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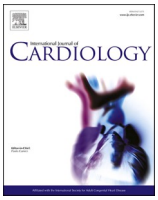

Clinical presentation and echocardiographic characteristics of women with peripartum cardiomyopathy: Insights from the Italian Multicentre Registry☆

Federica Ilardi [a,b,1], Rachele Manzo [a,1], Giovanni Peretto [c,d], Francesca Lanni [e], Vanessa Peano [f], Francesco S. Loffredo [g,h], Daniele Masarone [h], Donato Gerardi [i,l], Silvana di Maio [j], Luca Bardi [b], Marco Licciardi [c,d], Nicolò Montali [f], Enrica Pezzullo [g,h], Emilio Di Lorenzo [h], Eugenio Stabile [i,l], Ciro Battaglia [a], Maria Calanducci [c,d], Giuseppe Bifulco [a,b], Luigi Anastasia [c,k], Federica Carusone [a], Angelicarosa Cascone [c], Mariafrancesca Di Santo [a], Paolo Ivo Cavoretto [c,d], Dario D'Alconzo [a], Alessia Palmentieri [a], Martina Carotenuto [a], Attilio Di Spiezio Sardo [a,b], Danila Ioele [b], Roberta Paolillo [b], Pina Polese [b], Gabriele Saccone [a,b], Giovanni Esposito [a,b], Alaide Chieffo [c,d,2,*], Cinzia Perrino [a,b,2,**]

[a] Federico II University, Naples, Italy
[b] Federico II University Hospital, Naples, Italy
[c] Vita-Salute San Raffaele University, Milan, Italy
[d] IRCCS San Raffaele Scientific Institute, Milan, Italy
[e] S. G. Moscati Hospital, Avellino, Italy
[f] Molinette Hospital, Città della Salute e della Scienza, Turin, Italy
[g] University of Campania Luigi Vanvitelli, Naples, Italy
[h] Monaldi Hospital, Naples, Italy
[i] Azienda Ospedaliera San Carlo, Potenza, Italy
[j] IRCCS Humanitas Research Hospital, Milan, Italy
[k] IRCCS Policlinico San Donato, San Donato Milanese (MI), Italy
[l] University of Basilicata, Potenza, Italy

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ABSTRACT

Background: Peripartum cardiomyopathy (PPCM) is a rare, life-threatening form of heart failure occurring in late pregnancy or postpartum, with variable clinical course and outcomes. We report preliminary clinical and echocardiographic findings from a national Italian registry of PPCM patients

Methods: The study was approved by the institutional Ethics Committee and registered at ClinicalTrials.gov (NCT05878041). Twenty-eight patients aged ≥18 years with confirmed PPCM diagnosis were included. At enrollment, all patients underwent clinical assessment, echocardiography, and peripheral blood sampling for multi-omics profiling.

Results: Participants had a mean age of 33.9 ± 5.1 years and a median body mass index of 28 kg/m^2 (25.5–32.9). Key characteristics of enrolled patients included African ethnicity (10.7 %), assisted reproduction (14.3 %), pre-eclampsia (14.3 %), autoimmune disease (10.7 %), hypertension (21.4 %), diabetes mellitus (3.5 %), and smoking (32.1 %). Most patients were diagnosed PPCM with NYHA class III/IV symptoms within one month postpartum; mean Left Ventricular Ejection Fraction (LVEF) at admission was 33.2 ± 9.3 %. Arrhythmic presentation occurred in 25 % of patients. Despite initial severity, 50 % of patients recovered LVEF over 11 ± 19

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

* Correspondence to: A. Chieffo, San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy.
** Correspondence to: C. Perrino, Federico II University Hospital, Via Pansini 5, 80131 Naples, Italy.
E-mail addresses: chieffo.alaide@hsr.it (A. Chieffo), perrino@unina.it (C. Perrino).

[1] Equally contributing.
[2] Equally contributing.

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months, while persistent severe dysfunction (LVEF<35 %) requiring defibrillator implantation was observed in 14 % of patients. Several echocardiographic markers differed significantly in enrolled patients according to recovery status, and those with persistent dysfunction had larger LV end-diastolic diameters (61.2 ± 8.1 mm) and left atrial volumes (47.0 ± 24.7 ml/m^2), lower LV strain (9.0 ± 1.4 %), and TAPSE (17.5 ± 4.2 mm, $p <$ 0.005 for all).

