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【 ORIGINAL ARTICLE 】

Risk Factors for Complications Associated with Peripherally Inserted Central Catheters During Induction Chemotherapy for Acute Myeloid Leukemia

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Abstract:

Objective Peripherally inserted central catheters (PICCs) are widely used in patients with hematologic malignancies. However, the risks of PICC-related complications during chemotherapy for acute myeloid leukemia (AML) are not fully understood.

Methods We conducted a retrospective review of 128 adult patients with AML who received induction therapy by way of PICC insertion between 2012 and 2019.

Results The median duration of PICC insertion was 30 days. The incidence rate of catheter-related bloodstream infection (CRBSI) was 2.4% at 30 days, and women were more likely to suffer from CRBSI than men. Local reactions at the insertion site were observed in 56 patients; however, these events did not predict CRBSI. The incidence rates of catheter-related thrombosis (CRT) were 1.6% at 30 days. Obesity put patients at an increased risk for CRT. Unexpected PICC removal occurred in 59 patients, and women were at a higher risk of catheter removal than men.

Conclusion Low PICC-related complication rates, possibly associated with high rates of catheter removal, were observed during intensive chemotherapy for AML. Women and obese patients require careful monitoring of their PICC. Procedures to achieve appropriate PICC removal without increasing the complication rate need to be considered.

Key words: PICC, CRBSI, catheter-related thrombosis

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Introduction

Securing an intravenous access route, such as by a central venous catheter, is important for the treatment of acute myeloid leukemia (AML), since it enables the delivery of chemotherapeutic agents along with large amounts of fluid, blood products, and nutrition. The preferred device for patients with AML at high risk of infectious and hemorrhagic complications is one that is easily operable and facilitates a low complication rate. Catheter-related complications, which include catheter-related bloodstream infection (CRBSI) and catheter-related thrombosis (CRT), are associated with significant rates of morbidity and mortality in this high-risk population (1), and the management of such complications remains a critical issue in clinical practice.

Peripherally inserted central catheters (PICCs) offer the benefits of a simple insertion method and versatility and have been increasingly used to treat hematological malignancies. PICCs are also useful for complication manage-

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Table 1. Patient characteristics (n=128).

		n (%)
Age, years, median (range)		60 (15-83)
Male		90 (70.3)
BMI, kg/m^2, median (range)		23.0 (14.2-36.5)
AML type,	De novo AML	83 (64.8)
	Secondary AML	45 (35.2)
Cytogenetic risk,	Favorable	30 (23.4)
	Intermediate	58 (45.3)
	Adverse	40 (31.3)
Hypertension		31 (24.2)
Dyslipidemia		13 (10.1)
Diabate		12 (9.4)
History of thrombosis		4 (3.1)
History of cancer		14 (10.9)
Chronic kidney disease		37 (28.9)
PICC inserted right side		65 (50.8)
Catheter tip located in SVC		97 (75.8)
Year of insertion,	2012-2015	72 (56.3)
	2016-2019	56 (43.7)

BMI: body mass index, AML: acute myeloid leukemia, PICC: peripherally inserted central catheter, SVC: superior vena cava

ment, since it has been reported that PICCs ensure a lower incidence rate of CRBSI than conventional central venous catheters (CVCs) in patients with hematological malignancies (2-4). However, the literature suggests that the incidence rate of PICC-related CRBSI varies significantly, reportedly ranging from 0.47-6.6/1,000 PICC days of catheterization (5). In contrast, with regard to CRT, a meta-analysis showed that PICC placement was associated with a greater risk of deep vein thrombosis than CVCs, especially in patients with malignancies (6). The incidence rate of PICC-related CRT in hematological malignancies has been reported to be 0.05-7.7/1,000 PICC days of catheterization (5).

Little is known about the risks of catheter-related complications in the leukemia setting (7, 8). In addition, the nature of the relationship between skin findings at the insertion site and the onset of CRBSI/CRT remains unknown. The present study therefore explored risk factors for PICC-related complications in patients with AML and clarified which precautions should be taken to prevent these complications.

Materials and Methods

Patients and data collection

We evaluated a total of 128 patients who had received PICCs and underwent their first induction chemotherapy session for AML at Jichi Medical University Hospital from January 2012 to September 2019. A non-tunneled, double-lumen, 4.5-French polyurethane catheter (Argyle; Covidien, Dublin, Ireland) was inserted into the cubital fossa or brachial vein with maximum barrier precaution. Throughout the entire study period, we used the same type of PICC catheter. X-ray imaging of the chest was used to confirm the tip position of the catheter.

