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ORIGINAL ARTICLE

Peripherally inserted central catheters in allogeneic hematopoietic stem cell transplant recipients

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Abstract

Background Central venous catheters (CVC) are essential for the management of patients with hematologic malignancies, facilitating chemotherapy infusion, antibiotics, parenteral nutrition, blood products, and blood samples collection. In this population, peripherally inserted central catheters (PICC) seem to be associated with lower complications, compared with conventional percutaneously inserted devices (CICC). Data on the PICC in allogeneic hematopoietic stem cell recipients (allo-HSCT) are limited.

Methods We have prospectively evaluated the safety and efficacy of 100 polyurethanes or silicone PICC, inserted into 100 adult allo-HSCT recipients, at the Hematology of Sapienza University of Rome (Italy), between October 2012 and August 2017.

Results The median duration of PICC placement was 117 days. Overall, 68% of patients maintained the device for the entire transplant procedure and PICC were removed after day 100 from allo-HSCT; of these, 44% did not experienced any PICC-related complications. Catheter-related bloodstream infections (CRBSI) occurred in 32% of patients (2.5/1000 PICC days), associated with thrombosis in 8 cases. CRBSI were observed in 42% of patients with polyurethane and 20% with silicone PICC ($p = 0.02$). Catheter-related thrombosis occurred in 9% of patients, never requiring anticipated PICC removal. Mechanical complications occurred in 15% of cases (1.2/1000 PICC days). On the whole, adverse events were manageable and did not affect transplant outcome. No deaths related to PICC-complications were observed.

Conclusions PICC are a safe and reliable long-term venous access in allo-HSCT recipients.

Keywords PICC · Allogeneic hematopoietic stem cell transplantation · Infections · Thrombosis · Mechanical complications

Introduction

The use of central venous catheters (CVC) has considerably improved the management of patients with hematologic malignancies, facilitating the infusion of chemotherapeutic agents, antibiotics, parenteral nutrition, blood products, and blood samples collection. Nowadays, CVC is a mainstay in the management of patients undergoing an allogeneic hematopoietic stem cell transplant (allo-HSCT). Double-lumen catheters are to be preferred for the simultaneous infusion of physically incompatible drugs, blood products, and stem cells [1–3]. Peripherally inserted central catheters (PICC) may represent an alternative to tunneled-cuffed centrally inserted central catheters (CICC) in patients with hematologic malignancies, including allo-HSCT recipients at high risk of infectious and hemorrhagic complications [1, 4–6].

CICC often create problems for both implant and removal. McGee [6] reported that CICC insertions lead to complications (arterial puncture, hematoma, hemothorax, and pneumothorax), approximately in 6 to 19% of cases, and are associated with a higher incidence of complications, if compared with peripherally inserted central catheters (PICC). Thrombosis and infections are the most frequent PICC-related complications [7, 8]. Enlarging PICC diameter and malignancy resulted associated with PICC-related deep vein thrombosis. The multi-lumen PICC, frequently used in allo-HSCT patients, not only increased the risk, but also appeared to accelerate the time to infectious complications [7, 8]. Yoshinori

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Hashimoto [4] analyzed the safety of 142 PICC placements in 98 patients with hematologic diseases, including HSCT recipients. He also demonstrated no evidence of serious complications and a low catheter-related bloodstream infections (CRBSI) incidence rate (2.1 cases per 1000 catheter per day) with the use of PICC, supporting the results reported by Sakai [5] and Bellesi [1]. In these studies [1, 4–6], PICC was associated with fewer complications than CICC at the time of insertion and thereafter. In addition, the systematic use of PICC proved useful for the long-term medical home care after the allo-HSCT [9]. At present, the use of PICC in allo-HSCT recipients has been reported in a small pediatric population with good results [10], while very limited information is available in adult allografted patients. We report our experience on the use of PICC in a large cohort of adult allo-HSCT recipients.

Methods

Between October 2012 and August 2017, at the Hematology of Sapienza University of Rome, 100 polyurethanes or silicone PICC have been inserted in 100 patients candidate to allo-HSCT procedure. The characteristics of the patients, the PICC (type, place, arm of insertion, and presence of a single double lumen catheter or two single lumen PICC), the data regarding the transplant procedure, the total days of PICC use, the type and time of PICC-related complications, and the reasons for PICC removal, were collected.