Conclusions: Clinical and echocardiographic predictors of LV recovery in PPCM need further investigation.

Peripartum cardiomyopathy (PPCM) is a rare but potentially life-threatening condition, usually affecting women in the last month of pregnancy up to five months after delivery and characterized by signs and symptoms of heart failure (HF) resulting from left ventricle (LV) systolic dysfunction, in the absence of other identifiable causes of HF [1]. For yet unknown reasons, incidence and prevalence of PPCM is extremely variable among countries and regions [2], ranging from 1 in 100 deliveries in Nigeria to 1 in 20,000 in Japan [3]. Established risk factors for the development of PPCM include multiparity, advanced maternal age, smoking, anaemia, hypertension, or preeclampsia [1–3]. Genetic predisposition, angiogenic imbalance, and endothelial dysfunction, combined with the physiological changes of pregnancy, further increase susceptibility to this condition.

According to the Study Group on PPCM of the Heart Failure Association of the European Society of Cardiology (ESC), PPCM was defined as an idiopathic cardiomyopathy with LV ejection fraction (LVEF) <45 %, in the absence or presence of LV dilatation [4]. This definition was confirmed by 2018 ESC guidelines on cardiovascular diseases in pregnancy [5], and by a subsequent position statement of the same study group as well, that further underlined how patients with LVEF between 45 % and 50 % may occasionally be diagnosed with PPCM if have typical features of PPCM [6]. This aspect, and the lack of specific diagnostic criteria might also contribute to the under-recognition of this condition and uncertainty regarding its true incidence. The arbitrary temporal frame for diagnosis may also contribute to under-diagnosis.

Most affected patients experience recovery of LVEF. In the ESC EURObservational Research Programme PPCM (ESC EORP PPCM) Registry, a persistent reduction of LVEF to <50 % prior to subsequent pregnancies was reported in 26 % of patients, with only 6 % having a LVEF <40 % [7]. Nevertheless, significant regional disparities were observed, with LV recovery most frequently detected in the Asia-Pacific region (77.5 %) and lowest in the Middle East (32.7 %) [7]. The mechanisms responsible for PPCM development and regression, and predictors of recovery are still largely unknown. These data highlight the need for a deeper understanding and awareness of the wide and variable clinical presentations of this disease, to allow for early recognition, and accurate diagnosis to facilitate timely and appropriate interventions.

We conducted a national, multicenter, observational registry (NCT05878041) to investigate the incidence, prevalence, clinical and echocardiographic presentation, and evolution of PPCM in Italy. The research was funded by the Italian National Recovery and Resilience Plan (PNRR), project PNRR-MR1–2022-12376858, funded by the European Union (NextGenerationEU). The Institutional Ethics Committee approved the study protocol (protocol number 68, approved on 8th March 2023) and all patients provided written informed consent to participate. Women with history of PPCM or newly diagnosed cases, both based on 2018 ESC Guidelines definition of PPCM [5] were considered eligible. Inclusion criteria were: (i) age ≥ 18 years; (ii) development of HF signs or symptoms in the last month of pregnancy or within 5 months of delivery, (iii) absence of an identifiable cause of HF; (iv) LV systolic dysfunction demonstrated by classical echocardiographic criteria (LVFE ≤45 %) in the last month of pregnancy or within 5 months of delivery (v) absence of recognizable heart disease before the last month of pregnancy. According to current guidelines on HF [8], clinical manifestations suggestive of PPCM include dyspnoea, orthopnoea, chest pain, dizziness, palpitations, fatigue, depression, and cough, that may be accompanied by signs such as elevated jugular venous pressure, pulmonary crackles, and peripheral oedema.

From May 2023 to May 2025, 28 women with confirmed PPCM diagnosis were consecutively enrolled; at baseline, they underwent clinical assessment, ECG registration, evaluation of quality of life by Kansas City Cardiomyopathy Questionnaire (KCCQ), transthoracic echocardiography (TTE), blood sampling for standard laboratory tests, plasma and peripheral blood mononuclear cells isolation to perform whole exome sequencing, circulating RNA sequencing, metabolomics, and proteomics. At all enrolling centers, clinical and imaging evaluations were repeated at 1- and 6-month-follow-up visits, except for women with previous diagnosis of PPCM who were enrolled more than 12 months after delivery.