Data were extracted from the patients' medical records. This study was approved by the ethics committee at Jichi Medical University.

Study definitions

Bacteremia was defined as the confirmation of at least two sets of positive blood cultures taken simultaneously, although the detection of organisms with a low contamination potential in blood culture was defined as bacteremia, even if only one set was positive (9). CRBSI was diagnosed based on the criteria of CRBSI in the Infectious Diseases Society of America guidelines (10) as follows: (1) the same bacteria were detected in cultures of the peripheral blood and the extracted catheter tip, (2) the blood culture from the catheter was positive more than two hours earlier than that from the peripheral blood, and (3) the number of colonies of microorganisms generated from blood aspirated from the catheter was more than three times higher than that in blood aspirated from the peripheral veins in a quantitative blood culture.

Local inflammatory reactions at the insertion site were confirmed according to the following symptoms documented by a doctor or nurse: clinical signs of inflammation (e.g. redness, swelling, pain, purulent exudate) located ≤2 cm from the catheter insertion site in the absence of a concomitant bloodstream infection. Catheter-related thrombotic symptoms were defined as the appearance of redness and pain along the blood vessels in the limb into which the PICC was inserted. The diagnosis of CRT required confirmation by radiological imaging, such as ultrasound or contrast-enhanced computed tomography (11).

Statistical analyses

The relationship between the cumulative incidence of adverse events and each background factor was analyzed using the Gray test and Fine-Gray proportional-hazards modeling in univariate and multivariate analyses, respectively. The event-free survival (EFS) was defined as the time from PICC implantation to bacteremia, CRBSI, CRT, catheter removal or death. The EFS probability was estimated by the Kaplan-Meier method. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) (12).

Results

Patient characteristics

As shown in Table 1, the median age among study participants was 60 years old, and 70% of the study population were men. Thirty-five percent of the patients had secondary leukemia, and 9.4%, 24.2%, 28.9%, and 10.1% of the patients had histories of diabetes, hypertension, chronic kidney disease, and dyslipidemia, respectively. The PICC was in-

