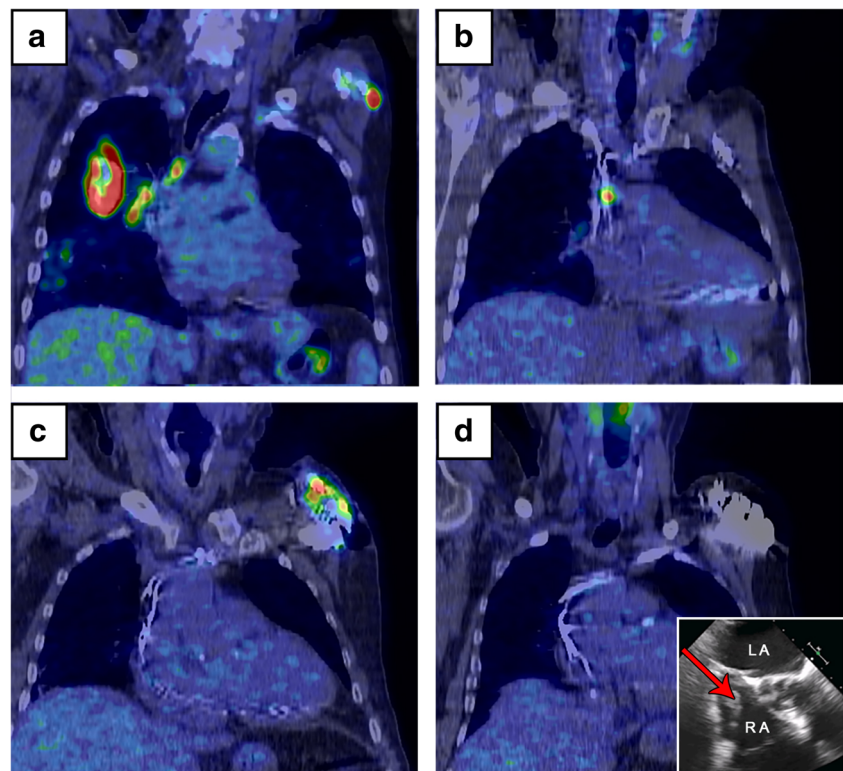
Table 1 Baseline and TLE characteristics of enrolled patients according to presence/absence of systemic involvement of CIEDI at ^{18}F-FDG PET/CT scan

	Not systemic CIEDI 65 patients	Systemic CIEDI 40 patients	P
Baseline characteristics			
Age (years; mean ± SD)	73.3 ± 10.0	71.8 ± 12.8	0.507
Male (%)	80.0	82.5	0.751
LVEF ≤35% (%)	30.8	30.0	0.934
GFR ≤ 60 (%)	64.6	77.5	0.164
CAD (%)	50.8	42.5	0.410
DCM (%)	47.7	50.0	0.818
CHF (NYHA >2; %)	10.8	27.5	0.027
HBP (%)	75.4	65.0	0.253
DM (%)	30.8	32.5	0.928
COPD (%)	9.2	12.5	0.595
ICD (any) (%)	52.3	65.0	0.202
PM dependency (%)	29.2	25.6	0.693
Prev. CIED generator replacement (%)	60.0	55.0	0.614
Prev. CIED upgrade (%)	10.8	5.0	0.305
CIED first implantation (%)	26.2	40.0	0.138
Anticoagulant therapy (%)	46.2	55.0	0.379
Antiplatelet therapy (%)	50.8	47.5	0.745
≥ 3 leads (%)	10.8	25.0	0.055
CRP (mg/l; mean ± SD)	1.6 ± 4.1	2.3 ± 2.6	0.406
WBC count (10^9/l; mean ± SD)	6.9 ± 1.9	6.9 ± 2.5	0.958
Lymphocyte count (10^9/l; mean ± SD)	1.5 ± 0.7	1.3 ± 0.7	0.186
RBC count (10^{12}/l; mean ± SD)	4.4 ± 0.7	4.0 ± 0.6	0.010
Platelets count (10^9/l; mean ± SD)	207.1 ± 74.3	193.8 ± 75.0	0.393
Drugs in use			
Steroid therapy (%)	5.0	0.0	0.263
Immunosoppressor therapy (%)	4.6	0.0	0.168
SGLT2 inihibitors (%)	1.5	0.0	0.431
Digoxin (%)	4.6	10.0	0.283
Diuretics (%)	70.8	75.0	0.638
ACEi and ARBs (%)	66.2	57.5	0.373
Beta blockers (%)	58.5	72.5	0.146
Ca antagonists (%)	16.9	12.5	0.540
AAD (%)	10.8	10.0	0.901
Anti-aldosterone (%)	23.1	22.5	0.945
Infection			
SUV max (mean ± SD)	6.6 ± 2.8	5.7 ± 2.9	0.155
Vegetations pre-TLE (%)	20.0	41.0	0.021
Positive BC (%)	30.8	55.0	0.014
Open pocket (%)	70.8	42.5	0.004
Abio. pre-TLE (%)	61.5	75.0	0.155
Pos. lead cult. (%)	47.7	57.5	0.329
Pos. CIED cult. (%)	50.8	52.5	0.863
S. aureus (%) (lead/BC)	23.1	22.5	0.945
Pulmunary Embolism (%)	0.0	30.0	<0.001
Ghost (%)	9.2	22.5	0.059