The age of clinical onset ranged from 21 to 42 years (mean age 33.9 ± 5.1 years). Advanced maternal age (>40 years) was observed in 7 % of enrolled patients, and premature pregnancy (<20 years) occurred in only 1 woman. Ten patients (37 %) had multiple gestations and 3.5 % of the enrolled patients had twin pregnancy. Three patients (10.7 %) were African, three had autoimmune disease, and a family history of cardiomyopathy was reported in 8 of them (28.6 %). Six patients (21.4 %) had hypertension during pregnancy and 4 (14.3 %) pre-eclampsia. Median BMI was 28 (25.5–32.9), overweight was observed in seven (25 %) patients, and three of them had severe obesity (Body Mass Index, BMI > 30 kg/m^2). Two women (7 %) had diabetes mellitus. One third developed symptoms before birth, 32 % immediately after delivery and 28.6 % in months 2–3 after delivery (Fig. 1).

In terms of clinical presentation, most patients (61 %) presented with New York Heart Association (NYHA) III/IV class symptoms, while in fewer cases (25 %) an arrhythmic profile was detected (3 patients with frequent ventricular extrasystole and 4 with nonsustained ventricular tachycardia). All patients received guideline-directed medical therapy for the management of HF: 50 % were prescribed angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, 14 % received angiotensin receptor-neprilysin inhibitors, 89 % beta-blockers, 18 % mineralocorticoid receptor antagonists and 32 % sodium-glucose cotransporter 2 inhibitors. Diuretics were prescribed in 39 % of patients. Three women (11 %) were treated with bromocriptine, and no patient required mechanical circulatory support (MCS) implantation or heart transplantation. LVEF nadir was 32.2 ± 9.3 %, with the lowest observed value of 15 % and the highest of 46 %.

Most patients improved their cardiac function, with a complete recovery of LVEF to a value >50 % achieved in half of the enrolled population. Median increase of LVEF from baseline was 14 % (5–27). A persistent severe LV dysfunction, requiring implantable cardioverter-defibrillator, was reported in 14 % of women. Table 1 outlines clinical and echocardiographic characteristics of the population according to long-term LVEF. Women with persisting severe LV dysfunction (defined as LVEF ≤35 %) were more likely to be smokers (75 %), overweight (50 %), and affected by chronic kidney disease (25 %) compared to those who partially or completely recovered LV systolic function (respectively, LVEF 36–49 % and LVEF ≥50 %). There was a poor correlation between symptoms at disease onset and LVEF recovery, except for chest pain that was observed only in a woman with persistent LV dysfunction (p = 0.045, Table 1). Patients with persisting LV dysfunction had more dilated LV (p = 0.017) and left atrium (p = 0.013), impaired global longitudinal strain (p = 0.001), right ventricular function (p = 0.024) and diastolic function (p < 0.001), compared to the other groups

(Table 1). A slight, but not significant increase in KCCQ score was observed in women who experienced a subsequent improvement in LVEF compared to those with persistent LV dysfunction. In particular, a non-significant trend toward improvement was observed in most domains of the KCCQ score (symptom frequency, quality of life, social limitation, Table 1). Medical therapy was consistent across the three study groups, except for diuretics, which were prescribed more in patients without or with partially recovered LV function. No death was reported in our study population between May 2023 to May 2025.

Significant regional disparities were previously observed in the ESC EORP PPCM Registry: one-year mortality ranged from 4.9 % in Europe to 18.9 % in the Middle East. These differences were paralleled by substantial variations in HF therapy use, particularly lower rates of optimal beta-blocker dosing in the Middle East [8]. Since the timing of clinical presentation, treatment, and outcomes of PPCM vary by region [2], creation of national Registries is crucial to accurately capture epidemiological and prognostic patterns, identify regional disparities in care, assess treatment effectiveness, and inform evidence-based guidelines tailored to specific populations. In this study, we provide an overview of the clinical phenotype of patients with PPCM in Italy. Our data on baseline characteristics show that the most common risk factors related to PPCM are present in small percentages of women, indicating that other factors, such as genetic predisposition, might have contributed to the development of the disease. Some patients in our study group exhibited arrhythmic manifestations, associated with only a mild reduction of LV systolic function, consistent with previous reports describing a possible predominantly "arrhythmic" presentation of PPCM [9]. In this subgroup of patients, where the disease progresses in a more subtle and insidious manner, LVEF alone might not be able to identify PPCM, confirming the need for more sensitive and specific echocardiographic parameters to detect the disease at an earlier stage.

