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Peripherally inserted central venous catheter for pediatric acute leukemia: A retrospective 11-year single-center experience

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Abstract

Background: Peripherally inserted central catheters (PICCs) are successfully increasingly used in children in onco-hematologic setting. PICC insertion, especially in oncologic patients, can be associated with adverse events (thrombosis, mechanical complications, and infections). Data regarding the use of PICC, as long-term access in pediatric patients with severe hematologic diseases, are still limited.

Methods: We retrospectively evaluated the safety and efficacy of 196 PICC, inserted in 129 pediatric patients with acute leukemia diagnosed and treated at Pediatric Hematology Unit, Sapienza University of Rome.

Results: The 196 PICC analyzed were in situ for a median dwell time of 190 days (range 12–898). In 42 children, PICC was inserted twice and in 10, three times or more due to hematopoietic stem cell transplant, disease recurrence, or PICC-related complications. The overall complication rate was 34%: catheter-related bloodstream infections (CRBSI) occurred in 22% of cases after a median time of 97 days; a catheter-related thrombosis (CRT) in 3.5% and mechanical complications in 9% of cases. Premature removal for complications occurred in 30% of PICC. One death from CRBSI was observed.

Conclusions: To our knowledge, this study represents the largest cohort of pediatric patients who have inserted the PICC for acute leukemia. In our experience, PICC was a cheap, safe, and reliable device for long-term intravenous access in children with acute leukemia. This has been possible with the help of dedicated PICC team.

Keywords

Peripherally inserted central catheters, children, acute leukemia, chemotherapy, supportive treatment

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Introduction

The management of patients with acute leukemia is complex and requires a collaborative program involving physicians, patients, nurses, and all other members of the health care team.[1,2] In children, the frequent limitation in peripheral venous access, together with the discomfort of the continuous venipunctures, a long-lasting venous access has become mandatory to safely administer treatments and improve quality of life.[3] A reliable intravenous access is required for the safe chemotherapy administration, in order to avoid ulcerative drugs peripheral extravasation, infuse blood products, anti-infective drugs, and parenteral nutrition. Furthermore, it allows to perform blood samples,

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necessary for the management of the complex patient. Peripherally-inserted central catheters (PICCs) are increasingly used in onco-hematological setting, both for adults and children.[4–8] PICC insertion is an easy and not-expensive procedure that can be performed at the bedside, whereas catheter removal is quick and simple. PICC line is inserted percutaneously into a peripheral vein with its tip residing in a central vein, mostly near the junction between the superior vena cava and the right atrium. Compared with centrally inserted central catheter (CICC), PICC allows to prevent, at insertion, complications such as pneumothorax and hemothorax, to reduce the risk of arterial punctures and hemorrhage, particularly severe in children with leukemia-induced thrombocytopenia and/or coagulopathy. However, as for traditional CICC, PICC insertion, especially in oncologic patients, can be associated with adverse events (thrombosis, obstruction, and infections) that could potentially result in catheter removal and delayed intravenous treatment.[3–7]

Information regarding the use of PICC, as long-term access in the fragile pediatric patients with leukemia, are still limited.

In our Institute, since January 2010, PICCs have been inserted to all children aged more than 1 year, with severe hematologic diseases requiring a long-term venous access devices for diagnostic procedures and treatments. We report here our 11-year experience in pediatric acute leukemias.

Patients and methods

Study design

This is a monocentric retrospective study including pediatric patients (age 1–18 years) with acute leukemia diagnosed and treated at the Institute of Hematology, Sapienza University of Rome, who received an ultrasound guided PICC line from January 2010 to August 2021. Pediatric acute promyelocytic leukemia at diagnosis and children with PICC placed outside our Institute were excluded.

Data collection

The following information were collected: (a) patients' clinical and laboratory characteristics (age, gender, underlying disease, peripheral blood count with platelets (PLTs) and white blood cells (WBC) at time of PICC insertion, coagulation profile, including known predisposing factors of venous thrombosis); (b) PICC insertion data and site, dwell time (calculated from insertion to removal), PICC line type; (c) data and reasons of PICC removal and PICC-related adverse events (AEs: occlusion, exit-site infection, PICC-related bacteremia or fungemia, thrombosis), or other reasons (accidental removal, end of intensive therapy, PICC damage, patient's death).