Legend: *AAD*, antiarrhythmic drugs; *Abio pre-TLE*, antibiotics before lead extraction; *ACEi*, ACE inihibitors; *ARBs*, Angiotensin II Receptor Blockers; *BC*, blood culture; *Ca antagonists*, calcium channel blockers; *CAD*, coronary artery disease; *CHF*, chronic heart failure; *CIED*, cardiovascular implantable electronic device; *CIEDI*, cardiovascular implantable electronic device infection; *COPD*; chronic obstructive pulmonary disease; *CRP*, C-reactive protein; *DCM*, dilated cardiomyopathy; *DM*, diabetes mellitus; *GFR*, glomerular filtration rate; *HBP*, high blood pressure; *ICD*, implantable cardioverter-defibrillator; *LVEF*, Left ventricular ejection fraction; *NYHA*, New York Heart Association, *PM*, pacemaker; *RBC*, red blood cells; *S. Aureus*, *Staphylococcus aureus*; *SD*, standard deviation; *SGLT2*, sodium/glucose cotransporter 2; *TLE*, transvenous lead extraction; *WBC*, white blood cells

hematoma. After a mean follow-up of 25.0 ± 9.0 months, 31 patients died. The cause of death was cardiovascular in 11 patients (progressive heart failure in five patients, myocardial infarction in three patients, ischemic stroke in two patients and sudden cardiac death in one patient, respectively) and non-cardiovascular in 15 (sepsis despite effective TLE in seven cases, multi-organ failure in five and cancer in five, respectively). In the remaining five patients it was not possible to clearly define the death cause.

Fig. 2 Patients classification according to modified Duke criteria [11] before (Duke – Standard) and after (Duke – PET) administration of ^{18}F-FDG PET/CT scan. Patients who have changed their score after ^{18}F-FDG PET/CT are represented with an arrow. The number inside the circle expresses the number of patients reclassified according to ^{18}F-FDG PET/CT results
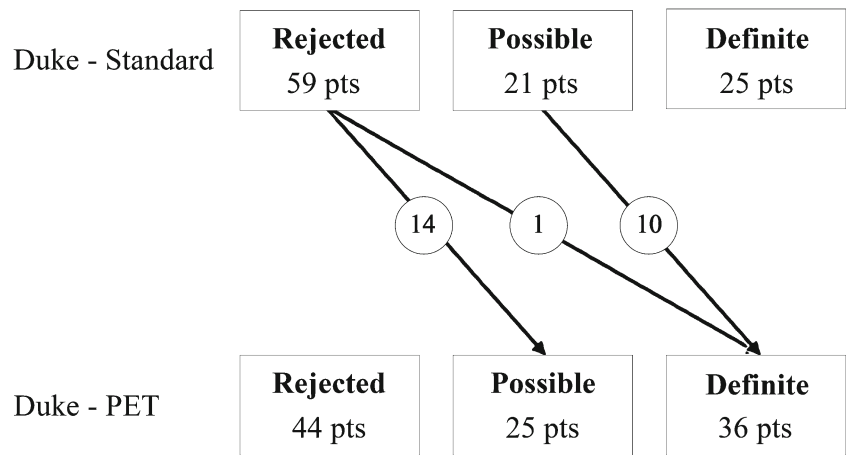