The clinical presentation at diagnosis was critical in most enrolled population: 61 % had NYHA III/IV symptoms, 32 % peripheral oedema, 43 % pulmonary crepitations and 67 % a LVEF ≤35 %, which is consistent to previous reports [10,11]. Despite the smaller number of observations, our follow-up data were broadly consistent with those reported in the ESC EORP PPCM Registry, according to which 66.1 % of PPCM patients recovered LV function, with a mean LVEF increase of 21.2 % ±13.6 from baseline [6]. In our population, bromocriptine was prescribed in about 11 % of patients, which is slightly lower than what has been previously described in other registries [10]. This may be related to the low percentage of patients with RV involvement, in whom the use of bromocriptine is more strongly recommended. Considering the low use of bromocriptine and MCS we cannot exclude that this could have impacted in the LV recovery in our population. One study limitation that needs to be acknowledged is that some patients were enrolled in the Registry after the acute phase of the disease. Since evaluation of some bio-humoral parameters was not performed in all patients in the acute phase, this information is missing. In addition, the small number of patients enrolled precludes drawing conclusions on the clinical and echocardiographic factors related to LV function recovery. A larger population and integration with multi-omics profiles might provide novel insights into PPCM pathophysiology and molecular mechanisms, allowing precision risk stratification, prompt detection, and tailored therapeutic interventions.

CRediT authorship contribution statement

Federica Ilardi: Conceptualization, Data curation, Formal analysis, Writing – original draft. **Rachele Manzo:** Data curation, Writing – original draft. **Giovanni Peretto:** Data curation, Funding acquisition, Writing – review & editing. **Francesca Lanni:** Data curation, Validation. **Vanessa Peano:** Data curation, Resources, Validation. **Francesco S. Loffredo:** Resources, Validation. **Daniele Masarone:** Data curation, Validation. **Donato Gerardi:** Resources, Validation. **Silvana di Maio:** Resources, Validation. **Luca Bardi:** Resources, Validation. **Marco Licciardi:** Data curation, Resources, Visualization. **Nicolò Montali:** Resources, Validation. **Enrica Pezzullo:** Data curation, Validation. **Emilio**

