BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-045895
Article Type:	Original research
Date Submitted by the Author:	18-Oct-2020
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Keywords:	RADIOLOGY & IMAGING, Interventional radiology < RADIOLOGY & IMAGING, Adult oncology < ONCOLOGY

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Title page

The catheter to vein ratio and risk of peripherally inserted central catheter (PICC) associated thrombosis according to diagnostic group: a retrospective cohort study

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Word count

3110 words

Keywords

Peripherally inserted central catheter (PICC), thrombosis, central venous access device

Abstract:

Objectives: determine the effect of the catheter to vein ratio (CVR) on rates of symptomatic thrombosis in patients with a peripherally inserted central catheter (PICC) and identify the optimal CVR cut-off point according to diagnostic group
Design: retrospective cohort study
Setting: 5 tertiary hospitals in Australia and New Zealand
Participants: adult patients who had undergone PICC insertion
Primary outcome measure: symptomatic thrombus of the limb in which the PICC was inserted
Results: 2,438 PICC insertions were included with 39 cases of thrombosis (1.6%; 95% CI 1.14% - 2.19%). Receiver operator characteristic (ROC) analysis was unable to be performed to determine the optimal CVR overall or according to diagnosis. The association between risk of thrombosis and CVR cut-offs commonly used in clinical practice were analysed. Overall, a 33% CVR cut-off was not associated with risk of thrombus, whereas, a 45% cut-off (≤45% versus ≥46%) was predictive, with those with a higher ratio having more than twice

the risk of thrombus (RR 2.30; 95% CI 1.202-4.383; p=0.01). This pattern continued when only those with malignancy were included in the analysis. The analysis of thrombosis risk for each CVR in those with an infection or other non-malignant diagnosis was limited by a low number of cases.

Conclusions: This study has demonstrated that in participants with cancer, the CVR should not exceed 45%, with the risk of thrombosis doubling when the CVR is ≥46%. Further research is needed to determine the optimal CVR for those with a non-malignant diagnosis.

ARTICLE SUMMARY

Strengths and limitations of this study

- Large, multi-site study with 2,438 peripherally inserted central catheters (PICCs)
- First study to analyse risk of thrombosis associated with the 33% and 45% catheter to vein ratio (CVR) cut-off rules commonly used in clinical practice for PICC insertion
- Analysed risk of thrombosis associated with CVRs according to diagnostic group
- Unable to perform planned analysis (receiver operator characteristic analysis) to determine the optimal catheter to vein ratio to prevent thrombosis in patients with a PICC
- The use of a tapered PICC impacted on the accuracy of the PICC diameter and hence CVR for those participants that had the tapered portion inserted.

INTRODUCTION

Peripherally inserted central catheter (PICC) associated thrombosis is painful, may result in loss of intravenous access for treatment and damage to the vasculature limiting further PICC insertions. In some cases, PICC associated thrombosis precipitates pulmonary embolism. [1] Approximately 2% of patients receiving antimicrobials as part of outpatient parenteral therapy (OPAT) develop thrombosis. [2, 3] Whilst those receiving cancer treatment suffer much higher rates, with 4-6% of patients with a Haematological malignancy and 2-5% of those with a solid tumour developing PICC associated thrombosis. [2, 4-6]

This adverse event can be explained using mechanisms related to Virchow's triad (stasis, endothelial damage and hypercoagulable state of the patient). PICCs may have a large impact on the interruption of blood flow (stasis). In a mechanical model, Nifong and McDevitt (2011) demonstrated that blood flow was dependant on the size of the catheter and cylinder (or vein) size and PICCs commonly used in clinical practice may impede blood flow up to 80%. [7]

PICC insertion decisions such as the use of an appropriate catheter to vein ratio (CVR) affect PICC associated thrombosis rates. [2] Contemporary insertion approaches include measurement of the target vein diameter using ultrasound and use of a minimum CVR to reduce the risk of thrombosis. [8] Different CVR cut-offs are used in clinical practice, many sites use a 33% CVR limit, that is only one third of the vein should be occupied by the catheter. [6, 9-12] Other sites use a 45% CVR limit as advocated by the Infusion Therapy Standards of Practice (Infusion Nurses Society 2016). [13] However, there is a lack of research investigating safe CVRs to use for PICC insertion. Previous research in an adult population that aimed to identify the optimal CVR using receiver operator characteristic (ROC) analysis found that a 45% CVR was the optimal cut-off to reduce the risk of thrombus. [14] Patients with a CVR of more than 45% were 13 times more likely to suffer from thrombosis. Yet these findings were based on just four cases and all participants with this adverse event had a haematological malignancy.

Most of the research investigating thrombosis rates associated with CVR cut-offs focus on cancer patients. [4, 6, 10, 12] This is problematic as many patients with an infection (without an underlying malignancy diagnosis) receive a PICC for antimicrobial treatment and it is

unknown whether the CVR cut-off may differ according to diagnosis. There is a need to investigate the association between the CVR and PICC-associated thrombosis in a larger sample and to determine a safe CVR cut-off in patients with both malignant and non-malignant health conditions. This study aimed to determine the effect of the CVR on rates of symptomatic thrombosis in patients with a PICC, identify the optimal CVR cut-off point and determine if the CVR cut-off is the same for patients with malignant and non-malignant disease.

METHOD

This was a retrospective cohort study set at hospitals in Australia (Calvary Mater Hospital, Newcastle, St Vincent's Hospital, Sydney and St George Hospital, Sydney) and New Zealand (Capital & Coast District Health Board, Wellington). Clinicians from PICC services at each site used an existing PICC database and hospital information systems to populate a standardised spreadsheet. Data regarding PICC insertion from 2015-2018 was included.

