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## Clinical Significance of Color Doppler Ultrasound Applied in Patients with Peripherally Inserted Central Venous Catheters before Extubation: A Retrospective Analysis of Real-World Data

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### ABSTRACT

**Aims and Objectives:** By comparing peripherally inserted central venous catheter (PICC)-related complications in real-life patients, we aimed to analyze the significance of color Doppler ultrasound (CDU) applied routinely or once with symptoms of thrombosis before extubation.

**Methods:** For this retrospective study, patient data from January to December 2020 were collected from an intelligent safe platform for infusion, which was embedded in the hospital information system (HIS). After screening by the inclusion and exclusion criteria, venous therapy liaisons were interviewed regarding the PICC procedures and complications of the enrolled patients. Then, the patient medical records were checked to verify the CDU usage and collect the CDU results. Difficulties in extubation and serious complications, including catheter fracture or pulmonary embolism during or after extubation, were also collected. This paper adheres to the RECORD checklist of EQUATOR guidelines.

**Results:** Of the 1455 patients, 489 underwent CDU examination before extubation. Among these, thrombosis was detected in 37 (7.6%) patients and only 1 (0.2%) patient without thrombosis experienced difficulties in extubation. No serious complications were observed in the CDU group. Meanwhile, among the 966 patients in the non-CDU group, three (0.3%) faced difficulties and one patient developed symptoms of pulmonary embolism. Furthermore, among patients with thrombosis in the CDU group, the duration of catheter retention was significantly shorter than that in patients without thrombosis (76.65±42.55 vs. 121.04±45.99 days,  $P < 0.001$ ).

**Conclusions:** After evaluation of their clinical symptoms, patients without symptoms could be directly removed according to conventional procedures, while patients with symptoms should undergo CDU examination before extubation.

**Relevance to Clinical Practice:** When removing the catheter for PICC carriers, it is assessed that the patients have no discomfort symptoms and can be directly extubated without B-ultrasound examination.

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### Background

Peripherally inserted central venous catheters (PICCs) have been widely utilized for long-term intravenous therapy including infusion, transfusion of blood products, chemotherapy, and total parenteral nutrition [1]. As an efficient tool for patient needs, even in children, PICCs provide the obvious advantages of simplified procedure and sound safety. Therefore, PICCs often yield reliable and satisfactory outcomes for patients and clinical physicians. To ensure maximum safety and welfare, any PICC procedure,

such as intubation, application, maintenance, and extubation, should be performed with high quality and comply with expert consensus [2-3]. Although PICCs have been well studied and administrated, increasing complications, including thrombosis; catheter-related bloodstream infection (CRBSI); and mechanical fracture, movement, and obstruction, have been reported [4]. Moreover, PICC-related complications may become ongoing.

Interventions should be carefully considered to minimize complications. For example, the use of a visualization technique can improve the achievement ratio of catheterization, electrocardiogram (ECG) guidance can improve the accuracy of catheter tip position,

and novel dressings and materials can reduce the incidence of infection and thrombosis during catheter indwelling [5]. As PICCs are widely used, more clinical physicians should be aware of the importance of extubation, which is a critical segment of the PICC procedure. The standard rules cannot avoid the risks of catheter fracture and obstruction, detachment of deep vein thrombus, and venous wall injury, but do guarantee the safety of the process [6-7]. For the minor complications of PICC, including skin reactions at the insertion site and resistance to flushing, conservative therapy is often sufficient to correct these symptoms without requiring PICC removal [8]. Minimized treatments for PICC complications typically decrease hospitalization time and costs.