Predictors of death or CIEDI relapse/recurrence

Figure 3 reports the Kaplan-Meier curves for long-term survival from overall death according to presence of systemic involvement at ^{18}F-FDG PET/CT and showing a non-significant trend in increased mortality in this subgroup. This was also confirmed after exclusion of the nine patients with negative PET/CT scan. However, when the results of ^{18}F-FDG PET/CT were implemented in modified Duke Criteria assessment (Duke-PET), the presence of definite CIEDIE reached significance in terms of long-term overall mortality, while it was non-significant considering the pre-PET evaluation (Duke-Standard) (Fig. 4). Notably, the type of involved bacteria (when identified by blood cultures and/or lead cultures) was not associated with different outcomes in our population, either considering presence/absence of Gram positive agents either presence/absence of *S. aureus* involvement. When considering the various predictors, only four factors were significantly associated with post-TLE overall mortality

both at univariate and multivariate analysis: a left ventricular ejection fraction equal or less than 35%, a glomerular filtration rate < 60 ml/min, presence of post-extraction ghosts [10] and presence of a "closed" CIED pocket, that is the absence of skin erosion/perforation in the pocket site (Table 2, Model 1). The only parameter originally derived by ^{18}F-FDG PET/CT scan data that reached significance (including SUV values) was the presence of definite CIEDIE at Duke-PET modified score ($p = 0.047$); however, it was not included in the final model since it was eliminated during the stepwise forward process, for lack of significance. Considering these results, we re-assessed the contribution of ^{18}F-FDG PET/CT in predicting long-term mortality, by focusing on the presence/absence of active CIED pocket infection, in view of the relevance of this data in the first model (in terms of open vs. closed CIED pocket). Then 77/105 patients presented a positive CIED pocket at PET/CT scan: 59/77 in patients with an open CIED pocket and 18/77 in patients with a closed CIED pocket. Notably, this factor was found to be statistically

Fig. 3 Kaplan - Meier curves of survival from death from any cause according to presence/absence of systemic involvement at baseline ^{18}F-FDG PET/CT scan
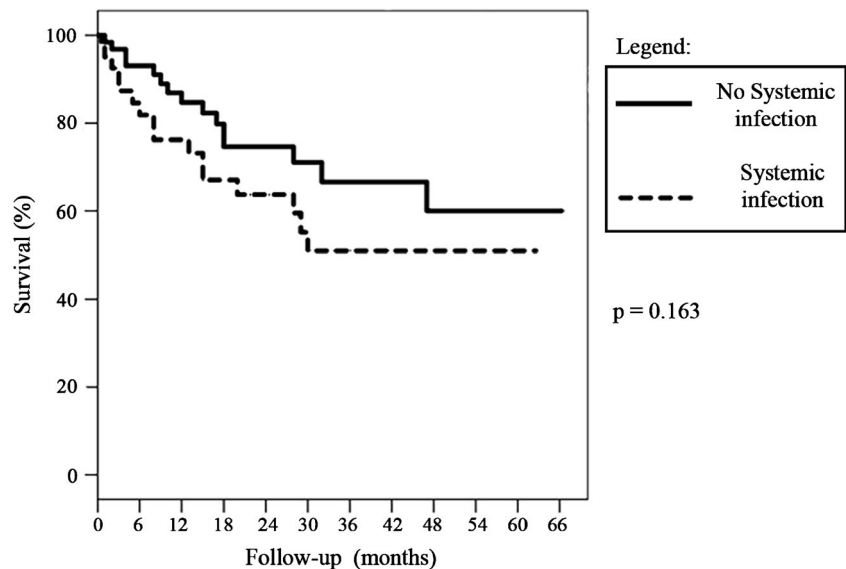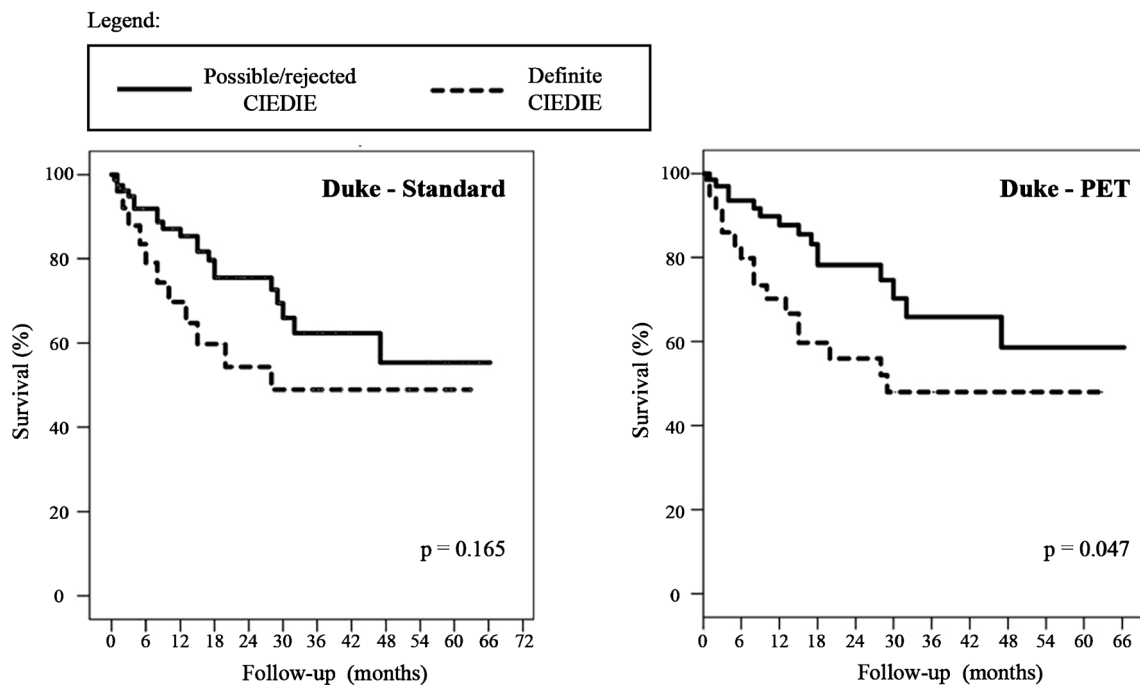
Fig. 4 Kaplan - Meier curves of survival from death from any cause according to presence of defined CIED infective endocarditis (CIEDIE) assessed before (Duke – Standard) and after ^{18}F-FDG PET/CT scan (Duke – PET)