Inclusion criteria: adult patients who had undergone PICC insertion that terminated in the superior vena cava/right atrium junction.

Exclusion criteria: cases where diagnosis, PICC size (Fr), external length and vein diameter measurement were missing.

Participants were allowed in the study more than once. PICCs were inserted as per usual clinical practice at each site. The anteroposterior diameter of the relevant vein (basilic, brachial or cephalic) was measured using ultrasound at the insertion point. No tourniquet was used during the measurement process to reflect the natural vein diameter. Veins were measured using a linear transducer angled at 90 degrees to the vein and from hypoechoic inner wall to inner wall of the vein excluding the echogenic rim of the vein. The measurement was conducted using inbuilt callipers in a Site~Rite® 8 Ultrasound System (C. R. Bard, Salt Lake City, UT) at Australian sites and a Sonosite micromax and SII at the New Zealand site (SonoSite, Bothell, WA).

A polyurethane, reverse taper PICC design was used by sites in this study. This catheter increases in diameter toward the hub (tapers 2Fr over 7cm). So that a 4Fr PICC is 4Fr

(1.33mm) at 7cm and 6Fr (2mm) at zero (near the hub). This is an increase in 0.67mm over 7cm toward the hub or 0.10mm per cm.

For those participants with an external length ≤6cm, the external length (measured from insertion site to zero at sites) was used to determine the additional taper diameter for those PICCs. This measurement was added to the diameter of the PICC (Fr) as stated in the manufacturer information (outer diameter). For participants with an external length ≥7cm (tapered part of the PICC not inserted), manufacturer information was used to determine the PICC diameter.

The participant medical record number was used to access hospital information systems for sonography reports performed on the same upper extremity as the site of PICC insertion. De-identified reports were copied by clinicians at each site and these reports were reviewed by two members of the project team at the University of South Australia (one an accredited medical Sonographer) to determine cases of thrombus.

Patient and Public Involvement

Patients and the public were not involved in any way in this study.

Outcome measure

The primary outcome measure was symptomatic thrombus of the limb in which the PICC was inserted, which included thrombus that occurred in the superficial (SVT) or deep venous system (DVT) post PICC insertion. SVT was defined as occlusive thrombus in a superficial vein in which the PICC was inserted (basilic or cephalic veins). DVT included occlusive thrombus in the vein the PICC was inserted (if brachial) or if it extended into adjacent deep vasculature (axillary or subclavian veins). All cases were confirmed using ultrasound after clinical signs and symptoms triggered diagnostic testing whilst the PICC was still in situ or within 8 weeks of removal.

Ethical considerations

Ethics approval was obtained from the South Eastern Sydney Local Health District, Australia (HREC/17/POWH/174), Northern A Health and Disability Ethics Committee, New Zealand (17/NTA/264) and the University of South Australia (20026) Human Research Ethics Committees.

Power analysis:

A power analysis using PASS 11 (NCSS, UT, USA) determined that to achieve 80% power and 0.05 significance level, 2,140 participants were required. A test of two independent proportions was based on an expected increased risk of thrombus (RR=2.0) where 80% have a catheter to vein ratio ≤45% and are considered low risk with a 3% thrombus rate and 20% a ratio of ≥46% will be high risk with a 6% thrombus rate. That is 1,712 in the low risk group and 428 in the high risk group. These thrombus rates are based on previous research. [14] It was possible for a patient to be in the study more than once (PICC reinsertion/exchange) However, we expected this to be a small proportion of patients and the impact of clustering to be minimal.

Statistical Analysis Plan

Descriptive statistics were used to present information about the study population. CVRs were determined by dividing PICC diameter (stated diameter or tapered diameter) by vein diameter and multiplying by 100 to generate a percentage. The association between the CVR and the risk of thrombus was analysed using a log binomial generalised linear model. This analysis was performed with all participants and according to diagnostic group. Receiver operator characteristic (ROC) analysis was used to plot the sensitivity and specificity of each ratio measurement using MedCalc for Windows, version 12.5 (MedCalc Software, Ostend, Belgium). The area under the curve (AUC) was used to identify the ideal CVR cut-off point with the aim to maximize sensitivity and specificity. All results with p≤0.05 were considered statistically significant.

RESULTS

There were 2,475 cases available, 37 were excluded due to missing data (11 with missing vein diameter and 26 missing diagnosis), leaving 2,438 PICC insertions in the analysis. Nearly equal numbers of participants were male and female (Table 1), with a mean age of 59 years old (SD 17.09). Most participants did not have a history of central venous access device (CVAD) insertion and had a cancer diagnosis. Participants with a cancer diagnosis had three times the risk of thrombosis than those with an infection as an underlying diagnosis.

Table 1: Participant factors and risk of thrombosis in patients with a PICC

Characteristic	Venous thrombosis			Univariate analysis
	No (n=2399)	Yes (n= 39)	Total (n= 2438)	

