Catheter-related thrombosis in stem cell recipients: comparison of different types of catheter

Patients undergoing hematopoietic stem cell transplantation (HSCT) require a versatile venous catheter for a variety of purposes, including chemotherapy infusion, administering antibiotics, transfusing blood products, providing parenteral nutrition, and collecting systematic samples. Due to the frequent occurrence of vasculature issues, an intermediate-term, large-bore catheter is typically necessary. Two types of catheters are commonly used - conventional central venous catheters (CICC) and peripherally inserted central catheters (PICC). CICC are inserted through large central veins, whereas PICC are inserted through smaller peripheral veins, typically in the upper limb.

The use of CICC remains prevalent in many transplant centers due to their accessibility, affordability, and operator preference. However, the insertion and removal of these devices pose considerable risks, including arterial puncture or catheterization, nerve damage, tissue hematoma, hemothorax, air embolism, and pneumothorax. McGee *et al.* found that 6-19% of CICC implantations result in mechanical complications, with a pneumothorax rate as high as 3%.[1]

PICC insertion is a safe procedure, deprived of life-threatening complications with fewer insertion and removal-related complications than CICC.[2,3]The PICC is typically inserted into the upper arm using ultrasound guidance and the modified Seldinger's technique. The basilic vein is the best location for insertion, and the medial distal part of the arm is the recommended puncture site. Catheter to vein ratio should not exceed 45% as advocated by the Infusion Therapy Standards of Practice.[4]

Alternative vascular devices to PICC are midline catheters (MLC). MLC are devices inserted into the peripheral veins of the upper and terminate in the peripheral veins, not the central veins. The tip of the MLC catheter should be located at or below the axillary vein, distal to the shoulder.[5,6]

One of the typical complications involving mid- to long-term vascular devices is catheter-related thrombosis (CRT). Thrombotic complications can occur with catheter use, with reported rates varying from around 5% to an overall rate of 18%.[7] Cancer patients with indwelling devices seem particularly prone to this complication due to frequent immobility, hyperinflammation, chemotherapy administration, and prolonged catheterization. In addition, CRT is associated with complications of pulmonary embolism, systemic sepsis, loss of intravenous access, and post-thrombotic syndrome.[8] Data on PICC-associated thrombosis present ambiguous results. A systematic review and meta-analysis concluded that PICC are associated with an increased risk of CRT compared to other tunneled CVC but not pulmonary embolism.[9] The data on MLC in non-malignant settings suggests that MLC cause more catheter-related thrombosis (CRT) than PICC.[10] It is worth emphasizing that most of the reported data derived from oncologic patients and stem cell transplant recipients may have altered CRT risk, especially in the case of severe thrombocytopenia, which is common in the transplantation setting. Additionally, in the context of stem cell transplantation, catheters are generally removed once therapy is completed. Conversely, in the case of oncology patients, vascular devices are typically left in place unless they become dysfunctional or infected.

This study presents the results of a comparative analysis of the feasibility and safety of PICC and MLC, in patients undergoing HSCT. The primary objective was to evaluate the incidence of CRT associated with PICC and MLC in comparison to CICC. This study was conducted in accordance with