PICC insertion and management

The device was usually a Power PICC 5 Fr bilumen (Bard Access Systems, Salt Lake City, UT). The patients who had a functioning single lumen PICC Groshong 4 Fr Bard, previously inserted, received a second single lumen PICC (Groshong 4 Fr) placement into the contralateral arm. PICC were inserted by a dedicated PICC team of specifically trained physicians and nurses, in a dedicated surgical facility within the Hematology Center, using aseptic techniques. The peripheral venous access was obtained through the basilic or brachial vein, using ultrasound guidance. The correct relationship, between vein caliber and catheter lumen, was carefully evaluated to reduce the risk of PICC-related deep vein thrombosis [7, 11–14]. Skin antisepsis, with 0.5% chlorhexidine in alcohol solution, was performed prior to PICC placement. A local anesthetic (carbocaine 2%) was injected into the subcutaneous tissue close to the anterior vein wall. A 21 gauge needle was systematically inserted under ultrasound guidance, until the anterior vein wall was reached and crossed. The needle was introduced into the vessel until a blood return was observed. A metallic guide wire was then introduced into the vein under fluoroscopic guidance. The puncture site was then enlarged slightly with a scalpel blade, and the micro-introducer assembly was introduced over the guide wire. The catheter was inserted into the micro-introducer sheath, and fluoroscopy was routinely performed in all patients to verify a correct location of the tip (close to the cavo-atrial junction). None of the PICCs was sutured; they were held in place with StatLock adhesive dressings (StatLock; Bard, Murray Hill, NJ). The hospitalized patients received routine PICC assessment, site care, cleaning of the insertion point of the PICC, administration set change, and evaluation of complications in the Transplant ward, while outpatients in a dedicated room by the PICC team. All patients were followed up weekly by the clinicians or nursing staff during hospitalization, and by the PICC team as outpatients, in order to verify PICC-related complications occurrence. In the absence of transplant-related complications, PICC were removed after 100 days post allo-HSCT. The PICC was instead maintained until necessary, in the presence of complications associated with the transplant procedure.

Definition of PICC-related complications and usual management

Catheter-related bloodstream infections (CRBSI) were defined and treated according to Infectious Diseases Society of America Guidelines [15]. A definitive diagnosis of CRBSI requires that the same organism grows from at least 1 percutaneous blood culture and from a culture of the catheter tip, or that 2 blood samples be drawn (one from a catheter hub and the other from a peripheral vein) that, when cultured, meet CRBSI criteria for quantitative blood cultures or differential time to positivity (DTP). Association between CRBSI and CRT (CRBSI+CRT) was considered as a CRBSI associated with vein occlusion, requiring combined treatment with antibiotics, and anticoagulant therapy.

Catheter-related thrombotic complications (CRT) were defined as a thrombotic episode, assessed using color-flow doppler ultrasonography imaging (direct visualization of thrombotic material in the venous lumen), upon overt symptoms and signs (pain or tenderness, warmth, swelling, or edema). In patients with CRT, the PICC remained in place and low-molecular-weight heparin (LMWH) was started. The schedule of anticoagulant treatment was based on the platelets count: (a) platelets $\geq 50 \times 10^9$/L: LMWH was employed at the standard dose of 100 UI/kg twice/day; (b) platelets $< 50 \times 10^9$/L $\geq 30 \times 10^9$/L: 50% dose of LMWH; and (c) platelets $< 30 \times 10^9$/L: platelets concentrates transfusion: in case of persistent thrombocytopenia, LMWH was discontinued.

Mechanical complications included malfunction, obstruction, dislocation, and rupture.

Statistical methods

Data were expressed as mean ± standard deviation (normally distributed data), median and interquartile range (IR) (non-normally distributed data), or as percentage frequencies and within-patient comparisons were made using paired *t* test and χ^2 test, as appropriate, at significance levels of $p < 0.05$. Catheter event-free survival was calculated from the date of PICC insertion to the date of PICC removal, due to any of the complications. For survival analysis, univariate Kaplan-Meier and multivariate Cox analyses were used. All calculations were made using a standard statistical package (SPSS for Windows Version 15.0, Chicago, IL).

Results

One hundred PICC were implanted into 100 patients. The main features of the patients, conditioning regimens, and PICC are reported in Table 1. All patients received antibacterial, antiviral, and antifungal prophylaxis. All devices were inserted without complications.