		n (%)	n (%)	n (%)	RR	95% CI	Sig¥
Gender	Female	1104 (98.13)	21 (1.87)	1125 (100)	1.00		
	Male	1294 (98.63)	18 (1.37)	1312 (100)	0.73	0.394-1.372	0.334
	Total	2398 (98.40)	39 (1.60)	2437 (100)			
Age (years)	19-45	457 (97.86)	10 (2.14)	467 (100)	1.00		
	46-65	946 (98.54)	14 (1.46)	960 (100)	0.68	0.304-1.521	0.349
	66-79	773 (98.35)	13 (1.65)	786 (100)	0.77	0.341-1.747	0.535
	80+	189 (98.95)	2 (1.05)	191 (100)	0.49	0.108- 2.210	0.353
	Total	2365 (98.38)	39 (1.62)	2404 (100)			
Previous CVAD	Y	718 (97.82)	16 (2.18)	734 (100)	1.61	0.858 -3.038	0.137
	N	1681 (98.65)	23 (1.35)	1704 (100)	1.00		
	Total	2399 (98.40)	39 (1.60)	2438 (100)			
Number of previous CVAD	0	1688 (98.48)	26 (1.52)	1714 (100)	1.00		
	1	534 (98.16)	10 (1.84)	544 (100)	1.21	0.588-2.496	0.602
	≥2	168 (98.25)	3 (1.75)	171 (100)	1.16	0.528-5.597	0.810
	Total	2390 (98.39)	39 (1.61)	2429 (100)			
Primary diagnosis^	Infection	859 (99.19)	7 (0.81)	866 (100)	1.00		
	Cancer	1285 (97.57)	32 (2.43)	1317 (100)	3.01	1.332- 6.779	0.008
	Other	255 (100)	0 (0)	255 (100)	-	-	-
	Total	2399 (98.40)	39 (1.60)	2438 (100)			

PICC= peripherally inserted central catheter; CVAD= central venous access device; ¥Based on log binomial generalized linear model; CI=confidence interval; RR=relative risk; ^As per treatment request

Most PICCs were inserted in the basilic vein in the right arm and required one needling attempt (Table 2). Nearly equal numbers of single lumen (4Fr) and double lumen (5 Fr) PICCs were used. Most PICCs were verified using electrocardiogram (ECG), using a combination of securement devices and were inserted by staff with 3-5 years of experience. The infusion of chemotherapy was associated with nearly four times the risk of thrombosis.

Table 2: PICC insertion factors and risk of thrombosis

Characteristic		Venous thrombosis			Univariate analysis		
		No (n=2399)	Yes (n= 39)	Total (n= 2438)			
		n (%)	n (%)	n (%)	RR	95% CI	Sig¥
Arm	Left	491 (97.61)	12 (2.39)	503 (100)	1.71	0.871-3.347	0.119
	Right	1906 (98.60)	27 (1.40)	1933 (100)	1.00		
	Total	2397 (98.40)	39 (1.60)	2436 (100)			
Vein	Basilic	1861 (98.52)	28 (1.48)	1889 (100)	1.00		
	Brachial	403 (97.58)	10 (2.42)	413 (100)	1.63	0.800-3.336	0.178
	Cephalic	130 (99.24)	1 (0.76)	131 (100)	0.51	0.071-3.755	0.513
	Total	2394 (98.40)	39 (1.60)	2433 (100)			
Needling attempts	1	2029 (98.50)	31 (1.50)	2060 (100)	1.00		
	2	203 (98.54)	3 (1.46)	206 (100)	0.97	0.298-3.138	0.956
	3+	65 (100)	0 (0)	65 (100)			
	Total	2297 (98.54)	34 (1.46)	2331 (100)			
Catheter size (Fr) and lumen	4 (Single lumen)	1251 (98.82)	15 (1.18)	1266 (100)	1.00		
	5 (Double lumen)	1136 (97.93)	24 (2.07)	1160 (100)	1.75	0 .920-3.312	0.088
	6 (Triple lumen)	12 (100)	0 (0)	12 (100)	-	-	-
	Total	2399 (98.40)	39 (1.60)	2438 (100)			
Tip confirmation method	CXR	101 (98.06)	2 (1.94)	103 (100)	1.00		
	ECG	1480 (98.40)	24 (1.60)	1504 (100)	0.82	0.197-3.429	0.788

	Both	817 (98.43)	13 (1.57)	830 (100)	0.98	0.185-3.524	0.775
	Total	2398 (98.40)	39 (1.60)	2437 (100)			
Securement device	Adhesive	895 (98.35)	15 (1.65)	910 (100)	1.00		
	Subcutaneous	521 (97.75)	12 (2.25)	533 (100)	1.37	0.644-2.895	0.416
	Combination	977 (98.79)	12 (1.21)	989 (100)	0.73	0.346-1.564	0.426
	Other∩	5 (100)	0 (0)	5 (100)	-	-	-
	Total	2398 (98.40)	39 (1.60)	2437 (100)			
Staff years of experience	0	40 (100)	0 (0)	40 (100)	1.00		
	1-2	898 (98.25)	16 (1.75)	914 (100)	1.58	0.530-4.680	0.413
	3-5	1103 (98.31)	19 (1.69)	1122 (100)	1.52	0.522-4.450	0.441
	6+	356 (98.89)	4 (1.11)	360 (100)	-	-	-
	Total	2397 (98.40)	39(1.60)	2436 (100)			
Infusion^							
	Antibiotics/Antivirals	976 (99.29)	7 (0.71)	983 (100)	1.00		
	Chemotherapy	1011 (97.31)	28 (2.69)	1039 (100)	3.78	1.660-8.623	0.002
	Blood products	29 (100)	0 (0)	29 (100)	-	-	-
	TPN	216 (99.08)	2 (0.92)	218 (100)	1.28	0.269- 6.159	0.751
	Other#	167 (98.82)	2 (1.18)	169 (100)	1.66	0.348- 7.932	0.524
	Total	2399 (98.40)	39 (1.60)	2438 (100)			

PICC= peripherally inserted central catheter; ¥Based on log binomial generalized linear model; CI=confidence interval; RR=relative risk; CXR=chest x-ray; ECG=electrocardiogram ∩ suture or glue; TPN=total parenteral nutrition #intravenous therapy, electrolytes, difficult access, frequent blood draws; ^As per treatment request, participants often had more than one listed, coded as chemotherapy if this was included in list

Cases of thrombosis

There were 39 cases of confirmed thrombosis, a rate of 1.6% (95% CI 1.14% - 2.19%). These comprised 13 cases of SVT (33%), 5 cases of DVT (13%) and 21 cases involving both the superficial and deep venous system (54%).