Color Doppler ultrasound (CDU), the conventional technique used for the detection of thrombosis, had been applied to evaluate vascular conditions before catheter removal, which can promote the early identification of risks during extubation [9-10]. Early intervention therapy for patients with difficulties in extubation can effectively reduce the incidence of complications, resulting in a safer PICC [11]. Compared to radiography detection, the non-invasive, simple CDU avoids iodine contrast agents and ionic radiation, resulting in increased cost-effectiveness and patient compliance. Moreover, the thrombosis rate decreased from 9.8% to 1.9% based on CDU findings [1]. Likewise, flushing with low-dose heparin or warfarin to treat thrombosis has also been reported. However, some studies have reported contrary findings; thus, the latest guidelines do not suggest the use of CDU or pharmacological prophylaxis to prevent thrombosis before extubation [3]. Hence, first-line PICC physicians are confused regarding the application of CDU for certain individuals or illnesses. In addition, patients with limited medical knowledge are often trouble with CDUs, especially when others are free for executing CDUs. In another way, the prophylactic CDUs may exclude the thrombosis problem in time, which will protect patients in all ways.

### Aims and Objectives

In this study, we designed an ordered interview flow for physicians to collect data on the use of CDUs before extubation in patients with PICC and retrospectively verified the clinical data on CDU examinations and PICC-related complications. By comparing the PICC-related complications in real-life patients, we aimed to analyze the significance of CDUs applied routinely or after the development of the symptoms of thrombosis.

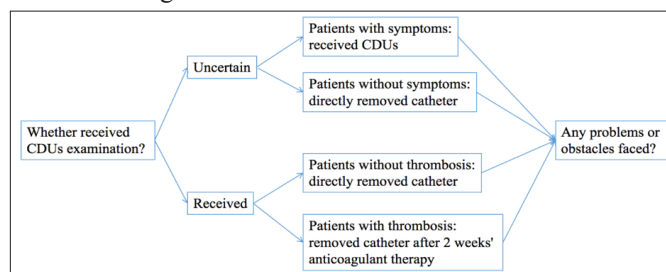
### Materials and Methods

#### Data Source and Patient Eligibility

For this retrospective study, data from patients in the inpatient department of a large general hospital from January to December 2020 were collected from the intelligent safe platform for infusion embedded into the hospital information system (HIS). Patients with PICC over 14 years of age were eligible for this study. The exclusion criteria were age below 14 years, undergoing intubation outside of the hospital, or planning extubation at the outpatient clinic. This study analyzed a total of 1455 patients, all of whom provided informed consent. Ethical approval for the collection of data was obtained from this hospital.

### Study Designs

Based on the descriptions of PICC procedures from three PICC experts, we designed an interview flow for all departments associated with PICC in this hospital. Briefly, venous therapy liaisons were interviewed regarding PICC procedures and complications. The first aspect of the interview was to determine whether the patient had received a CDU examination. If so, information on any problems with extubation in patients with or without thrombosis was further collected. If uncertain, any obstacles to extubation in patients with or without clinical symptoms were further investigated. The flowchart of the interview is shown in Figure 1.



**Figure 1:** The Flowchart of the Interview

After reviewing the inclusion and exclusion criteria, the enrolled patients with PICC identified through an intelligent safe platform for infusion were included in the analyses. In addition, the subjects were divided into the CDU and non-CDU groups based on whether they had undergone a CDU examination before extubation. We checked the patients' medical records to verify whether CDU had been performed and recorded the CDU results.

All information from interviews and HIS was recorded and analyzed. Situations with difficulties in extubation would be identified and tagged [3]. Moreover, serious complications, including catheter fracture or pulmonary embolism caused by thrombus shedding during or after extubation, were comprehensively documented.

### Statistical Analysis

The data were presented as medians  $\pm$  standard deviation and numbers (percentages) for continuous and categorical variables, respectively. A two-sided chi-square or Fisher's exact tests were used for categorical variables. T-tests were used for continuous variables, and  $p < 0.05$  was considered statistically significant. All data were analyzed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., NY, USA).