relevant: a positive CIED pocket in ^{18}F-FDG PET/CT scan was associated with a better prognosis (HR 0.493, 95% CI 0.240–0.984; $p = 0.048$), but it did not show to be an independent predictor at Cox regression analysis. Accordingly, we combined the ^{18}F-FDG PET/CT data on CIED pocket with the presence/absence of an evident open CIED pocket. The new resulting variable was called "**Cold Closed Pocket**" (i.e., a negative CIED pocket at 18F-FDG PET/CT without skin erosion/perforation). The resulting parameter, found in 24/ 105 patients, was strongly significant both at univariate (Fig. 5) and multivariate analysis (Table 2, Model 2). Notably, its contribution not only was more relevant than open CIED pocket alone, but also it prevented inclusion of two variables (i.e., presence of ghosts and reduced left ventricular ejection fraction) from being included in Model 2. Patients with **Cold Closed Pocket** (see Table 3) presented a longer time from last CIED procedures to CIEDI/TLE (median 29.0 months, interquartile range 8.9–59.6 months vs. 6.7 months, 3.4–30.1 months; $p = 0.006$) and a higher prevalence of first implant as the last CIED (and unique) procedure (54.17% vs. 24.69%; $p = 0.006$) before TLE. In particular, only 12.5% of patients with Cold Closed Pocket underwent TLE in the first 6 months after last CIED procedure vs. 45.7% of the remaining subjects ($p = 0.003$). Moreover, this group of patients more frequently had positive blood cultures (83.3 vs 27.2%, $p < 0.001$) and vegetations (66.7 vs 16.1%, $p < 0.001$), with involvement of S. aureus (37.5% vs. 18.5%, $p = 0.052$). On the opposite culturing of CIED generator, it was more frequently negative (20.8% vs. 60.5%, $p = 0.001$). Finally,

patients with a **Cold Closed Pocket** had a lower erythrocyte concentration and a higher prevalence of ghosts after TLE (33.3% vs. 8.6%, $p = 0.002$).

Discussion

In the present paper we reported the results of our experience with routine use of ^{18}F-FDG PET/CT in all candidates to TLE for CIEDI. This approach was adopted to improve sensitivity of pre-TLE diagnosis of systemic involvement to plan re-implantation strategy according to current guidelines and available technologies (i.e., transvenous, leadless or epicardial) on the basis of patient's needs. This approach allowed us to focus on the evaluation of the prognostic role of ^{18}F-FDG PET/CT after TLE for CIEDI.