PICC insertion and maintenance

A "PICC Team" including physicians, nurses and health personnel active in the daily PICC care, is present at our center.[7,8] The Italian Association of Pediatric Hematology and Oncology Group (AIEOP) guidelines for the management of central venous access devices, were followed.[3]

All PICCs, whether as an elective or urgent procedure, were inserted by the same single operator in a dedicated interventional surgical facility within the Hematology Center using aseptic techniques and occasionally at the patient's bedside. Before PICC insertion, all patients were screened with a complete peripheral blood count and standard coagulative tests. Critically ill children with PLT $< 20 \times 10^9$/L received concentrated PLT infusions prior to the PICC insertion, as recommended in the latest British Committee for Standards in Haematology (BCSH) guidelines and the Italian Group of Venous Access devices (GAVeCeLT).[9,10] In our children, we used the Groshong PICC produced by Bard (Bard, Inc), with a diameter of 4 Fr, an average length of 25/55 cm, in silicone material, with a valve placed on the tip. The relationship between catheter lumen and vein caliber was carefully evaluated to determine the more appropriate vein for insertion, using a cut off 33% catheter to vein ratio in order to reduce the risk of PICC-related deep vein thrombosis.[11] After the insertion, a fluoroscopy was routinely performed in patients to verify the correct location of the tip (i.e. cavo-atrial junction).

Details about PICC insertion and maintenance are provided in Supplemental Material.

Study endpoints and definition of PICC-related complications

The aim of the study was to assess the realibility and safety of PICC in pediatric patients who needed prolonged appropriate vascular access for management of acute leukemia and to evaluate the catheter life, the incidence of PICC-related AEs and PICC removal causes.

Overall PICC-related complications were defined as the presence of at least one of the above-described AEs.

Mechanical complications included complete or partial occlusions (inability to flush, infuse, or aspirate and resistance with flushing and aspiration), malfunction, dislocation, and rupture. Temporarily occlusions resolved with recanalization using flushing solutions (plasminogen activators-urokinase), were not included.

Catheter-related bloodstream infections (CRBSI) were defined, according to modified criteria of the National Nosocomial Infections Surveillance System of the CDC of Atlanta, as those occurring in patients who developed at least one clinical manifestation of systemic infection (e.g. fever, chills, hypotension), with positive blood cultures (two or more) from catheter and no apparent source for the

BSI, except the catheter.[12] The criteria of a different time to positivity (DTP) between blood cultures drawn from the central venous line and from a peripheral vein[13] was not used for the definition of CRBSI due to the lack of a semi-automatic blood culture system at our microbiology laboratory where a manual blood culture method (Oxoid Signal System, Oxoid, USA) was used. Exit-site infection was defined as the presence of purulent lesion with erythema and/or tenderness close to the PICC exit, confirmed by the positive swab culture and absence of concomitant positive blood culture.

Catheter-related thrombosis (CRT) were diagnosed by ultrasound.

Accidental removal was defined as an unplanned PICC removal by the child.

We divided our patients into the following subgroups based on age: very early childhood (1–3 years), early childhood (3–6 years), middle childhood (6–12 years), and adolescents (12–18 years).

Data and statistical analysis

Clinical data were retrospectively recorded for all patients in a database managed by the PICC Team. An informed consent for the use of the data for scientific purposes was requested from patient's parents.

The statistical analysis was carried out at the GIMEMA (Gruppo Italiano Malattie EMatologiche dell'Adulto) Data Center in Rome, Italy. Follow-up was updated on January 1, 2022.

Details are given in Supplemental Material.

Results

Patients profile and PICC characteristics

From January 2010 to August 2021, 196 PICC-lines were inserted in 129 patients aged ⩽18 years with acute leukemia; 42 of them underwent PICC insertion twice, and 10 patients three times or more (disease recurrence, need of reinsertion after accidental removal, PICC-related complications).

The demographic characteristics of the patients are shown in Table 1. In 108 patients (84%) the underlying diagnosis was acute lymphoblastic leukemia (ALL), and, in 21 (16%), acute myeloid leukemia (AML). In 84 (65%) children a complete thrombophilic screening was available at diagnosis and it was positive in 28 (22%) (Table 1).