Catheter to vein ratio

Based on ROC analysis, the CVR was not an effective diagnostic variable when treated as a continuous variable. The area under the curve was close to 0.5 when the ROC analysis was performed using the entire sample and according to diagnostic group. As the models lacked diagnostic ability, we analysed the association between risk of thrombosis and CVR cut-offs commonly used in clinical practice.

All participants

As per Table 3, a CVR cut-off of 33% did not appear to be associated with risk of thrombus, whereas, a 45% cut-off (≤45% versus ≥46%) was predictive, with those with a higher ratio having more than twice the risk of thrombus (RR 2.30; 95% CI 1.202-4.383; p=0.012).

Table 3: Catheter to vein ratio and risk of thrombosis in patients with a PICC

			All PICCs						Taper not inserted					
			Venous thrombosis			Univariate analysis			Venous thrombosis			Univariate analysis		
	Catheter to vein ratio		No (n=2399) n (%)	Yes (n= 39) n (%)	Total (n= 2438) n (%)	RR	95% CI	Sig¥	No (n=1085) n (%)	Yes (n=13) n (%)	Total (n=1098) n (%)	RR	95% CI	Sig¥
All participants	≤33%		914 (98.39)	15 (1.61)	929 (100)	1.00			563 (98.43)	9 (1.57)	572 (100)	1.00		
	≥34%		1485 (98.41)	24 (1.59)	1509 (100)	0.99	0.519-1.867	0.963	522 (99.24)	4 (0.76)	526 (100)	0.48	0.150-1.560	0.224
		Total	2399 (98.40)	39 (1.60)	2438 (100)				1085 (98.82)	13 (1.18)	1098 (100)			
	≤45%		1935 (98.72)	25 (1.28)	1960 (100)	1.00			1021 (98.93)	11 (1.07)	1032 (100)	1.00		
	≥46%		464 (97.07)	14 (2.93)	478 (100)	2.30	1.202-4.383	0.012	64 (96.97)	2 (3.03)	66 (100)	2.84	0.643-12.563	0.168
		Total	2399 (98.40)	39 (1.60)	2438 (100)				1085 (98.82)	13 (1.18)	1098 (100)			
			No (n=1285) n (%)	**Yes (n= 32)** n (%)	**Total (n=1317)** n (%)				**No (n=479)** n (%)	**Yes (n=8)** n (%)	**Total (n=487)** n (%)			
Cancer diagnosis	≤33%		361 (97.57)	9 (2.43)	370 (100)	1.00			210 (97.67)	5 (2.33)	215 (100)	1.00		
	≥34%		924 (97.57)	23 (2.43)	947 (100)	0.99	0.466-2.138	0.997	269 (98.90)	3 (1.10)	272 (100)	0.47	0.115-1.962	0.303
		Total	1285 (97.57)	32 (2.43)	1317 (100)				479 (98.36)	8 (1.64)	487 (100)			
	≤45%		943 (98.13)	18 (1.87)	961 (100)	1.00			445 (98.67)	6 (1.33)	451 (100)	1.00		
	≥46%		342 (96.07)	14 (3.93)	356 (100)	2.10	1.055-4.177	0.035	34 (94.44)	2 (5.56)	36 (100)	4.18	0.874- 19.950	0.073
		Total	1285 (97.57)	32 (2.43)	1317 (100)				479 (98.36)	8 (1.64)	487 (100)			
			No (n=1114) n (%)	**Yes (n= 7)** n (%)	**Total (n=1121)** n (%)				**No (n=606)** n (%)	**Yes (n=5)** n (%)	**Total (n=611)** n (%)			
Infection and other diagnoses^	≤33%		553 (98.93)	6 (1.07)	559 (100)	1.00			353 (98.88)	4 (1.12)	357 (100)	1.00		
	≥34%		561 (99.82)	1 (0.18)	562(100)	0.17	0.020-1.372	0.096	253 (99.61)	1 (0.39)	254 (100)	0.35	0.040-3.125	0.348
		Total	1114 (99.38)	7 (0.62)	1121 (100)				606 (99.18)	5 (0.82)	611 (100)			
	≤45%		992 (99.3)	7 (0.7)	999 (100)	1.00			576 (99.14)	5 (0.86)	581 (100)	1.00		
	≥46%		122 (100)	0 (0)	122 (100)	-	-	-	30 (100)	0 (0)	30 (100)	-	-	-
		Total	1114 (99.38)	7 (0.62)	1121 (100)				606 (99.18)	5 (0.82)	611 (100)			

PICC= peripherally inserted central catheter; ¥Based on log binomial generalized linear model; CI=confidence interval; RR=relative risk; ^ infection requiring intravenous antibiotics or other non-cancer diagnosis with difficult venous access requiring patient controlled analgesia, intravenous fluid etc.

The analysis was repeated with participants who didn't have the tapered portion of the PICC inserted (PICCs with an external length ≤6cm were excluded). This comprised 1,098 cases or 45% of the sample. Use of a CVR greater than 45% was associated with more than twice the risk of thrombosis. When a 33% CVR cut-off was analysed, the use of a CVR higher than 34% appeared protective of thrombosis. However, neither of these results were statistically significant.