We tested the hypothesis that a systemic involvement of CIEDI documented by ^{18}F-FDG PET/CT could predict a worse outcome. However, this concept was not confirmed by our results, in line with previous papers showing that long-term survival is poor for both local and systemic CIEDI [4, 12, 13]. A possible explanation could be the presence of a bias introduced by the use of antibiotic treatment before ^{18}F-FDG PET/CT in about two thirds of the patients. Beyond the correctness of this consideration, we have to take into account the following real-world issues: (1) availability of ^{18}F-FDG PET/CT scan in smaller center (spoke center for TLE), (2) delay in suspecting CIEDI and (3) difficulties introduced by the need to transfer the patient to a referral center for TLE in
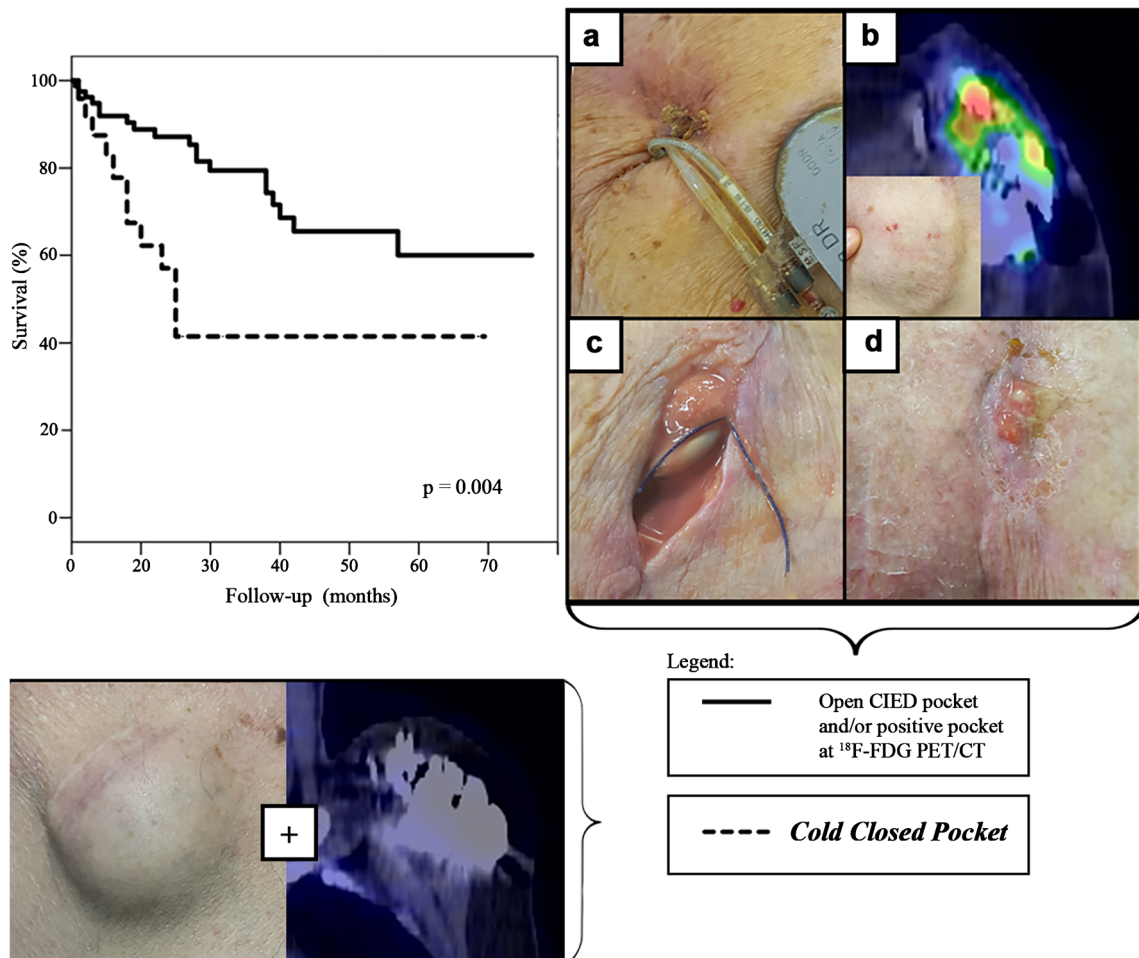
Fig. 5 Kaplan - Meier curves of survival from death from any cause according to presence/absence of a **"Cold Closed Pocket"** defined as absence of any pocket skin lesion or capitation at ^{18}F-FDG PET/CT scan. Legend: **a**, **c**, **d** = examples of CIED infection with overt pocket involvement. **b** = CIED infection with hidden pocket involvement, unmasked by ^{18}F-FDG PET/CT

proper condition to perform a safe and effective TLE. Limiting the analysis to patients naïve from antibiotics and/or with a prolonged antibiotics washout could bias the results (e.g., excluding more compromised patients) and/or provide data hardly transferable to current clinical practice. Moreover,

the lack of significance of systemic involvement at PET/CT scan as a predictor of long-term mortality is reinforced by the sensitivity analysis we performed by excluding the nine patients with "false" negative ^{18}F-FDG PET/CT. As previously said, several authors already reported that systemic CIEDI is