### Results

#### Patient Demographics

Of the 1455 patients, 632 (43.4%) were male and 823 (56.6%) were female. The average age of the patients was 53.3 years (range: 14–92 years). Malignancies (1353 patients, 93.0%) were the most common comorbidities; the rest (102 patients, 7.0%) were combined with other various diseases, both of whom came from 39 nursing units in this hospital. In this study population, 515 (35.4%) patients received polyurethane catheters and 940 (64.6%) received silicone catheters. Ultrasound-guided techniques were used for all catheter placement. The average duration of catheter retention was 89.5 days (range: 1–308 days) (Table 1).

**Table 1: Demographics of Patients in this Study**

Index	Total
<b>Gender (n, %)</b>	
Male	632 (43.4%)
Female	823 (56.6%)
Age (years, range)	53.3 (14~92)
<b>Comorbidities (n, %)</b>	
Malignancy	1353 (93.0%)
Others	102 (7.0%)
<b>Materials of catheters (n, %)</b>	
Polyurethane	515 (35.4%)
Silicone	940 (64.6%)
Duration of catheter retention (days, range)	89.5 (1~308)

**Differences in Extubation Procedures among Departments**

After arranging all interview data based on the flowchart, we found that the extubation procedures differed among the departments. Briefly, we identified the following three main themes of extubation procedures.

**First Theme:** All patients underwent a CDU examination before extubation. Patients with thrombosis were administered 20 mg of oral rivaroxaban once daily for 2 weeks and reexamined by CDU. The catheters were then removed. However, in some patients, thrombus resolution failed even after rivaroxaban treatment for 1 month.

**Second Theme:** All patients underwent a CDU examination before extubation. Patients with thrombosis were administered 20 mg of oral rivaroxaban once daily for 2 weeks. The catheters were then removed without reexamination by CDU.

**The Third Theme:** CDUs were only conducted when patients exhibited any clinical symptoms of thrombosis. Related problems were treated according to recommendations following consultation with relevant departments. The extubation procedures were successful without any challenges.

**Cdu Influenced the Incidences of Complications, With Limited Effects**

The CDU group included 489 patients (96 [19.6%] males and 393 [80.4%] females) with an average age of 51.30±10.83 years who underwent CDU examination before extubation. Thrombosis was detected in 37 (7.6%) patients in the CDU group among those who did not experience serious complications (catheter fracture or pulmonary embolism) or difficulty in extubation. Meanwhile, only one (0.2%) patient without thrombosis in the CDU group experienced difficulties in extubation, with a fibrin sheath around the catheter wall after routine regimes of hot compression, adjusting posture, and relaxing muscle.

The remaining 966 patients (536 [55.5%] males and 430 [44.5%] females) who did not undergo CDU examination before extubation (non-CDU group). The average age was 54.36±12.65 years and both sex and age differed significantly from those in the CDU group (both p<0.001). No thrombosis occurred in this group and the three patients (0.3%) who experienced difficulties in extubation and were successfully treated by routine regimens. One case (0.1%) in the non-CDU group experienced complications of pulmonary embolism and finally returned to normal (Table 2). This patient had sudden serious chest pain during doings after extubation, and the pain relieved spontaneously after sweating profusely. CTPA examination showed pulmonary embolism at the beginning of the left lower pulmonary extra-posterior basal segment, D-dimer was significantly increased. Monitor the patient’s vital signs, maintain absolute bed rest, low molecular weight heparin anticoagulation, and relieve pain if necessary.

**Table 2: Comorbidities in the CDU and Non-CDU Groups**

Groups	Number of cases	Thrombosis	Difficult in extubation	Pulmonary embolism	Catheters fracture
a	444	19 (1.31%)	1 (0.07%)	0 (0.0%)	0 (0.0%)
b	45	18 (1.24%)	0 (0.0%)	1 (0.07%)	0 (0.0%)
c	966	0 (0.0%)	3 (0.21%)	0 (0.0%)	0 (0.0%)
Total cases	1455	37 (2.54%)	4 (0.3%)	1 (0.07%)	0 (0.0%)
$\chi^2$		290.934	0.134	51.444	0
*P value		<0.0001	0.935	<0.0001	

a: PICC removal without any previous US study, b: PICC removal with US study only if justified by clinical signs and symptoms, c: PICC removal always performed after US study. \*: p value calculated by two-sided chi-squared test between two groups was <0.001.