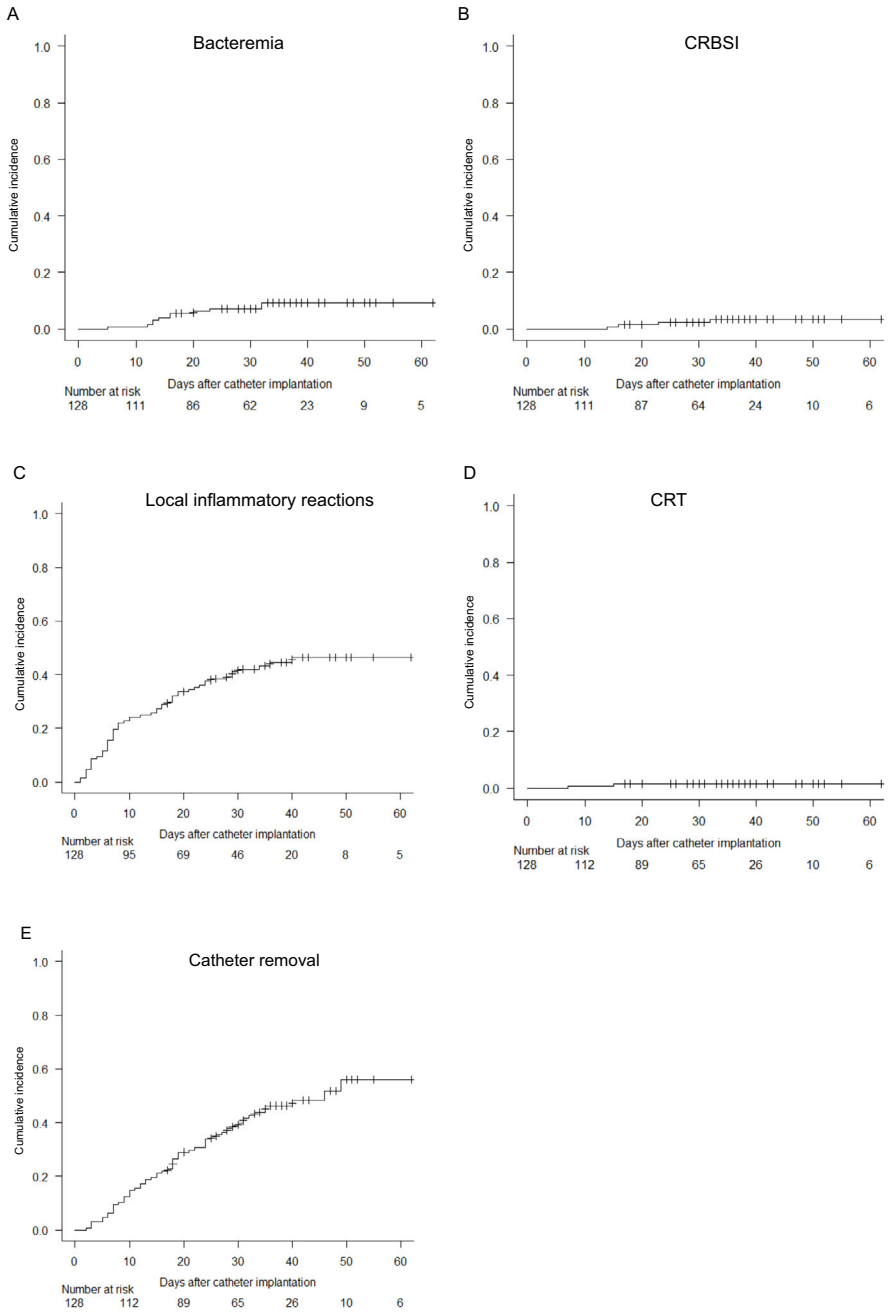

Figure 1. Cumulative incidence of bacteremia (A), CRBSI (B), local inflammatory reactions (C), CRT (D), and catheter removal (E); these cumulative incidence rates at 30 days after PICC insertion were 8.6%, 2.4%, 42%, 1.6%, and 39.7%, respectively.

serted with nearly equal frequency on the right and left sides. The total number of days with PICC insertion was 3,700, and the median duration of PICC insertion was 30 (range: 2-73) days.

Infectious complications

The cumulative incidence rate of febrile neutropenia (FN) in patients with PICCs was 94.5% [95% confidence interval (CI): 88.5-97.4%] at 30 days after PICC insertion. FN was observed in 60 of 128 patients on the day of PICC insertion. Levofloxacin was prophylactically administered in the remaining 68 patients without FN on admission.

During induction therapy, 11 patients showed bacteremia due to *Corynebacterium* (n=8), *Staphylococcus haemolyticus* (n=2), *Enterococcus faecalis* (n=1), *Bacillus cereus* (n=1), and *Gemella morbillorum* (n=1), while 2 patients were coinfected by *Corynebacterium* with *B. cereus* and *Corynebacterium* with *E. faecalis* (1 each). The cumulative incidence rate of bacteremia in patients with PICCs was 7.1% (95% CI: 3.5-12.4%) at 30 days (Fig. 1A). Bacteremia was reported more frequently among patients over 60 years of age than in patients under 60 years of age (cumulative incidence at 30 days: 11.9% vs. 1.7%; p=0.044).

Four of 11 cases of bacteremia met the definition of

Table 2. Risk Factors for CRBSI, Catheter-related Thrombotic Symptom and CRT.