Table 2 Results of multivariate cox regression analysis for prediction of overall death

	Model 1 Not including PET data Mortality HR (95% CI)		Model 2 Including PET data Mortality HR (95% CI)	
GFR < 60 ml/min	4.22 (1.45–12.28)	$p = 0.008$	4.34 (1.51–12.48)	$p = 0.006$
LVEF ≤ 35%	2.07 (1.01–4.24)	$p = 0.047$		n.s.
Closed CIED pocket	2.13 (1.02–4.46)	$p = 0.045$		n.s.
Post-TLE Ghost	2.39 (1.05–5.40)	$p = 0.037$		n.s.
Closed pocket + Negative PET scan	N.I.	N.I.	2.84 (1.37–5.89)	$p = 0.005$

Legend: *CI*, confidence interval; *CIED*, cardiac implantable electronic device; *LVEF*, left ventricular ejection fraction; *GFR*, glomerular filtration rate; *HR*, hazard ratio; *N.I.*, not included; *n.s.*, no significance; *TLE*, transvenous lead extraction

Table 3 Comparison between clinical characteristics of subgroup with a *Cold Closed Pocket* (negative ^{18}F-FDG PET/CT scan and no clinical signs of pocket infection) and other patients

	Cold Closed Pocket 24 patients	No Cold Closed Pocket 81 patients	P
Baseline characteristics			
Age (years; mean ± SD)	69.4 ± 11.9	73.7 ± 10.7	0.097
Male (%)	91.7	77.8	0.128
LVEF ≤35% (%)	41.7	27.2	0.175
GFR ≤ 60 (%)	66.7	70.4	0.729
CAD (%)	54.2	45.7	0.465
DCM (%)	54.2	46.9	0.532
CHF (NYHA >2; %)	33.3	12.4	0.017
HBP (%)	58.3	75.3	0.106
DM (%)	41.7	28.4	0.209
COPD (%)	16.7	8.6	0.260
ICD (any) (%)	66.7	54.3	0.202
PM dependency (%)	12.5	32.1	0.055
Prev. CIED generator replacement (%)	37.5	64.2	0.020
Prev. CIED upgrade (%)	4.2	9.9	0.380
CIED first implantation (%)	54.2	24.7	0.006
Anticoagulant therapy (%)	62.5	45.7	0.148
Antiplatelet therapy (%)	45.8	50.6	0.681
≥ 3 leads (%)	16.7	16.1	0.943
CRP (mg/l; mean ± SD)	2.2 ± 2.0	1.8 ± 4.0	0.601
WBC count (10^9/l; mean ± SD)	6.9 ± 3.0	6.9 ± 1.8	0.984
Lymphocyte count (10^9/l; mean ± SD)	1.3 ± 0.7	1.5 ± 0.7	0.333
RBC count (10^{12}/l; mean ± SD)	4.0 ± 0.7	4.3 ± 0.6	0.035
Platelets count (10^9/l; mean ± SD)	191.3 ± 77.7	205.0 ± 73.7	0.445
Drugs in use			
Steroid therapy (%)	4.2	1.2	0.356
Immunosuppression therapy (%)	4.2	2.5	0.661
SGLT2 inhibitors (%)	0.0	1.2	0.771
Digoxin (%)	4.2	7.4	0.576
Diuretics (%)	70.8	72.8	0.847
ACEi and ARBs (%)	45.8	67.9	0.049
Beta blockers (%)	66.7	63.0	0.740
Ca antagonists (%)	12.5	16.5	0.671
AAD (%)	8.3	11.1	0.696
Anti-aldosterone (%)	29.2	21.0	0.402
Infection			
SUV max (mean ± SD)	5.9 ± 3.1	6.1 ± 2.8	0.800
Vegetations pre-TLE (%)	66.7	16.1	<0.001
Positive BC (%)	83.3	27.2	<0.001
Abio. pre-TLE (%)	100.0	56.8	<0.001
Pos. lead cult. (%)	50.0	51.9	0.873
Pos. CIED cult. (%)	20.8	60.5	0.001
S. Aureus (lead/BC; %)	37.5	18.5	0.052
Pulmonary Embolism (%)	20.8	8.6	0.099
Ghost (%)	33.3	8.6	0.002