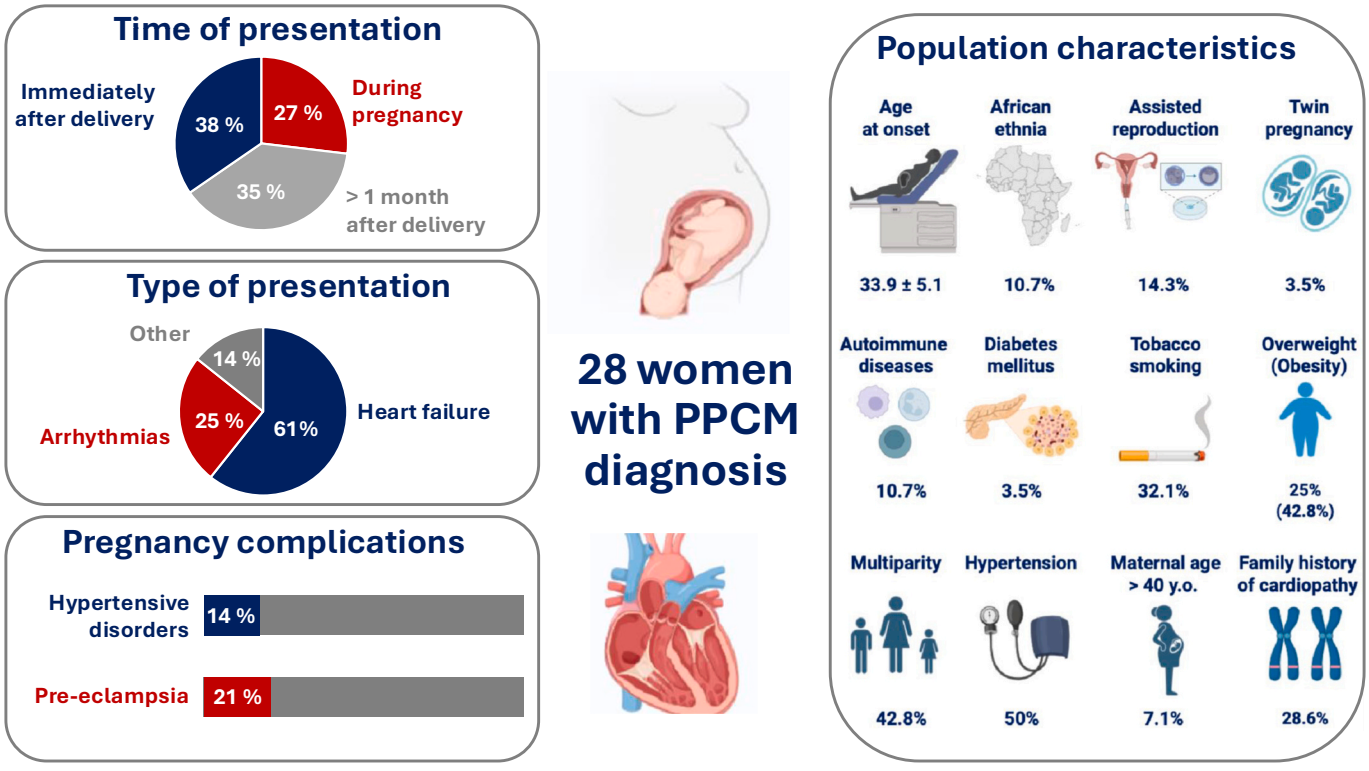

Fig. 1. Schematic representation of patients' characteristics, time of presentation, type of presentation and major pregnancy complications of women with PPCM diagnosis enrolled in the Registry.

Table 1
Clinical and echocardiographic variables and disease course of PPCM patients enrolled in the Italian Registry, separated according to subsequent LV systolic function.

	LVEF ≤35 % (*n* = 4)	35 % < LVEF <50 % (*n* = 10)	EF ≥ 50 % (*n* = 14)	*p*
Age at clinical onset	36.5 ± 4.4	35.6 ± 3.8	32.0 ± 5.6	0.128
Comorbidities				
Diabetes, n (%)	1 (25)	0	1 (7)	0.260
Smoking, n (%)	3 (75)	3 (33)	3 (21)	0.134
Overweight, n (%)	2 (50)	4 (40)	1 (7)	0.086
Obesity, n (%)	0	1 (10)	2 (14)	0,715
Chronic kidney disease, n (%)	1 (25)	0	0	0.057
Hypertension, n (%)	3 (75)	5 (56)	4 (29)	0.184
Pre-eclampsia, n (%)	1 (25)	1 (10)	2 (14)	0.769
Multiparity, n (%)	1 (25)	4 (40)	7 (50)	0.655
Signs and symptoms				
Chest pain, n (%)	1 (25)	0	0	0.045
Palpitations, n (%)	0	4 (40)	3 (21)	0.269
Dizziness, n (%)	1 (25)	1 (10)	5 (36)	0.358
Cough, n (%)	0	1 (10)	2 (14)	0.715
Dyspnea, n (%)	3 (75)	7 (70)	11 (77)	0.892
Peripheral oedema, n (%)	1 (25)	2 (20)	6 (43)	0.471
Pulmonary crepitations, n (%)	2 (50)	3 (30)	7 (50)	0.592
Echocardiography				
Septal thickness, mm	8.2 ± 1.3	7.9 ± 1.3	8.9 ± 1.6	0.239
Posterior wall thickness, mm	8.2 ± 0.5	7.6 ± 0.8	11.3 ± 10.9	0.508
LVEDD, mm	61.2 ± 8.1	51.8 ± 7.0	44.7 ± 11.7	0.017
RWT	0.3 ± 0.03	0.3 ± 0.06	0.36 ± 0.07	0.025
LV mass/BSA, g/m^2	89.3 ± 45.0	96.3 ± 37.9	85.8 ± 24.8	0.811
LVEDV, ml	193.7 ± 96.2	131.7 ± 36.9	103.8 ± 22.8	0.004
LVESV, ml	144.0 ± 84.2	73.4 ± 23.4	45.1 ± 10.9	<0.001
LVEF, %	28.2 ± 7.4	44.6 ± 3.0	57.0 ± 5.5	<0.001
GLS, %	9.0 ± 1.4	15.2 ± 3.1	19.1 ± 1.9	0.001
LA volume/BSA, ml/m^2	47.0 ± 24.7	30.0 ± 7.1	27.4 ± 7.0	0.013
E/A	1.5 ± 0.8	1.4 ± 0.7	1.2 ± 0.3	0.590
E/E'	11.9 ± 5.5	9.7 ± 3.0	5.6 ± 1.2	<0.001
TAPSE, mm	17.5 ± 4.2	22.4 ± 2.0	21.5 ± 2.9	0.024
RV end-diastolic diameter, mm	31.3 ± 5.7	33.0 ± 11.1	32.0 ± 3.2	0.939
LVEF nadir, %	24.5 ± 7.8	34.2 ± 10.6	33.1 ± 8.0	0.192
Time to LVEF recovery (months)	-	9.3 ± 9,7	12.1 ± 22.5	0.948
KCCQ summary score	41.3 ± 25.5	59.7 ± 28.4	63.0 ± 32.2	0.541
Physical limitation domain	58.3 ± 22.0	76.8 ± 21.0	62.2 ± 37.7	0.498
Symptom frequency domain	59.0 ± 26.4	61.8 ± 27.5	72.7 ± 29.7	0.599
Quality of life domain	8.3 ± 7.2	45.8 ± 33.1	53.8 ± 9.9	0.125
Social limitation domain	38.9 ± 52.9	53.7 ± 38.2	60.9 ± 35.4	0.662
Medical therapy				
ACE-I/ARB	2 (50)	5 (50)	7 (54)	0.980
ARNI	1 (25)	2 (20)	1 (7)	0.542
Beta-blockers	3 (75)	10 (100)	12 (86)	0.326
Calcium-channel blockers	0	1 (10)	1 (7)	0.806
MRA	0	4 (40)	1 (7)	0.070
Diuretics	3 (75)	6 (60)	2 (14)	0.022
Antiarrhythmics	1 (25)	1 (10)	0	0.210
SGLT2 inhibitor	1 (25)	4 (44)	4 (29)	0.681
Bromocriptine	0	1 (10)	2 (14)	0.715