		CRBSI		CRT	
Factors		% (95% CI)	p	% (95% CI)	p
Age, years	<60	1.7 (0.1-7.9)	0.375	3.3 (0.6-10.3)	0.131
	≥60	3.0 (0.6-9.4)		0 (0)	
Sex	Male	0 (0)	0.051	1.1 (0.1-5.4)	0.524
	Female	7.9 (2.0-19.4)		2.6 (0.2-12.0)	
BMI, kg/m^2	<18.5	2.6 (0.7-6.9)	0.548	1.7 (0.3-5.5)	0.663
	≥18.5	0 (0)		0 (0)	
	<25	3.2 (0.9-8.4)	0.897	0 (0)	0.0183
	≥25	0 (0)		5.9 (1.0-17.4)	
AML type	De novo AML	2.4 (0.5-7.7)	0.496	2.4 (0.5-7.6)	0.296
	Secondary AML	2.2 (0.2-10.4)		0 (0)	
Cytogenetic risk	No adverse	1.1 (0.1-5.6)	0.424	1.1 (0.1-5.4)	0.581
	Adverse	5.1 (0.9-15.2)		2.4 (0.2-11.2)	
Hypertension	No	2.1 (0.4-6.6)	0.981	2.1 (0.4-6.6)	0.422
	Yes	3.4 (0.2-14.9)		0 (0)	
Dyslipidemia	No	2.6 (0.7-6.9)	0.492	1.7 (0.3-5.6)	0.633
	Yes	0 (0)		0 (0)	
Diabetes	No	2.6 (0.7-6.9)	0.334	1.7 (0.3-5.6)	0.648
	Yes	0 (0)		0 (0)	
History of thrombosis	No	2.4 (0.7-6.5)	0.705	1.6 (0.3-5.2)	0.799
	Yes	0 (0)		0 (0)	
History of cancer	No	7.1 (3.3-12.8)	0.896	1.8 (0.3-5.6)	0.619
	Yes	7.1 (0.4-28.8)		0 (0)	
Chronic kidney disease	No	2.2 (0.4-7.1)	0.345	2.2 (0.4-7.0)	0.365
	Yes	2.7 (0.2-12.3)		0 (0)	
PICC insertion site	Left	3.2 (0.6-9.9)	0.999	3.1 (0.6-9.7)	0.156
	Right	1.6 (0.1-7.5)		0 (0)	
Position of PICC tip	In SVC	2.1 (0.4-6.6)	0.931	1.0 (0.1-5.1)	0.39
	Outside SVC	3.2 (0.2-14.5)		3.2 (0.2-14.4)	
Year of insertion	2012-2015	1.4 (0.1-6.9)	0.718	0 (0)	0.108
	2016-2019	3.6 (0.6-11.0)		3.6 (0.7-11.0)	

CRBSI: catheter-related bloodstream infections, CRT: catheter-related thrompbosis, CI: confidence interval, BMI: body mass index, AML: acute myeloid leukemia, PICC: peripherally inserted central catheter, SVC: superior vena cava

CRBSI. Regarding the causative organism of CRBSI, *Corynebacterium* was detected in three patients (one each on days 14, 16, and 32), while *S. haemolyticus* was detected in the fourth patient on day 23. The cumulative incidence rate of CRBSI was 2.4% (95% CI: 0.6-6.3%) at 30 days (Fig. 1B) or 1.1/1,000 PICC days. CRBSI was more frequently observed in women than men, and this difference was marginally significant (cumulative incidence at 30 days: 7.9% vs. 0%; p=0.051) (Table 2). As a treatment for CRBSI, beta-lactam agents and vancomycin were administered to four patients, and PICCs were removed in three, excluding the patient with *S. haemolyticus* infection. Under these treatments, blood cultures showed negative results within a few days, and the fever improved after 1, 5, 19, and 23 days (n=1 each).

Local inflammatory reactions at the PICC insertion site

During the study period, 56 patients experienced local inflammatory reactions at the PICC insertion site. Symptoms included redness (n=10), pain (n=4), redness and pain (n=6), redness and a heat sensation (n=14), and redness, pain, and a hot sensation (n=9). The cumulative incidence rate of local inflammatory reactions in patients with PICCs was 42% (95% CI: 33-50.5%) at 30 days after PICC insertion (Fig. 1C). Local inflammatory reactions occurred more frequently in women than in men (cumulative incidence at 30 days: 63.5% vs. 32.8%; p=0.002) and patients treated from 2012 to 2015 than in patients treated from 2016 to 2019 (cumulative incidence at 30 days: 47.7% vs. 34.4%; p=0.051). A multivariate analysis showed that female sex was a risk factor for local reactions [female sex, hazard ratio (HR) 2.29, 95% CI: 1.34-3.89, p=0.022; patients treated from 2012 to 2015, HR 1.66, 95% CI 0.96-2.86, p=0.07].