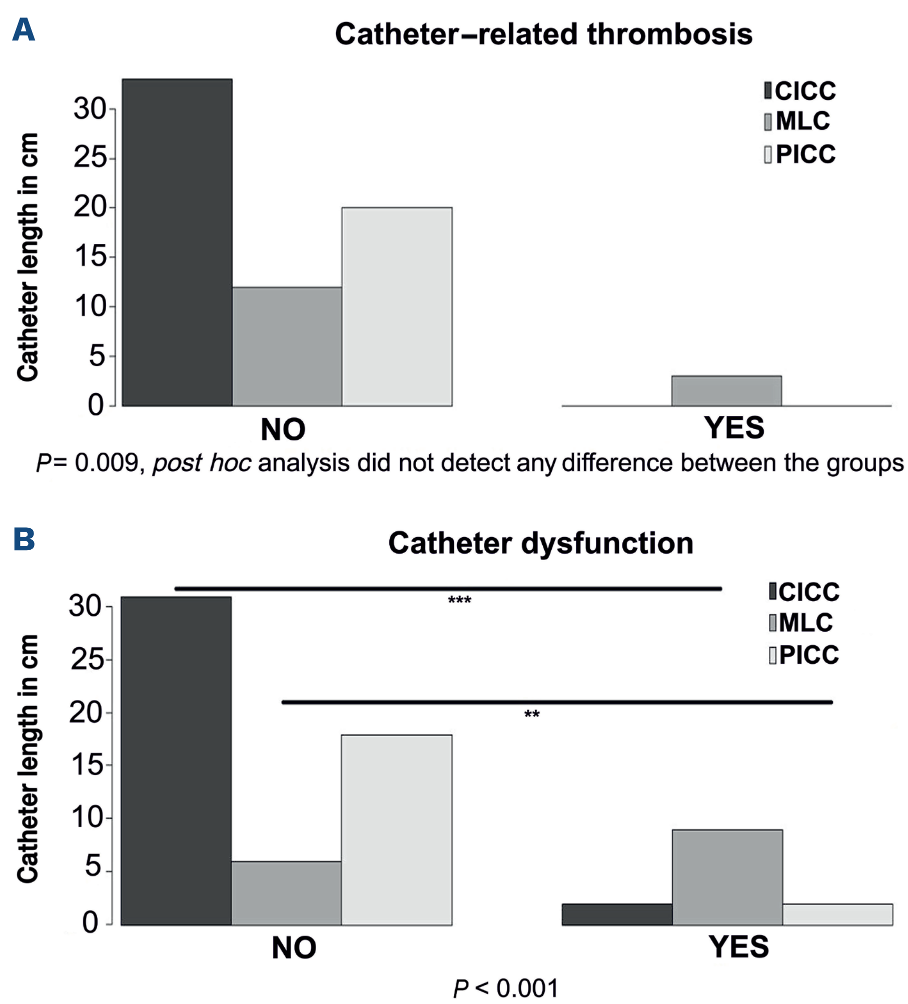

Figure 1. Analysis of conventionally inserted central venous catheter and a catheter dysfunction in a given type of device. (A) Catheter-related thrombosis. (B) Cathether dysfunction. Fisher exact test was implemented for the study. Since there was a statistically significant difference between the devices, *post hoc* analysis with Bonferroni correction for multiple testing was conducted. *P* value <0.05 was considered statistically significant. $^{**}P<0.01$; $^{***}P<0.001$. PICC: peripherally inserted central venous catheter; MLC: midline catheter; CICC: conventionally inserted central venous catheter.

the Declaration of Helsinki and approved by the Bioethical Committee of Pomeranian Medical University in Szczecin (approval number: RPW/10177/2022P). Informed consent was obtained from all subjects involved in the study.

We conducted a retrospective observational study investigating 68 consecutive autologous and allogeneic HSCT procedures. The *Online Supplementary Appendix* presents detailed patients and catheter characteristics (*Online Supplementary Table S1*). The patients were divided into two groups: the study group consisted of 35 patients undergoing transplantation with peripheral catheters (PICC or MLC), and the control group consisted of 33 patients with CICC. We have analyzed subgroups regarding catheter length, diameter, and particularly in terms of CRT and catheter dysfunction (CD). CD was defined as the inability to either aspirate or infuse fluids.

The prevalence of CRT did not differ between CICC and peripheral catheters (PICC and MLS combined). Subsequently, we examined if CRT is associated with a particular type of intravenous device. We analyzed CICC, PICC, and MLC separately. Although Fisher's exact test revealed a statistically significant result (*P*=0.009), indicating increased CRT prevalence in MLC, the *post hoc* analysis did not confirm the difference between the catheters (Figure 1A). Subsequently, we examined if CRT is associated with a particular type of intravenous device. We analyzed CICC, PICC and MLC separately. Although Fisher's exact test revealed a statistically significant result (*P*=0.009), the *post hoc* analysis did not confirm the difference between the catheters (Figure 1A).

Catheter dysfunction occurred significantly more frequently in the peripheral catheters (*P*=0.01) (Table 1). We analyzed CICC, PICC and MLC separately (*P*=0.009) (Figure 1B). Our findings indicate that MLC have a significantly higher incidence of dysfunction compared to CICC and PICC (*P*<0.001 and *P*<0.01, respectively). However, there were no significant differences between PICC and CICC (Figure 1B).

We used a multiple logistic regression model to determine predictors for a CD. Results are presented in *Online Supplementary Table S2* and depicted in Figure 2. We considered catheter length and diameter as potential predictors, as there were significant differences in these parameters between the groups. Additionally, we included the type of HSCT and the length of stay in our model, as a longer hospitalization duration is associated with a higher probability of CD acquisition. We observed that a smaller catheter diameter was significantly associated with device dysfunction (odds ratio [OR] =0.012; *P*<0.001). However, we found no significant association between CD and catheter length, length of stay, or type of HSCT.

Regarding CRT, studies have presented ambiguous results, mainly deriving the data from studies limited to oncology patients. According to our knowledge, this study is the first specifically conducted to compare different peripheral vascular devices in adult patients undergoing stem