PICC lines were inserted in operating room in 82 (64%) patients with moderate sedation; all aged <12 years and in phase of acute illness.

The characteristics of the 196 PICCs and the details about PICC insertion are reported in Table 2. One hundred seven/196 (95%) PICC lines were placed on a single attempt. The majority of PICCs was inserted in the right arm (66%) and in the basilica vein (86%). No children developed PICC-related bleeding after insertion. The PICC tip was confirmed to be in central circulation by fluoroscopy. At PICC insertion, 13 (7%) patients presented PLT count $<20 \times 10^9$/L, 30 (15%) had PLTs ranging from 20 to 50×10^9/L, and 153 (78%) more than 50×10^9/L. Severe neutropenia (PMN $< 0.5 \times 10^9$/L) at the time of PICC insertion was present in 33 (17%) children (28 ALL, 5 AML).

Table 1. Demographic characteristics for distinct patient.

Variables	N. patients 129 (%)
Gender	
Male/Female	76/53 (59/41)
Age (years): median	9.3
Range	1.7–18.0
1–3	13 (10)
3–6	30 (23)
6–12	39 (30)
12–18	47 (36)
Type of hematologic disease	
Acute lymphoblastic leukemia (ALL)	108 (84)
B-ALL	89
T-ALL	19
Acute myeloid leukemia	21 (16)
Thrombophilic screening	
Total number available	84
Positive	28 (33)
Protein C deficiency	11
Protein S deficiency	4
Factor V leiden	4
LAC	6
Protein C deficiency + LAC	1
Factor II	2
Negative	56 (66)

LAC: lupus anticoagulant.

The 196 PICC were in situ for a median dwell time of 190 days (range 12–898); the median duration of PICC is shorter for patients undergoing hematopoietic stem cell transplantation (HSCT) compared to those who inserted PICC in the other disease's phases (onset 244 days; relapse 152 days; remission 134 days; HSCT 95 days; $p < 0.001$).

PICC-related complications

In our series, PICC-related complications occurred in 66/196 PICCs, with an overall PICC-related complications rate of 34% (1.64/1000 PICC days).

PICC-related infections were documented in 47/196 (24%) cases. CRBSI occurred in 43/196 cases (22%); exit-site infection in 4/196 (2%) cases. Median time interval between PICC insertion and CRBSI onset was 97 days (range 10–881). The incidence of CRBSIs was 1.07/1000 PICC days. Gram-positive bacteria were documented in 22

Table 2. Characteristics of the 196 PICCs.

Characteristics	Number 196 (%)
PICC site	
Right	129 (66)
Left	67 (34)
PICC position	
Basilic vein	168 (85.7)
Brachial vein	25 (12.8)
Cephalic vein	3 (1.5)
PICC type	
Groshong	192 (98)
Bilume	4 (2)
Phase of hematologic disease	
Onset	95 (48)
Complete Remission	61 (31)
Relapse	23 (12)
Pre-HSCT	17 (9)
Platelets ($\times 10^9$/L) at time of PICC insertion	
$<$20.0	13 (7)
20.0–50.0	30 (15)
$>$50.0	153 (78)
Neutrophils ($\times 10^9$/L) at time of PICC insertion	
$<$0.5	33 (17)
0.5–1.0	39 (20)
$>$1.0	124 (63)

HSCT: hematopoietic stem cell transplant.

Table 3. PICC-related adverse events.

Adverse event	Number (%)
Infections	47 (100)
CRBSI	43 (91.5)
Gram-positive (+) bacteria	22
Gram-negative (−) bacteria	13
Mixed (Gram+/Gram−)	1
Fungemia	7
Exit-site infections	4 (8.5)
CRT	7 (100)
Age (years)	
⩽3	1 (14)
3–6	2 (29)
6–12	2 (29)
12–18	2 (29)
Disease	
Acute lymphoblastic leukemia	5 (71.4)
Acute myeloid leukemia	2 (28.6)
Mechanical complications	18 (100)
Age (years)	
⩽3	4 (22)
3–6	5 (28)
6–12	5 (28)
12–18	4 (22)
Type of mechanical complication	
Occlusion	1 (5.5)
Malfunctioning	10 (55.5)
Breakage	3 (16.6)
Malpositioning	4 (22.2)

CRBSI: catheter-related bloodstream infection; CRT: catheter-related thrombosis.