Of the 56 patients with local inflammatory reactions, blood cultures were collected from 24 patients at the time of the appearance of local findings, and 1 patient thereafter was diagnosed with CRBSI. PICCs were removed from 38

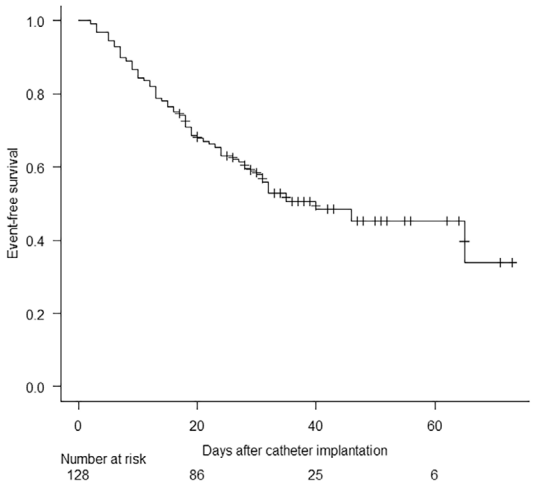

Figure 2. Kaplan-Meier plot of the event-free survival (EFS). The EFS was defined as the time from PICC implantation to bacteremia, CRBSI, CRT, catheter removal, or death.

patients, while 18 continued to use PICCs without additional episodes of CRBSI.

Thrombotic complications

Catheter-related thrombotic symptoms were observed in 21 patients, and 2 of 19 patients showed elevated D-dimer levels. Among the 21 patients with thrombotic symptoms, 4 underwent imaging tests, and CRT was detected in 2 patients on days 7 and 15. Following catheter removal in both patients, ultrasound examinations confirmed venous thromboses along the catheter in the upper arm. The cumulative incidence rate of CRT was 1.6% (95% CI: 0.3-5.1%) at 30 days after PICC insertion (Fig. 1E). Patients with body mass index values greater than 25 kg/m^2 experienced CRT more frequently than those with values less than 25 kg/m^2 (cumulative incidence at 30 days: 6.2% vs. 0%; p=0.018) (Table 2). Both patients with CRT required PICC removal and anticoagulant therapy.

Catheter removal and the survival

During induction therapy, PICCs were removed from 59 patients due to CRBSI (n=3), bacteremia (n=6), CRT (n=2), catheter-related thrombotic symptoms (n=19), persistent fever (n=17), local inflammatory reactions (n=12), and elevation of the C-reactive protein level (n=1). The cumulative incidence rate of catheter removal was 39.7% (95% CI: 31.1-48.2%) at 30 days after PICC insertion (Fig. 1F). The median interval between insertion and removal of the PICC was 18 days (range: 2-66 days). Catheter removal was more frequently observed in women than in men (cumulative incidence at 30 days: 58.1% vs. 31.8%; p=0.017).

Of the 128 total patients, 3 died due to acute myocardial infarction (day 20), cerebellar hemorrhaging (day 23), and severe sepsis (day 67) during induction therapy, respectively. The cumulative incidence rate of non-relapse mortality was 2.2% (95% CI: 0-5.3%) at 30 days after PICC insertion. The probability of an EFS at 30 days was 57.9% (95% CI, 48.7-66%), and the median survival was 40 days (95% CI, 29 days-not reached) (Fig. 2).

Discussion

The current study identified risk factors for PICC-related complications in patients with AML receiving induction chemotherapy. Women tended to develop CRBSI more often than men, while skin findings observed at the insertion site were not necessarily correlated with CRBSI. Thrombotic complications were shown to be associated with obesity.

The incidence rates of bacteremia and CRBSI at 30 days after PICC insertion were 8.6% and 2.4%, respectively. Although the patients' background characteristics and antimicrobial prophylaxis varied, the incidence rates of PICC-related infectious complications were equal to those reported previously among adult patients with AML (4, 7, 8, 13, 14) (Table 3). Women showed a trend toward an increased risk of CRBSI compared with men. Some reports in the literature have suggested that men are at a higher risk for bloodstream and surgical-site infections, while others indicate that women show higher infection rates for surgical-site infections (15). Local inflammatory reactions at the PICC insertion site were indeed observed more frequently in women than in men. While the precise mechanisms by which a female sex influences the infection risk among patients with AML remain unclear, sex differences in the skin structure, physiology, blood vessel diameter, effect of sex hormones, and skin bacterial colonization under chemotherapy-induced neutropenia may be involved.