**Thrombosis Shortened the Duration of Catheter Retention in the CDU Group**

As mentioned above, CDU examination detected thrombosis in 37 (7.6%) of 489 patients; the other 452 (92.4%) patients were thrombus negative. Comparison of patients with and without thrombosis in the CDU group showed a significantly shorter duration of catheter retention in patients with thrombosis than that in patients without thrombosis (76.65±42.55 vs. 121.04±45.99 days, P<0.001).

With respect to sex, the percentages of males (51.4%) and females (48.6%) were similar in patients with thrombosis; however, the percentage of patients without thrombosis was significantly lower in male patients (17.0%) than that in female patients (83.0%) (P<0.001). Regarding catheter material, neither silicone nor polyurethane showed significant influences in the thrombosis (43.2% and 56.8%, respectively) or non-thrombosis (58.4% and 41.6%, respectively) groups. However, the increasing proportion of double-cavity

catheters (13.5%) was slightly linked with thrombosis status (5.5%) ( $P=0.051$ ). The PICC punctured the brachial, cephalic, basilic, femoral, and internal jugular veins in 8.1%, 2.7%, 75.7%, 10.8%, and 2.7% of patients with thrombosis, respectively, and 5.5%, 1.1%, 75%, 2.0%, and 1.3%, respectively, of patients without thrombosis. Analysis of the two subgroups suggested the significant impact of venous puncture site on thrombosis ( $P=0.024$ ). As malignancy is often accompanied by hematology disorders, the comorbidities of patients in the CDU group were categorized as malignancy and other diseases. The ratio of malignancy in both subgroups was far greater than that in other diseases ( $>90\%$ ) but it was not the main factor during thrombosis (Table 3).

**Table 3: Analysis of Factors of Patients, Catheter or PICC Procedure During Thrombosis in CDU Group**

Subgroups	Number of cases	Duration of catheter indwelling	Gender		Material of catheter		Cavity of catheter		Vein punctured					Comorbidities	
			Male	Female	Silica gel	Polyurethane	Single	Double	Brachial vein	Cephalic vein	Basilic vein	Femoral vein	Internal jugular vein	Malignancy	Others
With thrombosis	37 (7.6%)	76.65 ±42.55	19 (51.4%)	18 (48.6%)	16 (43.2%)	21 (56.8%)	32 (86.5%)	5 (13.5%)	3 (8.1%)	1 (2.7%)	28 (75.7%)	4 (10.8%)	1 (2.7%)	35 (94.6%)	2 (5.4%)
Without thrombosis	452 (92.4%)	121.04 ±45.99	77 (17.0%)	375 (83.0%)	264 (58.4%)	188 (41.6%)	427 (94.5%)	25 (5.5%)	16 (3.6%)	5 (1.1%)	339 (75%)	9 (2.0%)	6 (1.3%)	443 (98.0%)	9 (2.0%)
$\chi^2$		278	31.838		3.213		3.784				1.781			0.593	
P value		<0.001	<0.001		0.073		0.051				0.024			0.441	

PICC: peripherally inserted central venous catheter; CDU: color Doppler ultrasound. All p values were calculated by two-sided chi-squared test or Fisher’s exact test.

**Anticoagulant Treatments were not Necessary for Thrombosis before Extubation**

Thrombus-positive patients in the CDU group were administered relevant anticoagulant treatments. Of these 37 patients, 24 received oral rivaroxaban or subcutaneous low-molecular-weight heparin. Then, extubation mostly followed CDU reexaminations or was performed without reexamination. CDU reexamination 1 or 2 weeks later showed benign thrombus size, shape, number, and sites, but no complete resolution. The remaining 13 patients with thrombosis had their catheters removed without any therapy and without complications.