(51%) cases and the most frequent isolated agent was coagulase-negative *Staphylococcus*. Gram-negative bacteria were involved in 13 cases (30%) and one case of mixed gram-positive and gram-negative bacteremia was documented. Seven catheter-related fungemias (16%) were observed (6 *Candida glabrata* and 1 *Roduturela glutinis*) (Table 3). CRBSI occurred during severe neutropenia (PMN $< 0.5 \times 10^9$/L) in 7/43 (16%) cases. PICC was removed in 42/43 cases of CRBSI and in two-fourths of the exit-site infections (Table 4). One patient died from infection. Median PICC dwell time was significantly shorter in patients with CRBSI compared with the others (104 vs 226 days, respectively; $p = 0.02$).

A CRT was recorded in 7/196 (3.5%) cases (2 AML, 5 ALL) (Table 3). Time between PICC insertion and thrombosis spanned between 38 and 399 days (median 165). The incidence of CRT was 0.17/1000 PICC days. At time of CRT, PLT count was $>50 \times 10^9$/L in five patients and between 20 and 50×10^9/L in the other two children. Four children with ALL who developed CRT had previously received Peg-Asparaginase (CRT rate in ALL treated with asparaginase: 4.5% (4/88)); one CRT event was observed in an allotransplanted ALL patient. In three-sevenths CRT cases, the thrombophilic screening was positive (2 Lupus Anticoagulant positivities and one protein C deficiency). All seven patients, not previously receiving thromboprophylaxis, underwent low-molecular-weight heparin (LMWH) therapy while the catheters remained in place; PICC was removed in one/seven CRT after 165 days, for physician decision (Table 4). No fatal event related to CRT was observed.

Mechanical complications occurred in 18/196 (9%) PICCs: malfunctioning in 10, complete obstruction in one, ruptures in three, and malpositioning in four cases. Mechanical complications were documented at a median time of 186 days (range 24–399) from PICC insertion, with an incidence of 0.45/1000 PICC days. In 15/18 (83%) cases, PICC was immediately removed.

Accidental removal occurred in five children (Table 4).

A total of 158/196 (72%) PICCs were removed; 100/196 (51%) were electively removed at the end of treatment. PICC removal for catheter-related complications occurred in 60/196 (30%) cases: in 42/196 (21%), for CRBSI, in 2/196 (1%) for exit-site infections, in 1/196 (0.5%) for CRT, and in 15/196 (7.6%) cases for mechanical problems. In 12/196 (6%) cases, PICC was prematurely removed for suspected but unconfirmed catheter-related infections (Table 4).

Table 4. Causes of PICC removal.

Event	Number (%)
Chemotherapy completion	100 (51)
Infections	56 (28.6)
PICC-related infections	44 (22.4)
CRBSI	42 (21.4)
Exit-site infections	2 (1)
Other systemic infections[a]	12 (6.1)
CRT	1 (0.5)
Mechanical complications	15 (10.2)
Occlusion	1
Malfunctioning	7
Breakage	3
Malpositioning	4
Accidental removal	5 (2.5)

CRBSI: catheter-related bloodstream infection; CRT: catheter-related thrombosis.
[a]Suspected but unconfirmed catheter-related infections.

PICCs were successfully removed without complications.

Regarding the remaining 19/196 (9.6%) cases, three patients were transferred to another hospital before PICC removal, six children still had PICC in situ at the time of analysis and 10 children died with PICC in situ.

PICC-related complications' incidence per 1000 PICC days is reported in Table 5.

Factors affecting the PICC-related complications and dwell

The incidence of complications was not influenced by age; median age of children who developed PICC-related AEs was 6.4 years (range 1.7–18.0) compared with 9.3 years (range 2.3–18.0) for those without AEs, but the difference was not statistically significant ($p=0.10$). According to age subgroups, the cumulative complications rate was 33%, 49%, 26%, and 30% ($p=0.07$), respectively for very early, early, middle childhood, and adolescents. Type and phase of disease did not influenced the incidence of PICC-related AEs ($p=0.25$, $p=0.24$, respectively); no significant difference was observed in PICC-related complication incidence between the 17 allotransplanted patients and those treated with chemotherapy alone. The neutrophil count (<0.5 and $>0.5\times10^9$/L) at time of PICC insertion and previous PICC placement did not influenced the incidence of complications or PICC-related infections ($p=0.84$ and $p=0.43$, respectively).