Effect of diagnosis on risk of thrombosis

Cancer

When only participants with cancer were included in the analysis, a 45% CVR cut-off remained associated with twice the risk of thrombus (RR 2.10; 95% CI 1.055-4.177; p=0.035), whilst the use of a 33% CVR cut-off was not associated with risk of thrombosis (Table 3). When this analysis was repeated in participants without the tapered portion of the PICC inserted, the use of a CVR greater than 45% was associated with four times the risk of thrombosis. Whilst the use of a CVR higher than 34% appeared protective, with reduced risk of thrombosis when compared to a CVR 33% or less, although, these latter results were not statistically significant.

Non-cancer patients

In participants with an infection or other non-cancer diagnosis, the association between a 45% cut-off and risk of thrombosis could not be analysed as none of the participants with a ratio of 46% and above developed thrombus (Table 3). Although results were not statistically significant and based on only one case, a 33% CVR cut-off appeared to be protective in this cohort, with those with a CVR higher than 34% having less risk of thrombosis. This trend continued when only non-tapered PICCs were included in the analysis.

DISCUSSION

We aimed to identify an optimal CVR cut-off for PICC insertion to prevent the risk of thrombosis. However, ROC analysis demonstrated that the CVR as a continuous measure was not an effective

diagnostic variable overall, probably due to the low number of cases with higher CVRs. Hence, we analysed the risk of thrombosis associated with CVR cut-offs used in clinical practice.

All patients: CVRs – 33% vs 45%

This study is the first to examine the difference in risk of thrombus between these two cut-off points. A CVR greater than 45% was associated with twice the risk of PICC associated thrombosis. However, a CVR greater than 33% was not associated with increased risk. The latter finding is potentially due to the low rates of thrombosis in this study population, and future research would need to include many thousands of participants to make a definitive conclusion about the 33% CVR cut-off.

CVRs and risk of thrombosis according to diagnosis

Infection

We found a thrombosis rate of 0.7% in patients with an infection or other non-cancer indication for the PICC. The analysis of thrombosis risk for each CVR in this cohort was limited by a low number of cases of thrombosis. It is difficult to compare our results to previous research as most includes a mixed cohort which includes cancer patients (who have increased risk of thrombosis) and don't report results separately. Where research does examine only those receiving a PICC for the treatment of infection, with no underlying malignancy, insertion decisions such as the use of a minimum CVR are not documented. Whilst the optimal CVR is not available for these patients, we still recommend that a minimum CVR is used until a more accurate estimate of risk is established.

Cancer

For those participants with malignancy, a CVR 45% cut-off was associated with more than twice the risk of thrombosis. Although not statistically significant, this pattern continued when this was reanalysed with participants who did not have the reverse taper portion of the PICC inserted. In contrast, a 33% CVR cut-off was not associated with risk of thrombosis. When tapered PICCs were removed from the analysis, the use of a CVR >33% appeared to be protective, this appears counterintuitive, however it must be noted that these results were not statistically significant and were based on a small number of events.

These results suggest that the use of a CVR ≤45% is integral in reducing the risk of PICC associated thrombosis in cancer patients. Thrombosis is a significant adverse event in patients with cancer and is associated with increased morbidity and mortality. [15, 16] Factors such as the selection of an appropriate sized vein are especially important in the cancer patient cohort as larger, multi-

lumen PICCs may be required which exacerbates thrombosis risk. These results support the use of a 45% CVR cut-off as advocated in the Infusion Nurses Society clinical guidelines (2016) and previous research that used ROC analysis to determine the optimal CVR cut-off. [14]

IMPLICATIONS FOR CLINICAL PRACTICE

This study has demonstrated that a CVR should not exceed 45% for those with a cancer diagnosis. Whilst the optimal CVR for those with infection and other non-malignant conditions is inconclusive, the low thrombosis rate found in the present study supports the use of minimum vein size strategy.

The minimum vein diameters needed to achieve ≤45% CVR are detailed in table 4. If a vein of this size cannot be identified, then a smaller catheter should be used. If this is not possible, then an alternative vascular access device may be considered for this cohort. Research in cancer patients that has compared thrombosis risk according to different CVADs has found that PICCs were associated with more than 7 times the risk of thrombosis (HR 7.48, 95% CI 1.03-54.1, p=0.046) when compared to other non-tunnelled vascular access devices (central venous catheters), whilst implanted ports were associated with half the risk (HR 0.47 95% CI 0.03-7.90 p=0.597). [17] Although insertion decisions such as the use of a minimum CVR are not documented in this research, perhaps high CVRs account for increased risk of thrombosis for those with a PICC.

Table 4:Minimum vein sizes to achieve ≤45% CVR

PICC size (fr)	Minimum vein size
4Fr	2.96 mm
5Fr	3.70 mm
6Fr	4.44mm

CVR=catheter to vein ratio

CVR with a tapered PICC

Our results indicate that clinicians who use a reverse taper PICC should be aware of the increased diameter of the taper and depending on vein size, increased risk of thrombosis should the taper be advanced into the vein. It is important to recognise the significant impact that the taper has on PICC diameter. For example, a 6Fr longer tapered PICC would be 8Fr at

the hub or 2.67mm so to meet the 45% CVR cut-off, a vein would need to be 5.8mm in diameter rather than 4.5mm if it was inserted to the hub.

Alternatively, clinicians may avoid the use of the tapered part of the PICC by avoiding insertion of the taper. This will leave an external length of ≥7cm. Whilst increased external length may be thought to increase dislodgement rates, anecdotally, this has not been the case with clinicians in this study. Some sites have introduced a sub-cutaneous device to fix the PICC in place which provides additional security for those with longer external lengths.