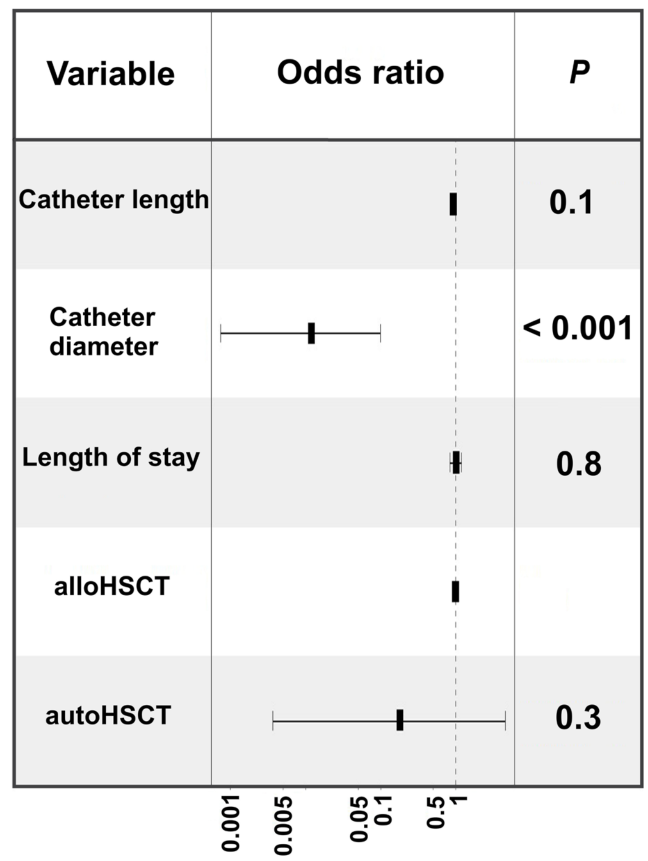

Figure 2. Forest plot of a multiple regression model demonstrating odds ratios for a catheter dysfunction. Catheter length, catheter diameter, length of stay and type of HSCT were used as independent variables. *P* value <0.05 was considered statistically significant. AlloHSCT: allogenic hematopoietic stem cell transplantation; autoHSCT: autologous stem cell transplantation.

Table 1. Comparison between central and peripheral catheters.

Parameter	Peripheral catheter N mean (median), IQR	Central catheter N mean (median), IQR	*P*
Catheter length, cm	31.45 (33), 20.00-45.00	16 (16), 16	<0.001
Catheter diameter, French gauge	4.77 (5), 4-6	7 (7), 7	<0.001
CRT: Yes/No	3/32	0/35	0.1145
CD: Yes/No	11/24	2/31	0.01

Mann-Whitney U test was used to analyze differences between the continuous variables. Fisher exact test was implemented to compare categorical data. *P* value <0.05 was considered statistically significant. N: number; IQR: interquartile range; CRT: catheter-related thrombosis CD: catheter dysfunction.

cell transplantation. We have focused on catheter-related thrombosis and dysfunction, which are usually intertwined. We demonstrated that although CRT occurred more often in patients with peripherally inserted venous catheters, the difference between the CICC group was not statistically significant. Detailed analysis of different catheter types revealed that MLC tend to be associated with a greater risk of CRT. However, after *post hoc* analysis, catheter types did not differ. Nonetheless, it is worth emphasizing that all cases of CRT occurred in patients with MLC. The lack of statistically significant difference could be attributed to a relatively small sample size. Therefore, further studies should investigate the relationship between different types of peripherally inserted catheters and CRT in the transplantation setting. According to the latest literature data, no consensus exists on whether MLC are associated with lower CRT incidence than PICC. Bahl and co-workers demonstrated that patients with MLC are far more likely to develop CRT than individuals with PICC.[10] Still, Xu *et al*. demonstrated that MLC were not different from PICC regarding CRT.[11] Similar results were revealed in other studies,[12,13] in which MLCs were not inferior to PICC concerning the frequency of CRT.

CRT in our cohort was diagnosed exclusively after engraftment when the platelet count was greater than 20×10^9/L. This may suggest that thrombocytopenia may have a protective effect against CRT. Indeed, this observation is coherent with other studies investigating thrombotic complications after HSCT.[14,15] Therefore, it might be concluded that individuals undergoing HSCT during the pre-engraftment phase exhibit features, of potentially protective qualities, different from other populations of patients.

On top of CRT, another catheter-related complication is CD which can be defined as the inability to either infuse fluids or aspirate them. Dysfunction arises from total or partial loss of catheter patency. Thrombotic and non-thrombotic events could elicit CD. Our results revealed that peripherally inserted catheters were associated with an increased risk for a catheter failure than CICC (P<0.001). After the *post hoc* analysis, we found that CD occurred more frequently in MLC than in PICC and in CICC. The difference was statistically significant (P<0.01 and P<0.001, respectively). After that, in a multiple logistic regression model, we have identified catheter diameter to be a predictor for a CD (OR=0.01; P<0.001).

Our study reveals that PICC are safe and feasible in the transplantation setting and seem not associated with an increased CRT incidence compared to CICC. Due to the low rate of infectious and mechanical complications, easy maintenance, and patient comfort, PICC and MLC should be preferred whenever feasible.[16] Increased CD rate is a concerning issue and efforts should be made to identify potential risk factors contributing to this complication, and a preventive strategy should be introduced. CD is a mild complication that does not alter the procedure outcomes or hospital stay and usually doesn't require catheter removal. Furthermore, it is possible to reverse the disfunction in some instances with additional flushing or heparin lock.

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Data-sharing statement
Data are available upon request addressed to the corresponding author.

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