CRT occurred in seven cases; age subgroups, type and phase of disease, PLT count at insertion, positive thrombophilic screening did not affect the incidence of CRT ($p=0.79$, $p=0.62$, $p=0.44$, $p=0.58$, $p=0.66$, respectively). Five of the 67 children with PICC in the left side, developed CRT, compared with 2/129 patients with PICC in the right arm ($p=0.047$).

Table 5. PICC-related complications' incidence per 1000 PICC days.

Complication	Incidence/1000 PICC days
Overall	1.64
CRBSI	1.17
CRBSI in patients with ALL	1.22
Catheter-related thrombosis	0.17
Mechanical complications	0.45

CRBSI: catheter-related bloodstream infection; ALL: acute lymphoblastic leukemia.

In our series, the median age of patients who developed mechanical complications was younger compared with the others (5.8 vs 8.5 years; $p=0.033$), and there was a trend towards a lower incidence of this complication with increasing age (27%, 10%, 8%, and 6% for very early, early, middle childhood, and adolescents; $p=0.12$). No other characteristics influenced the occurrence of mechanical complication. The median duration of catheterization was 186 and 190 days for those with and without mechanical complication, respectively ($p=0.92$).

Discussion

Central line is mandatory for pediatric patients requiring prolonged venous access and, in our experience PICC provides a reliable access for long-term treatments in children with acute leukemia. In our patients, PICC has been used to administer fluid, blood products, anticancer agents, antibiotics, and for blood sampling. This device resulted also in reduction of physical pain and psychological stress of children/adolescents with improvement of quality of life. PICC has been beneficial for medical staff engaged in frequent blood sampling and drug administrations.

Consistent with the literature,[4–6,14–21] in our experience, the basilic vein was generally the first choice vein for PICC insertion (86%). The cephalic and brachial veins were cannulated in 14% of patients. The basilic vein has a large diameter and follows a straight trajectory, so the passage of the catheter into axillary, subclavian, anonymous veins, and into the superior vena cava is easier. Therefore, the procedure is more likely to be successful and there are fewer AEs.[18]

Besides the advantages, PICC is associated with complications, particularly in children with active cancers. Rate of PICC-related complications in children, range from 34% to 56%.[16,19–28] In our series, including only children with acute leukemia, PICC-related complications occurred in 34% of cases, requiring PICC removal in 30%. Differently from what reported in literature, in which younger children show an increased incidence of PICC-related complications, in our series age did not influence the occurrence of overall complications ($p=0.07$), nor

infectious one ($p=0.25$). This data is probably attributable to the severity of the illness affecting the children, which certainly leads to an increased risk of infectious complications. Most of our patients were affected by ALL, whose prognosis has improved with the employment of intensive and prolonged chemotherapies; the infectious risk is associated with compromised patient's immune status, steroid use, frequent hospitalizations, together with the large number of venous accesses for chemotherapy and supportive measures administrations. In addition, the intensive chemotherapeutic regimens determine long periods of severe neutropenia which further increases the infectious risk. In our study, CRBSI occurred in 22% of cases with incidence rate of 1.07/1000 PICC days, with a median interval of 97 days from PICC insertion. Our results are in line with other reports. A similar CRBSI incidence rate (1.19/1000 PICC days) was reported in a retrospective multicenter study of four pediatric intensive care units, where oncologic/immunocompromised children were only 11.9% (85/715).[29] In another monocentric retrospective study conducted at our Institute, in 144 adults with AML, the CRBSI incidence rate was 22% (1.8/1000 PICC days) with a median interval from PICC insertion to CRBSI of 56 days (range 7–365)[17]; in this study, despite less prolonged chemotherapeutic regimens and a shorter median catheter-dwell time (83 days; range 41–175), a moderately higher CRBSI incidence has been reported. Baier et al.[30] found a higher CRBSI incidence rate of 10.6/1000 catheter days and a CRBSI prevalence of 18.2%, in 610 hematologic/oncologic patients. These variations in CRBSI incidence and prevalence rates are due to heterogeneity in hematologic patients' characteristics, the presence of individual risk factors, type of chemotherapy, proportion of neutropenic patients, and lastly to the expertise in catheter lines management and care.