Abbreviations used: ACE-I/ARB, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; LV, Left Ventricle; EF, Ejection Fraction; RWT, Relative Wall Thickness; BSA, Body Surface Area; LVEDD, Left Ventricle End-Diastolic Diameter; LVEDV, Left Ventricle End-Diastolic Volume; LVESV, Left Ventricle End-Systolic Volume; LVEF, Left Ventricular Ejection Fraction; LA, Left Atrium; MRA, mineralocorticoid receptor antagonists; SGLT2, sodium-glucose cotransporter 2; TAPSE, Tricuspid Annular Plane Systolic Excursion; RV, Right Ventricle; RWT, relative wall thickness; KCCQ, Kansas City Cardiomyopathy Questionnaire, Values are mean ± SD.

Di Lorenzo: Resources, Validation, Writing – review & editing. **Eugenio Stabile:** Validation, Writing – review & editing. **Ciro Battaglia:** Data curation, Resources, Validation. **Maria Calanducci:** Data curation, Validation. **Giuseppe Bifulco:** Funding acquisition, Validation. **Luigi Anastasia:** Resources, Validation. **Federica Carusone:** Data curation, Resources, Validation. **Angelicarosa Cascone:** Data curation, Validation. **Mariafrancesca Di Santo:** Data curation. **Paolo Ivo Cavoretto:** Supervision. **Dario D'Alconzo:** Data curation, Resources. **Alessia Palmentieri:** Data curation, Resources. **Martina Carotenuto:** Data curation, Resources. **Attilio Di Spiezio Sardo:** Supervision. **Danila Ioele:** Data curation, Validation. **Roberta Paolillo:** Data curation, Resources. **Pina Polese:** Data curation, Resources. **Gabriele Saccone:** Funding acquisition, Validation. **Giovanni Esposito:** Supervision. **Alaide Chieffo:** Funding acquisition, Validation, Writing – review & editing. **Cinzia Perrino:** Funding acquisition, Writing – review & editing.

Declaration of competing interest

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