Table 1 Patients and PICC characteristics

	Patients *n* 100 (%)
Male/Female	62/38
Median Age, years	51.5
Interquartile range (IR)	(24.3–57.6)
Type of disease	
Acute leukemia	56 (56)
Chronic lymphoproliferative disease	44 (44)
Donor source	
Matched unrelated donor (MUD)	51 (51)
Sibling	33 (33)
Haploidentical	16 (16)
Conditioning regimen	
Myeloblative regimen	62 (62)
Reduced intensity regimen	38 (38)
Type of device	
Material	
Polyurethane	52 (52)
Silicone	48 (48)
Number of PICC lumen inserted	
Single lumen	52 (52)
Double lumen	48 (48)
Place of insertion	
Basilic vein	85 (85)
Brachial vein	15 (15)
Arm of insertion	
Right arm	55 (55)
Left arm	45 (45)

The total number of PICC days was 12.800. Overall, the median duration of in situ PICC placement was 117 days (IR 53.75–152.75) and the rates of PICC in situ, without the occurrence of any complication, at 100 and 200 days from HSCT, were 61.8% and 40.5% respectively (Fig. 1). The type and incidence of all PICC-related complications are reported in Table 2.

On the whole, 68% of patients maintained the device for the entire transplantation needs: 44% witnessed no PICC-related complication (30 patients removed the PICC following completion of the procedure, 14 died with functioning in situ PICC), while 24% developed PICC-related complication, not requiring immediate PICC removal. Thirty-two patients (32%) required anticipate PICC removal for PICC-related complications.

Infective complications

CRBSI occurred in 32 patients (32%) with an incidence of 2.5 CRBI per 1000 PICC days. The median interval between PICC insertion and CRBSI onset was 41 days (IR 22–92). The majority of CRBSI were monomicrobial (27/32, 84%) while 5 were polymicrobial (16%). Gram-positives were involved in 26 CRBSI (81%) and coagulase-negative *Shaphylococcus* was the most frequently isolated agent (19 of 32 CRBSI, 59%), 16 monomicrobial and 3 polymicrobial CRBSI. Gram-negatives were involved in 10 CRBSI (10% of patients, 31% of CRBSI), monomicrobial and mixed with Gram-positive cocci in 5 cases each. Carbapenem-resistant *P.aeruginosa* and KPC-*K.pneumoniae* were detected in 1 case of CRBSI each. *Candida glabrata* and *Candida parapsilosis* were documented in 2 polymicrobial CRBSI.

CRBSI occurred during neutropenia (absolute neuthrophils count $< 0.5 \times 10^9$/L) in 13 out of 32 patients (40%) and appropriate therapy, systemic antibiotics or antifungals, was administered in all patients. The PICC was removed in all 32 cases. Twenty-five out of 32 patients (78%), who developed a CRBSI (6 profoundly neutropenic), responded to antibacterial treatment and PICC removal was postponed after engraftment at neutrophils recovery. Seven patients required a PICC removal during profound neutropenia for persistence of fever and bacteremia (4 gram-negative and 1 *C.glabrata* CRBSI, respectively). Overall, the median interval between insertion and anticipated PICC removal for CRBSI was 57 days (IR 41.25–10.5), and the median interval, between the onset of the infection and PICC removal, was 10 days (IR 2.25–27). Fourteen patients died with the PICC in situ; however, the CRBSI never represented the primary cause of death. No difference in the incidence of CRBSI was observed in patients with a single double lumen PICC (19/48, 39.5%) and patients with 2 single lumen PICC (13/52, 25%). In general, a