Legend: *AAD*, antiarrhythmic drugs; *Abio pre-TLE*, antibiotics before lead extraction; *ACEi*, ACE inhibitors; *ARBs*, Angiotensin II Receptor Blockers; *BC*, blood culture; *Ca antagonists*, calcium channel blockers; *CAD*, coronary artery disease; *CHF*, chronic heart failure; *CIED*, cardiovascular implant-able electronic device; *CIEDI*, cardiovascular implantable electronic device infection; *COPD*; chronic obstructive pulmonary disease; *CRP*, C-reactive protein; *DCM*, dilated cardiomyopathy; *DM*, diabetes mellitus; *GFR*, glomerular filtration rate; *HBP*, high blood pressure; *ICD*, implantable cardioverter-defibrillator; *LVEF*, Left ventricular ejection fraction; *NYHA*, New York Heart Association, *PM*, pacemaker; *RBC*, red blood cells; *S. Aureus*, *Staphylococcus aureus*; *SD*, standard deviation; *SGLT2*, sodium/glucose cotransporter 2; *TLE*, transvenous lead extraction; *WBC*, white blood cells

not associated per se with a bad prognosis [4, 12, 13], suggesting the presence of additional factors influencing patients' outcomes; however, all these studies did not include PET/CT scan data, the reason for which aimed our analysis. Two possible explanations for these findings can be the importance of a patient-specific worse clinical profile [13] or a later referral for TLE as the driving factors leading to an increased

mortality. However, another more intriguing hypothesis reinforced by our results is that CIEDI can develop by two different mechanisms, which are associated with different long-terms outcomes: (1) spreading from CIED pocket or (2) direct colonization of the leads (by acute or recurrent bacteremia). It is commonly thought that in almost all patients CIEDI starts from the CIED pocket and later spreads to blood stream

(mechanism "1"). However, there is also the chance that a primary blood stream infection (secondary to temporary or repeated bacteremia) can seed onto the leads and start a metastatic infection (mechanism "2"). Factors supporting the second mechanism in a specific subject should be: (1) no temporal association between CIED pocket opening and CIEDI occurrence; (2) increased association between recent deployment of hardware in the blood stream (before endothelialization) and development of CIEDI; (3) absence of pocket involvement in CIEDI; and (4) evidence of lead involvement in CIEDI. The latter mechanism can be the case of many subjects with a "**Cold Closed Pocket**", the following results support this hypothesis (see Table 3):

- The higher prevalence of positive blood cultures (and vegetations) with CIED cultures being usually negative;
- The lower number of CIED related procedures performed before TLE with less CIED replacement (involving only the device pocket) and a higher prevalence of first implant as the last CIED procedure (involving a higher "burden" of non-endothelialized hardware in the blood stream);
- A longer time from last CIED procedure to CIEDI/TLE (which decreases the temporal association between CIEDI procedure and CIEDI).

A recently published registry focusing on CIEDI [14], and in particular on a cohort of patients with lead-related endocarditis, showed that this kind of infection when it occurs after 6 months from last CIED procedure are more frequently due to sources different from CIED pocket manipulation. However, this observation presented two limitations: the specific subgroup of patients involved and the arbitrary time cut-off from last CIED procedure. The relevance of a "seeding from remote" mechanism underlying CIEDI is not only theoretical but also practical for CIEDI prevention and post-TLE management. Current prevention of CIEDI is based on reducing surgical site infection [15, 16], which may not be effective for this subgroup of subjects, while a greater benefit could derive from leadless technologies [17, 18]. The results of the ongoing Worldwide Randomized Antibiotic EnveloPe Infection PrevenTion Trial (WRAP-IT) trial [19] comparing a strategy with or without the adoption of a new absorbable envelope with antibiotic release, a strategy associated with impressive results in non-randomized studies, will provide further insights on this topic.