LIMITATIONS

A limitation with this study was the inclusion of PICCs with reverse taper design and resulting imprecise diameter to inform the CVR. Whilst we developed an equation to determine the adjusted PICC diameter based on the external length this did not allow for the impact of subcutaneous tissue on this measurement. However, we expected this to have minimal impact on the overall CVR. Furthermore, we also presented analysis which excluded PICCs were the tapered portion of the PICC was inserted. There is a possibility that some participants presented to a regional hospital rather than the major hospitals in this study with symptoms of thrombus, hence, we would miss cases of thrombus. However, we expected this to be unlikely as most would be managed by their treating team at the specialist centres in the hospitals where the study was conducted. A further limitation, as with all retrospective studies is the reliance on existing data which in this study was evident in problems with missing data and although participants were allowed into the dataset more than once, missing data meant that clustering could not be allowed for. However, we expected this to be a small proportion of patients and the impact of clustering to be minimal.

CONCLUSION

The use of an appropriate vein size for PICC insertion is an important strategy to reduce PICC associated thrombosis in clinical practice. A CVR cut-off of 33% was not useful in predicting PICC-associated thrombosis in cancer patients or those with other diagnoses. This study has demonstrated that in participants with cancer, the CVR should not exceed 45%, with the risk of thrombosis doubling when the CVR is ≥46%. This cut-off was not associated with risk of thrombosis for those with an infection and other non-cancer diagnosis. Whilst further research is needed to determine the optimal CVR for those with infection, minimum CVRs are still recommended to reduce the risk of thrombosis.

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Author statement

RS: contributions to conception and design, literature search, data analysis and interpretation, writing, final approval of the version to be published
PC, GJ: contributions to conception and design, data interpretation, writing, final approval of the version to be published.
AS, MY, TF, CK : contributions to conception and design, acquisition of data, data interpretation, writing, final approval of the version to be published.
AE, JC: contributions to conception and design, data analysis and interpretation, writing, final approval of the version to be published.

Funding statement
This work was supported by a Pathfinder grant from the University of South Australia, Adelaide, Australia (School of Nursing and Midwifery). Award/Grant number is not applicable. There was no conflict of interest, activities or potential for influencing this work by the funders. The grant organisation had no financial interest or role in the design, conduct, analysis or manuscript preparation for this project.

Competing interests
The authors declare that they have no competing interests

Data sharing statement
Data are available upon reasonable request from the corresponding author.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4-5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-5
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5-6
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6-7
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	Report numbers of outcome events or summary measures over time	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-10
		(*b*) Report category boundaries when continuous variables were categorized	7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-12
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The catheter to vein ratio and risk of peripherally inserted central catheter (PICC) associated thrombosis according to diagnostic group: a retrospective cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-045895.R1
Article Type:	Original research
Date Submitted by the Author:	04-Mar-2021
Complete List of Authors:	Sharp, Rebecca; University of South Australia, Clinical and Health Sciences/Rosemary Bryant AO Research Centre Carr, Peter; National University of Ireland Galway, School of Nursing and Midwifery; Griffith University, Alliance for Vascular Access Teaching and Research (AVATAR) Childs, Jessie; University of South Australia, Clinical & Health Sciences Scullion, Andrew; Calvary Mater Hospital, Vascular Access Team Young, Mark; St Vincent's Hospital Sydney, Peri-Operative Services Flynn, Tanya; St George Hospital, Cancer Services Kirker, Carolyn; Capital and Coast District Health Board, Department of Anaesthesia and Pain Management Jackson, Gavin; Fiona Stanley Hospital, Medical Imaging Esterman, Adrian; University of South Australia, Clinical & Health Sciences
Primary Subject Heading:	Nursing
Secondary Subject Heading:	Oncology, Infectious diseases, Radiology and imaging
Keywords:	RADIOLOGY & IMAGING, Interventional radiology < RADIOLOGY & IMAGING, Adult oncology < ONCOLOGY

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Title page

The catheter to vein ratio and risk of peripherally inserted central catheter (PICC) associated thrombosis according to diagnostic group: a retrospective cohort study

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Word count

3001 words

Keywords

Peripherally inserted central catheter (PICC), thrombosis, central venous access device

Abstract:

Objectives: determine the effect of the catheter to vein ratio (CVR) on rates of symptomatic thrombosis in patients with a peripherally inserted central catheter (PICC) and identify the optimal CVR cut-off point according to diagnostic group
Design: retrospective cohort study
Setting: 4 tertiary hospitals in Australia and New Zealand
Participants: adult patients who had undergone PICC insertion
Primary outcome measure: symptomatic thrombus of the limb in which the PICC was inserted
Results: 2,438 PICC insertions were included with 39 cases of thrombosis (1.6%; 95% CI 1.14% - 2.19%). Receiver operator characteristic (ROC) analysis was unable to be performed to determine the optimal CVR overall or according to diagnosis. The association between risk of thrombosis and CVR cut-offs commonly used in clinical practice were analysed. A 45% cut-off (≤45% versus ≥46%) was predictive of thrombosis, with those with a higher ratio having more than twice the risk (RR 2.30; 95% CI 1.202-4.383; p=0.01). This pattern

continued when only those with malignancy were included in the analysis, with cancer patients having twice the risk of thrombosis with a CVR greater than 45%. Whereas none of the results for the 33% CVR cut-off were statistically significant in these cohorts. Neither the 33% or 45% CVR cut-off produced statistically significant results in those with infection or other non-malignant conditions.

Conclusions: Adherence to CVR cut-offs are an important component of PICC insertion clinical decision-making to reduce the risk of thrombosis. These results suggest that in participants with cancer, the use of a CVR ≤45% should be considered to minimise risk of thrombosis. Further research is needed to determine the risk of thrombosis according to malignancy type and the optimal CVR for those with a non-malignant diagnosis.