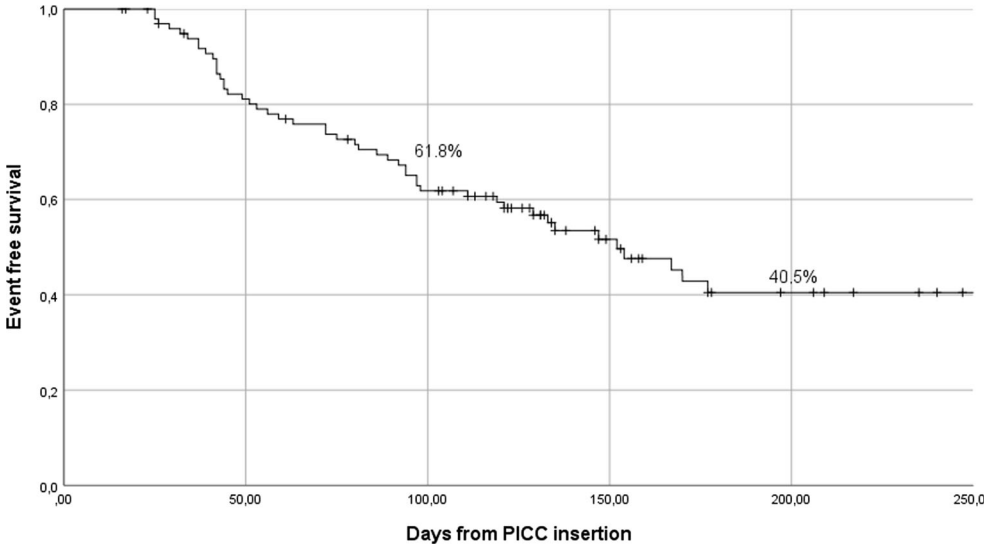

Fig. 1 Catheter event-free survival

significant difference in the incidence of CRBSI was observed, according to the type of PICC used: 42% (22/52) with the polyurethane PICC and 21% (10/48) with the silicone PICC ($p = 0.02$) (Table 3). In particular, the incidence of CRBSI was similar during the first 100 days from PICC insertion and the transplant procedure, while after 100 days CRBSI occurred more frequently in patients with a polyurethane PICC compared with those with a silicone PICC (10 of 32, 31% vs 22 of 32, 66% respectively, $p = 0.021$). The 200-day cumulative incidence was 61% and 21% with the polyurethane and silicone PICC, respectively (hazard ratio (HR) 0.37–95% CI 0.17–0.80; $p = 0.006$) (Fig. 2).

In 8 cases (8% of patients, 25% of CRBSI), the CRBSI was associated with a vein occlusion (CRBSI+CRT). The incidence of CRBSI+CRT was 0.6 per 1000 PICC days. Five patients (62.5%) were thrombocytopenic (number of PLT < 50×10^9/L) at the time of the episode. All patients received LMWH associated with the antimicrobial therapy and a median treatment duration of 19 days (IR 8.25–31.25) (Table 4). The PICC was removed in all cases after a median of 11 days (IR 1.5–52.5) from the onset of the complication. All CRBSI+CRT episodes occurred in patients who received a myeloablative conditioning regimen, while no episodes were observed in patients undergoing a reduced intensity conditioning regimen (8 of 62, 13% vs 0 of 38, $p = 0.021$). The conditioning regimen was related to a higher cumulative incidence of CRBSI+CRT at 200-day (myeloablative 16.7% vs reduced intensity conditioning regimen 0%; $p = 0.03$).

Thrombotic complications

CRT were observed in 9 patients (9%). The median interval between PICC insertion and the onset of a thrombotic episode was 37 days (IR 10–45). When CRT occurred, platelets were between 30 and 50×10^9/L and lower than 30×10^9/L in one case each (11%). All patients received anti-coagulant therapy, discontinued in 1 case due to severe thrombocytopenia and coagulopathy. The median duration of LMWH was 40 days (IR 27.5–54.5) (Table 3). CRT never represented the cause of PICC removal, the PICC continued to be used and vessel recanalization was obtained in all cases. No episode of pulmonary embolism was observed.

The incidence of CRT resulted different depending on the arm of insertion: 15% (7/45) in patients with PICC inserted in the left arm, and 3.6% (2/55) in those with PICC inserted in the right arm ($p = 0.038$). The cumulative incidence of CRT, according to the place of insertion, was 18.5% in the left arm vs 4.1% in the right arm (HR 0.229–95% CI 0.048–0.894; $p = 0.04$).

Mechanical complications

Mechanical complications occurred in 15 (15%) cases, 1.2 per 1000 PICC days. They were malfunctioning in 8 cases, obstructions in 4, ruptures in 2, and malpositioning in 1 case. In all cases, the PICC was unusable and/or unsafe and was removed the same day. Mechanical complications occurred after

Table 2 Type and incidence of PICC-related adverse events

Adverse events	*n* (%)	Incidence per 1000 PICC days
Catheter-related bloodstream infections (CRBSI)	32 (32)	2.5
Mechanical complications	15 (15)	1.2
Catheter-related thrombotic complications (CRT)	9 (9)	-

Table 3 Polyurethane and silicone PICC comparison

Complications	Silicone (total number 48)	Polyurethane (total number 52)	*p* value
CRBSI	10 (20.8%)	22 (42.3%)	0.021
CRT	4 (8.3%)	5 (9.6%)	0.82
CRT+CRBSI	4 (8.3%)	4 (7.6%)	0.9
Mechanical complications	6 (12.5%)	9 (17.3%)	0.47

day 100 from HSCT in 6 cases (40%), and the median interval between PICC insertion and PICC removal was 94 days (IR 44–152).