A second interesting, albeit less novel, result of our study is the evidence that about one fourth of the patients with a final diagnosis of CIEDI already candidate to TLE can be re-stratified in terms of presence/absence of CIEDIE (Fig. 2). The systematic adoption of ^{18}F-FDG PET/CT (considering systemic involvement and/or septic embolism) indeed allowed us to reclassify 25 of 105 patients, with 11 new diagnosis of definite CIEDIE. ^{18}F-FDG PET/CT capability to

improve diagnostic sensitivity of CIEDI has already been highlighted [6, 7, 20], in particular for the contribution in identifying septic emboli, a task of considerable importance for "staging" of CIEDI and management of antimicrobial therapy [21]. This information is of paramount importance to plan post-TLE antimicrobial therapy (up to 6 weeks of antibiotic therapy in case of diagnosis of endocarditis [3]) and timing of CIED reimplantation (without CIEDIE a re-implant can be performed 3 days after TLE, while a longer wait is recommended otherwise [22]). ^{18}F-FDG PET/CT, however, is not included in current guidelines as a standard for to CIEDI diagnostic work-up, being costs and availability as the main issues for routine implementation.

Despite these encouraging findings, we had nine patients with a false negative ^{18}F-FDG PET/CT (sensitivity 91.4%). Current literature reported a good performance of this technique with a sensitivity ranging between 82.0 and 88.6% for CIEDI [6, 23] in general, which is higher for CIED pocket infections (94%) [24], and lower for lead infection (65%) [24]. In our cohort the 8/9 subjects with a "false" negative ^{18}F-FDG PET/CT scan presented several signs of systemic involvement, and they underwent prolonged antibiotic therapy, more often targeted to the specific agent antibiotic (8/9 had positive blood cultures). Similar findings were reported by Amraoui et al. [21] who showed a high percentage (88%) of patients with prior antimicrobial therapy among false negatives cases. Prolonged antibiotic therapy is a known cause of false-negative ^{18}F-FDG PET/CT scans for infective endocarditis [25], while we lack targeted studies for CIED infection [24]. These findings suggest that ^{18}F-FDG PET/CT scan should be performed early in the diagnostic work-up of patients with CIED infection, possibly before starting an empiric antibiotic therapy, or (in selected cases) after an antibiotic wash-out period.

From a practical point of view, adoption of ^{18}F-FDG PET/CT scans in 100% of the candidates to TLE for CIEDI infection could improve patient management by dramatically increasing the sensitivity for CIEDIE (+44%) and the prediction of long-term survival. However, it could be speculated that we could obtain similar improvements by limiting this test to patients with diagnosis of CIEDI + closed CIED pocket and patients with possible CIEDIE (according to standard Duke criteria) with an open CIED pocket, being about a half of our population (50/105; respectively 42 and eight patients). Future studies are warranted to confirm our findings in broader populations.

Strengths and limitations

One of the major limitations of the present study is the size of the examined population with a number of 105 cases, which limits the possibility to establish a definite correlation between

^{18}F-FDG PET/CT scan results and outcome. However, to our knowledge, this is the largest study regarding ^{18}F-FDG PET/CT utilization in CIED infection for a prognostic assessment. Another potential issue is the single center nature of this study. It should be noted, nevertheless, that our hospital is a regional referral center for TLE, thus being representative of a wide population. Furthermore, our findings may be influenced by the administration of antimicrobial therapy before execution of ^{18}F-FDG PET/CT scan in a significant number of patients, often started before a definite diagnosis of CIED infection, decreasing ^{18}F-FDG PET/CT diagnostic sensitivity. This is, however, a widespread practice of emergency care givers in the context of a patient with clinical signs of infectious disease of still unknown origin, allowing our results to be representative of a "real-world" context. Finally, we have not performed a systematic revision of non-corrected PET/CT to assess the role of additional parameters, like a semi-quantitative ratio as reported in a recent paper [20], since until the middle of the study they were visually inspected to finalize the report but not systematically saved.

Conclusions

According to our results the promising role of ^{18}F-FDG PET/CT in CIEDI management can potentially extend beyond the improvement of diagnostic sensitivity to prediction of post-TLE outcomes. In particular integration of ^{18}F-FDG PET/CT with CIEDI clinical characteristics, leading to identification of patients with a ***"Cold Closed Pocket"*** (i.e., a negative CIED pocket at ^{18}F-FDG PET/CT without skin erosion/perforation) can be clinically relevant, in view of the poor outcome found in this subset of patients. Moreover, about one fourth of the patients with a final diagnosis of CIEDI can be re-stratified in terms of presence/absence of CIEDIE with the integration of ^{18}F-FDG PET/CT data. Future researches are needed to confirm the role of ^{18}F-FDG PET/CT as a standard of care in all candidates to TLE without a confirmed CIEDIE and/or a closed CIED pocket to improve patient management.

Compliance with ethical standards

Conflict of interest   All the authors have no conflict of interest.

Ethical approval   All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments.

Informed consent   Informed consent was obtained from all individual participants included in the study.

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