Previous PICC placement is reported as a risk factor for CRBSI[31]; in our series, the 48 children who underwent $\geqslant 2$ PICC installations, did not showed an increased risk of infections ($p=0.60$). Other factors including platelet and neutrophil count at PICC insertion, type of PICC line, PICC site, and altered thrombophilic screening, did not influenced the incidence of PICC-related complications and dwell.

In our study, the incidence rate of symptomatic CRT was lower than most published data (3.5%).[2,5,6,14,19–21] In literature, it is estimated that over one-third of deep venous thrombosis in the upper extremity is caused by PICCs.[20] In critically ill children, the reported prevalence of CRT varies from 1% to 9%,[22] and, among different cancer centers, the venous thromboembolism rates, in patients with acute leukemia, range from $<1\%$ to 81%.[20–23,32] In a large meta-analysis of 15 studies involving 5420 adult patients (5914 PICCs), the weighted CRT frequency was 2.4%, with an higher thrombotic rate in the onco-hematologic patients (5.9%).[33] The CRT incidence rate was quite similar (2.6%; 0.2/1000 PICC days) in a monocentric retrospective study, including 612 PICCs/483 adults, treated in our institute.[14] The employment of ultrasound guided PICC insertion has remarkably reduced the risk of insertion failure and consequently avoided the vascular endothelial damage. It should be noted that five/seven CRTs occurred in PICCs inserted in the left arm ($p=0.047$). The choice of the left arm is mainly related to the fact that it was a second or subsequent PICC. Thrombophilic genetic abnormalities are also an important risk factors for CRT[34]: in our patients' cohort, the thrombophilic screening documented a high thrombophilic predisposition in three/seven patients. Finally, the CRT risk increases with age. In our group, three/seven patients who developed CRT were adolescents (age$>$12 years). Despite the well known prothrombotic effects of some chemotherapeutic drugs, such as asparaginase,[20,21,35] we did not observe an increased incidence of CRT in the ALL subgroup who had received asparaginase ($p=0.38$). In this regard, recent studies have suggested thromboprophylaxis in these children[36–38]; our patients, according to current guidelines, did not receive antithrombotic therapy.[29]

The incidence of mechanical complications was influenced by patients' age with higher incidence in younger children ($p=0.033$). Accidental dislodgement is a typical PICC complication in children with reported rates ranging from 0.12 to 3.0/1000 catheter days.

Our study presents some limitations, above all its retrospective nature with problems of some incomplete documentation. Relevant factors that may contribute to CRBSIs, such as hospital stay lengths, were not collected. Furthermore, important innovations have been recently introduced in this field, leading to new insertion methods, new materials, and new strategy in the overall management of the device: use of polyurethane PICCs, intracavitary ECG method to check the catheter tip position, and the DTP method for the identification of CRBSIs. These limitations could have affected the clinical results with an overestimation of infections and a higher incidence of CRT and mechanical complications. However, this was a single-center study including only children with acute leukemia, followed by the same PICC-Team and with all PICCs inserted by the same doctor. Data were collected by doctors/nurses that have followed the patients. Our findings were consistent with other published data for patients, both adults and children, with severe onco-hematologic diseases. Our results suggest that PICC line is a safe device that can be maintained for a long period of time, even in children with profound disease- and therapy-related immunosuppression.

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Author contributions

AMT, SL, FK managed the patients, collected data, wrote the manuscript, and reviewed the literature; SGM inserted all PICC and participated in writing the manuscript; AC managed all the thrombotic complications and critically reviewed the manuscript; AM managed all infective complications and critically reviewed the manuscript; VA, AP performed the statistical analysis of data; MF, GG, PB managed the PICC. All authors reviewed the final manuscript version and gave approval for submission.

Availability of data and materials

Data may be made available from the corresponding author upon reasonable request.

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Ethical approval and consent to participate

Compliance with Italian ethical standards; Informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable.

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Supplemental material

Supplemental material for this article is available online.

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