Discussion

This study is the first specifically conducted on the use of PICC in adult patients with hematologic malignancies receiving an allo-HSCT. PICC may represent a good alternative to a CVC in this setting [1, 4–7, 9, 14]. Recently, good results have been obtained with the PICC use in a small population of pediatric hematologic patients, submitted to an auto- or allo-HSCT: 13 PICC were inserted in 11 patients without insertion-related complication, but with late complications as catheter ruptures and line occlusions (1.2 per 1000 PICC days). No CRT, CRBSI, accidental removal, or permanent lumen occlusion were observed. The indications for catheter removal were the completion of therapy in 8 patients and death in 2 [10].

In our series of adult allo-HSCT recipients, the use of PICC appears safe and can be considered a reliable long-term venous access in this high risk population: 68% of patients maintained the device for the entire transplant procedure, and PICC were removed after day 100 from allo-HSCT, while anticipate PICC removal was necessary in 32% of cases.

Forty-four percent of patients did not experience any PICC-related complications; 30% of these removed the PICC at the completion of treatment and 14% died for transplant-related complication with PICC still in place.

PICC-related complication occurred in 56% of cases but notably in 24% of cases the complication did not require PICC removal, neither immediate nor later. PICC-related adverse events were manageable and did not affect transplant outcome, also they never represented the primary cause of death. The higher CRBSI and CRT rates reported in our cohort, compared with those reported in hematologic patients, [7, 8] could be explained by the higher risk of our selected population of heavily immunosuppressed patients, such as allo-HSCT recipients.

The occurrence of CRBSI was the most frequently observed PICC-related complication and Gram-positives represented the most common pathogens isolated, in agreement with literature data [15]. However, the early PICC removal for the infection was required only in 7% of patients with CRBSI during the aplastic phase of the transplant procedure, and in the majority of cases, the infectious complication was managed until engraftment. Notably, CRBSI never represented the primary cause of death. Previous retrospective studies, conducted on non-homogeneous cohorts of patients and on different types of devices, have not given univocal results on the relationship between infection and PICC materials. In our

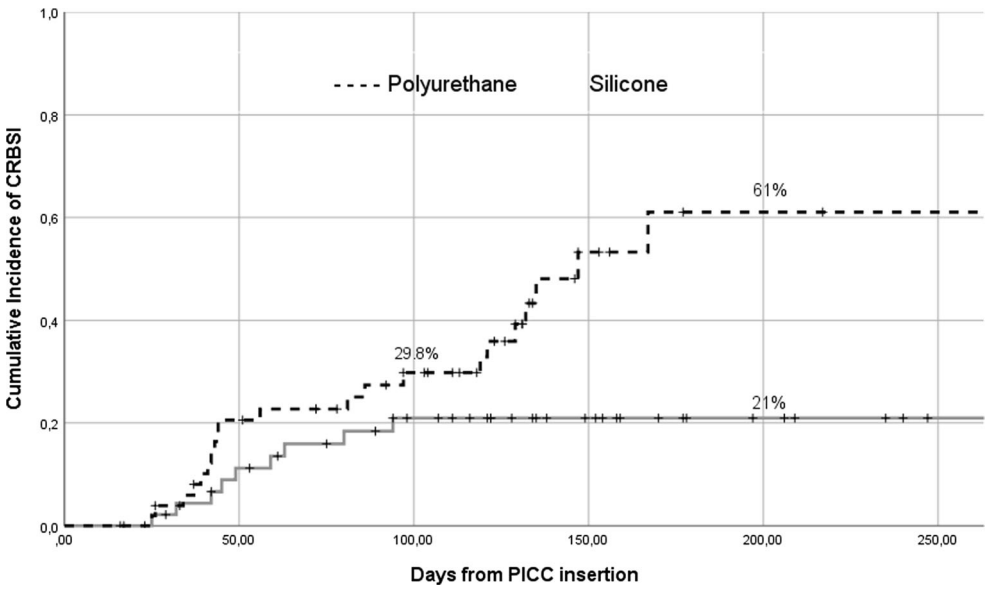

Fig. 2 Cumulative incidence of CRBSI according to PICC material

Table 4 Type and duration of treatment in CRT and CRBSI+CRT

Adverse event	Type of treatment	Median duration of treatment days (IR)	Days from onset of complication and PICC removal (IR)
CRT	LMWH	40 (27.5–54.5)	40 (30–90)
CRBSI+CRT	LMWH+Antibiotics	19 (8.25–31.25)	11 (1.5–52.5)