Infection of the exit site is defined as clinical signs of inflammation (e.g., redness, swelling, pain, purulent exudate) located ≤2 cm from the catheter insertion site in the absence of a concomitant bloodstream infection. Exit site infections usually respond to management with exit site care, local dressing, and antibiotics, but CVC removal is recommended if the following are present: systemic signs of infection, positive blood culture results, purulence, clinical state deterioration, or severe complications per clinical guidelines (10, 16). In the present study, purulent exudate warranting catheter removal was not observed. Although controversy persists as to how local inflammatory reactions in feverish patients during neutropenia should be managed, about 70% of patients with local inflammatory reactions underwent catheter removal based on the attending doctor's judgment. The remaining 30% of patients with catheter preservation did not develop CRBSI, which was observed in only 1 of 56 patients with local inflammatory reactions. In addition, such reactions were uncommon in patients with CRBSI (found in 1 of 4 CRBSI cases; sensitivity of 25% and specificity of 56.1%), and as previously reported, local inflammatory reactions at the insertion site do not predict CRBSI in patients with AML (17). Thus, our findings suggest that local inflammatory reactions do not necessarily require removal of the catheter in patients with AML.

Catheter-related thrombotic symptoms were observed in

Table 3. Reports on PICC in Adult Patient with AML.

Publication	No. of patient	Duration of PICC, days, median (range)	Bacteremia	CRBSI	CRT	PICC removal
(13)	52 catheters	63 (3-441)	33%‡	NA	3.8%	32.6%
(14)	84	NA	9.4%‡	2.4%, 1.0/1,000 PICC days	12.9%, 5.5/1,000 PICC days	27.1%
(7)	43	24 (7) †	20.9%	NA	0%	23.3%
(4)	46	NA	NA	4.3%, 1.4/1,000 PICC days	8.7%, 2.9/1,000 PICC days	13%
(8)	144	83 (0-365)	22%§	NA	12.5%	33%
This study	128	30 (2-73)	8.6%	3.1%, 1.1/1,000 PICC days	1.6%, 0.5/1,000 PICC days	46.1%

PICC: peripherally inserted central catheter, AML: acute myeloid leukemia, CRBSI: catheter-related bloodstream infections, CRT: catheter-related thrompbosis, NA: not applicable

†mean (standard deviation), ‡bloodstream infection, §central line associated bloodstream infection

21 patients, and the cumulative incidence rate of catheter-related thrombotic symptoms was 18% at 30 days after PICC insertion. Catheter-related thrombotic symptoms were more strongly associated with female sex than male sex and with a catheter tip located in the brachiocephalic/subclavian vein than in the superior vena cava. The incidence of CRT during chemotherapy for AML was lower than in previous studies (Table 3), probably due to the low performance rate of imaging studies in patients with thrombotic signs. As a result, the incidence of thrombosis was probably underestimated in this study.

Unexpected catheter removal was observed in 59 of the 128 patients, and the PICC removal rate at our institute was higher than in previous reports (Table 3). This indicates that early PICC removal tended to be considered readily by the doctor when CRBSI or CRT was suspected. This behavior may have led to the low prevalence rates of CRBSI and CRT. However, catheters may have been removed unnecessarily. For example, 17 of 59 PICCs were removed due solely to the presence of a fever, in the absence of a diagnosis of CRBSI. A randomized control study demonstrated that mortality did not differ between cases where early CVC removal or watchful waiting was adopted for suspected catheter-related infection in patients in the intensive-care unit. However, this randomized study excluded neutropenic patients, and 16 of 42 catheters were removed in the watchful waiting group (18). A further study of the appropriate timing for PICC removal in patients with AML, especially those with complicated FN, is needed.

Several limitations associated with the present study warrant mention. First, evaluations of local inflammatory reactions and the decision regarding PICC removal were based on the judgment of the treating physician, without any objective criteria. Second, blood cultures were collected in about half of patients at the time of the occurrence of local inflammatory reactions, which might have masked the impact of local reactions on the diagnosis of CRBSI. Third, data on the number of trials or time required for PICC insertion, which are risk factors for CRBSI at the time of PICC insertion, were not available. Fourth, this study was limited to AML, and whether or not these findings can be applied to other hematologic malignancies is unclear. Acute leukemia was reportedly associated with a higher incidence of PICC-related CRBSI than other hematological malignancies (19). It should be noted that different types of hematological malignancies have different risks of PICC-related complications.

Conclusion

Our present findings suggest that PICCs constitute a safe and useful venous access route in AML patients with manageable complications. According to our experience, local reactions at the insertion site did not predict CRBSI. Female sex and obesity are risk factors for PICC-related complications, and such patients should be carefully monitored, with early PICC removal performed in relevant cases. Further effort is required to reduce PICC-related complications without increasing the occurrence of unnecessary catheter removal.

The authors state that they have no Conflict of Interest (COI).

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