**Discussion**

Since the 1980s, PICC has been widely utilized as convenient intravenous access for patients requiring long-term infusion therapy [1]. Although PICC may result in complications, the risks can be controlled to acceptable levels by following the standard procedures. However, extra diagnosis or therapy should be considered at the individual level as complications differ between patients [12]. CDU is important in PICC extubation to avoid catheter-related thrombosis [9-10]. In our study, the interview data showed that while the standards of CDU application before extubation varied among departments, CDUs influenced the PICC complications, with limited effects. Moreover, sex and venous puncture site were the two main factors that predicted PICC-related thrombosis. When thrombosis occurred after CDU examination, the catheter retention was disturbed; however, anticoagulant treatments before extubation did not effectively prevent PICC-related thrombosis.

There remains no consensus in the literature regarding the significance of CDU or B ultrasound (BU) examination before extubation. Some studies have reported the BU examination of the upper arm with catheter placement could earlier identify venous thrombosis and allow timely therapy, which might be safer than extubation without confirmation of thrombosis [11]. However, other studies have demonstrated that PICC insertion does not increase risks of pulmonary embolism; therefore, BU before extubation was not necessary. In addition, considering the actual volume of PICC-related thrombus, the average diameter detected by BU was not sufficient to induce symptomatic pulmonary

embolism. Therefore, CDU or BU before PICC extubation was not recommended as a standard procedure in patients without symptoms or signs of deep venous thrombosis.

The incidence of thrombosis in the CDU group in this study was 7.6%, which was lower than the incidence of 51.4% reported in a previous prospective study in tumor patients. Because of the gaps between these various data, the role of CDU in excluding thrombosis was not decisive and might have been affected by objective factors such as lifestyle, comorbidities, and concomitant medication [13-14]. The difficulties in extubation also include vasospasm, which advance CDU cannot predict. Similarly, one case in the present study that experienced difficulties in extubation developed vasospasm even after a CDU examination [15].

When PICC-related thrombosis results in clinical symptoms, both patients and physicians concerned about the deterioration of primary diseases may request extubation. This phenomenon violates the criteria for PICC retention when the catheter was able to draw back blood, the infusion rate was normal, and the tip was located in the lower third of the superior vena cava. Anticoagulant therapy can then be conducted using the preserved catheters [16]. However, for patients not meeting these criteria, extubation should first be considered. As catheters are the largest risk factor for thrombosis, anticoagulant therapy cannot completely resolve thrombus, or the thrombus could resolve naturally safer extubation without secondary complications [17]. An interesting finding in the present study was the significantly higher frequency of thrombosis in men than that in women with PICC. This sex-based difference in PICC requires more research and stronger evidence. Another correlation analysis of the venous puncture site verified the optimum choice of basilic vein for PICC [18]. Only when the basilic vein was unavailable should another candidate vein be punctured.

An important limitation of this study was that it dealt with real-life data. Although we checked all the available medical records, subjective complications reported by the patients themselves may have been missed. The sample size differed between the two groups, which may have affected the statistical calculations. However, this retrospective observation of real-life patients

comprehensively considered variability in patients and treatments was closer to clinical practice compared to controlled clinical trials. In conclusion, the results of this study suggested that clinical symptoms should be evaluated first. Catheters may be removed directly according to conventional procedures in patients without symptoms, while patients with symptoms should undergo CDU examination before extubation.

### What is Known?

This study compared the significance of color Doppler ultrasound in different extubation processes. It was found that paying attention to the feelings of the patients before extubation and using color Doppler ultrasound reasonably according to the actual situation can not only ensure the safety of patients, but also simplify the process of extubation.

### What is New?

The extubation process of PICC was further clarified. It provides evidence for clinical frontline personnel to choose the extubation process of PICC. Unnecessary color Doppler ultrasound examination was eliminated, and the burden of medical staff was reduced.

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