ARTICLE SUMMARY

Strengths and limitations of this study

- Large, multi-site study with 2,438 peripherally inserted central catheters (PICCs)
- First study to analyse risk of thrombosis associated with the 33% and 45% catheter to vein ratio (CVR) cut-off recommendations commonly used in clinical practice for PICC insertion
- Analysed risk of thrombosis associated with CVRs according to diagnostic group
- Unable to perform planned analysis (receiver operator characteristic analysis) to determine the optimal catheter to vein ratio to prevent thrombosis in patients with a PICC
- The use of a tapered PICC impacted the accuracy of the PICC diameter and hence CVR for those participants that had the tapered portion inserted.

INTRODUCTION

Peripherally inserted central catheter (PICC) associated thrombosis is often uncomfortable for the patient, may result in loss of intravenous access for treatment and damage to the vasculature limiting further PICC insertions. In some cases, PICC associated thrombosis precipitates pulmonary embolism and post thrombotic syndrome. [1, 2] Approximately 2% of patients receiving antimicrobials as part of outpatient parenteral therapy (OPAT) develop thrombosis. [3, 4] Whilst those receiving cancer treatment suffer much higher rates, with 4-6% of patients with a haematological malignancy and 2-5% of those with a solid tumour developing PICC associated thrombosis. [3, 5-7]

This adverse event can be explained using mechanisms related to Virchow's triad (stasis, endothelial damage and hypercoagulable state of the patient). PICCs may have a large impact on the interruption of blood flow (stasis). In a mechanical model, Nifong and McDevitt (2011) demonstrated that blood flow was dependant on the size of the catheter and cylinder (or vein) size and PICCs commonly used in clinical practice may impede blood flow up to 80%. [8]

PICC insertion decisions such as the use of an appropriate catheter to vein ratio (CVR) affect PICC associated thrombosis rates. [3] Contemporary insertion approaches include measurement of the target vein diameter using ultrasound and limiting the CVR to reduce the risk of thrombosis. [9] Different CVR cut-offs are used in clinical practice, many sites use a 33% CVR limit, that is only one third of the vein should be occupied by the catheter. [7, 10-13] Other sites use a 45% CVR limit as advocated by the Infusion Therapy Standards of Practice (Infusion Nurses Society 2016). [14] However, there is a lack of research investigating safe CVRs to use for PICC insertion. Previous research in an adult population that used receiver operator characteristic (ROC) analysis found that a 45% CVR was the optimal cut-off to reduce the risk of thrombus. [15] Patients with a CVR of more than 45% were 13 times more likely to suffer from thrombosis. Yet these findings were based on just four cases and all participants with this adverse event had a haematological malignancy.

Most of the research investigating thrombosis rates associated with CVR cut-offs focus on cancer patients. [5, 7, 11, 13] This is problematic as many patients with an infection (without an underlying malignancy diagnosis) receive a PICC for antimicrobial treatment and it is

unknown whether the CVR cut-off may differ according to diagnosis. There is a need to investigate the association between the CVR and PICC-associated thrombosis in a larger sample and to determine a safe CVR cut-off in patients with both malignant and non-malignant health conditions. This study aimed to determine the effect of the CVR on rates of symptomatic thrombosis in patients with a PICC, identify the optimal CVR cut-off point and determine if the CVR cut-off is the same for patients with malignant and non-malignant disease.

METHOD

This was a retrospective cohort study set at hospitals in Australia (Calvary Mater Hospital, Newcastle, St Vincent's Hospital, Sydney and St George Hospital, Sydney) and New Zealand (Capital & Coast District Health Board, Wellington). Clinicians from PICC services at each site used an existing PICC database and hospital information systems to populate a standardised spreadsheet. Data regarding PICC insertion from 2015-2018 was included.

Inclusion criteria: adult patients who had undergone PICC insertion that terminated in the superior vena cava/right atrium junction.

Exclusion criteria: cases where diagnosis, PICC size (Fr), external length and vein diameter measurement were missing.

Participants were allowed in the study more than once. PICCs were inserted as per usual clinical practice at each site. The anteroposterior diameter of the relevant vein (basilic, brachial or cephalic) was measured using ultrasound at the insertion point. No tourniquet was used during the measurement process to reflect the natural vein diameter. Veins were measured using a linear transducer angled at 90 degrees to the vein and from hypoechoic inner wall to inner wall of the vein excluding the echogenic rim of the vein. The measurement was conducted using inbuilt callipers in a Site~Rite® 8 Ultrasound System (C. R. Bard, Salt Lake City, UT) at Australian sites and a Sonosite micromax and SII at the New Zealand site (SonoSite, Bothell, WA).

A polyurethane, reverse taper PICC design was used by all sites (figure 1).

This catheter increases in diameter toward the hub (tapers 2Fr over 7cm). So that a 4Fr PICC is 4Fr (1.33mm) at 7cm and 6Fr (2mm) at zero (near the hub). This is an increase in 0.67mm over 7cm toward the hub or 0.10mm per cm. For those participants with an external length ≤6cm, the external length (measured from insertion site to zero at sites) was used to determine the additional taper diameter for those PICCs (table 1). This measurement was added to the diameter of the PICC (Fr) as stated in the manufacturer information (outer diameter). For example, if a participant had a 4Fr PICC (1.33 mm) with an external length of 3cm, the additional taper diameter would be 0.4mm and the overall PICC diameter would be 1.733mm. For participants with an external length ≥7cm (tapered part of the PICC not inserted), manufacturer information was used to determine the PICC diameter.