limited experience, we observed a lower incidence of CRBSI in patients with silicone PICC after 100 days from the device insertion, when the main risk factors for infection are usually resolved. Prospective randomized studies are needed to confirm a reduction of infection with the use of silicone PICC. Almost half of our patients maintained an already inserted functional PICC, used for the previous chemotherapeutic cycles, and a second single lumen device was placed into the contralateral arm, specifically for the transplant procedure. The presence of two venous accesses could represent an increased risk factor for infectious complications; however, in our series, we did not observe a higher CRBSI incidence in patients with two PICC compared with those with a single PICC. In our opinion, this strategy should be considered a possible option allowing to avoid an unnecessary PICC removal and insert a smaller caliber PICC (4 vs 5 Fr) with less endothelial damage.

In our patients, the incidence of CRT was 9%. In other experiences in high-risk hematologic patients, the reported CRT incidence was similar to our data, between 7.8 and 11.7%, [16–19]. The high incidence observed could be associated to allo-HSCT procedures and complications: acute graft-vs-host disease and high dosages of steroids treatment [20].

In our experience, we did not observe difference in CRT incidence related to the lumen size, 4 vs 5 French. In a recent retrospective study in hematologic patients, PICC lumen size influenced the risk of thrombotic complication, with 20 and 13% of thrombosis observed with 6 and 5 French catheters, respectively [16]. In our study, CRT did not represent a severe complication in allo-HSCT and the occurrence of CRT never required an early PICC removal. Even if routine PICC removal for CRC is not recommended, especially if the catheter is functional, literature data report a heterogeneous behavior: the thrombotic PICC removal was reported in less than 4% of cases [21–23]. We used the device until there was an ongoing need for PICC use and even when anticoagulant treatment was contraindicated: no worsening of thrombosis or pulmonary embolism complication were observed as documented also by others [24–26]. As already observed in a recent randomized controlled trial [27], we reported less thrombotic complications when PICC was inserted in the right arm.

CRBSI+CRT occurred in 8% of patients and a CRT was documented in the 25% of CRBSI. A prolonged profound neutropenia, the high risk of bacteremia and consequent PICC bacterial colonization could have contributed to activate the thrombosis. The increased risk of catheter-related thrombosis, due to catheter site infections and neutropenic sepsis, following chemotherapy, is reported in patients with acute myeloid leukemia [28].

In our patients, a diagnosis of acute leukemia and the use of myeloablative conditioning regimens seem to be associated to a higher incidence of CRBSI+CRT. CRBSI+CRT resolution time was shorter when compared with CRT, confirming the different pathogenesis of the two complications, a septic thrombus for CRBSI+CRT. Differently from CRT, in the presence of CRBSI+CRT, a PICC removal is mandatory to control and treat the complication.

We observed that mechanical complications are the second most frequent events and represented the second cause of an anticipated PICC removal. The high incidence of this complication may be related to the intensity of treatments, performed in allo-HSCT recipients, that require a very frequent and intensive use of the intravenous devices. Training of nursing staff in PICC management is, therefore, crucial to prevent and reduce the occurrence of mechanical complications that always lead to PICC removal.

Conclusion

In this study, we observed a low rate of complications with the use of PICC in a high-risk population, specifically adult patients undergoing a HSCT. Indeed, 68% of our patients did not develop PICC-related complication, requiring anticipated PICC removal. We conclude that PICC are a safe and reliable long-term venous access for adult patients with hematologic malignancies requiring an allogenic HSCT.

Data availability The authors have full control of all primary data and agree to allow the journal to review their data if requested.

Compliance with ethical standards

All procedures followed were in accordance with the ethical standards. All patients were informed about the procedure and its potential complications, and they gave a written informed consent for the insertion of the catheter and for the use of the data for scientific purposes.

Conflict of interest The authors declare that they have no competing interests.

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