Table 1: Taper diameter as per external length

External length (cm)	Additional taper diameter (mm)
0	0.7
1	0.6
2	0.5
3	0.4
4	0.3
5	0.2
6	0.1

The participant medical record number was used to access hospital information systems for sonography reports performed on the same upper extremity as the site of PICC insertion. De-identified reports were copied by clinicians at each site and these reports were reviewed by two members of the project team at the University of South Australia (one an accredited medical Sonographer) to determine cases of thrombus.

Patient and Public Involvement

Patients and the public were not involved in any way in this study.

Outcome measure

The primary outcome measure was symptomatic thrombus of the limb in which the PICC was inserted, which included thrombus that occurred in the superficial (SVT) or deep venous system (DVT) post PICC insertion. SVT was defined as occlusive thrombus in a superficial vein in which the PICC was inserted (basilic or cephalic veins). DVT included occlusive thrombus in the vein the PICC was inserted (if brachial) or if it extended into adjacent deep vasculature (axillary or subclavian veins). All cases were confirmed using ultrasound after clinical signs and symptoms triggered diagnostic testing whilst the PICC was still in situ or within 8 weeks of removal.

Ethical considerations

Ethics approval was obtained from the South Eastern Sydney Local Health District, Australia (HREC/17/POWH/174), Northern A Health and Disability Ethics Committee, New Zealand (17/NTA/264) and the University of South Australia (20026) Human Research Ethics Committees.

Power analysis:

A power analysis using PASS 11 (NCSS, UT, USA) determined that to achieve 80% power and 0.05 significance level, 2,140 participants were required. A test of two independent proportions was based on an expected increased risk of thrombus (RR=2.0) where 80% have a catheter to vein ratio ≤45% and are considered low risk with a 3% thrombus rate and 20% a ratio of ≥46% will be high risk with a 6% thrombus rate. That is 1,712 in the low risk group and 428 in the high risk group. These thrombus rates are based on previous research. [15] It was possible for a patient to be in the study more than once (PICC reinsertion/exchange).However, we expected this to be a small proportion of patients and the impact of clustering to be minimal.

Statistical Analysis Plan

Descriptive statistics were used to present information about the study population. CVRs were determined by dividing PICC diameter (stated diameter or tapered diameter) by vein diameter and multiplying by 100 to generate a percentage. The association between the CVR and the risk of thrombus was analysed using a log binomial generalised linear model. This analysis was performed with all participants and according to diagnostic group. The

same PICC design, with reverse taper capability was used in this study, but not all participants had the reverse taper portion inserted. As we were unsure about the accuracy of the PICC diameter (and hence CVR) of those with the tapered portion of the PICC inserted, analysis was repeated for those who didn't have the tapered portion of the PICC inserted. Receiver operator characteristic (ROC) analysis was used to plot the sensitivity and specificity of each ratio measurement using MedCalc for Windows, version 12.5 (MedCalc Software, Ostend, Belgium). The area under the curve (AUC) was used to identify the ideal CVR cut-off point with the aim to maximize sensitivity and specificity. All results with $p \leq 0.05$ were considered statistically significant.

RESULTS

There were 2,475 cases available, 37 were excluded due to missing data (11 with missing vein diameter and 26 missing diagnosis), leaving 2,438 PICC insertions in the analysis. Nearly equal numbers of participants were male and female (table 2), with a mean age of 59 years old (SD 17.09). Most participants did not have a history of central venous access device (CVAD) insertion and had a cancer diagnosis. Participants with a cancer diagnosis had three times the risk of thrombosis than those with an infection as an underlying diagnosis. Those with a solid tumour appeared to have higher risk of thrombosis than those with a haematological malignancy, however this was not statistically significant.

Table 2: Participant factors and risk of thrombosis in patients with a PICC

Characteristic		Venous thrombosis			Univariate analysis		
		No (n=2399) n (%)	Yes (n= 39) n (%)	Total (n= 2438) n (%)	RR	95% CI	Sig¥
Gender	Female	1104 (98.13)	21 (1.87)	1125 (100)	1.00		
	Male	1294 (98.63)	18 (1.37)	1312 (100)	0.73	0.394-1.372	0.334
	Total	2398 (98.40)	39 (1.60)	2437 (100)			
Age (years)	19-45	457 (97.86)	10 (2.14)	467 (100)	1.00		
	46-65	946 (98.54)	14 (1.46)	960 (100)	0.68	0.304-1.521	0.349
	66-79	773 (98.35)	13 (1.65)	786 (100)	0.77	0.341-1.747	0.535
	80+	189 (98.95)	2 (1.05)	191 (100)	0.49	0.108- 2.210	0.353
	Total	2365 (98.38)	39 (1.62)	2404 (100)			
Previous CVAD	Y	718 (97.82)	16 (2.18)	734 (100)	1.61	0.858 -3.038	0.137
	N	1681 (98.65)	23 (1.35)	1704 (100)	1.00		
	Total	2399 (98.40)	39 (1.60)	2438 (100)			
Number of previous CVAD	0	1688 (98.48)	26 (1.52)	1714 (100)	1.00		
	1	534 (98.16)	10 (1.84)	544 (100)	1.21	0.588-2.496	0.602
	≥2	168 (98.25)	3 (1.75)	171 (100)	1.16	0.528-5.597	0.810
	Total	2390 (98.39)	39 (1.61)	2429 (100)			
Primary diagnosis^	Infection	859 (99.19)	7 (0.81)	866 (100)	1.00		
	Cancer	1285 (97.57)	32 (2.43)	1317 (100)	3.01	1.332- 6.779	0.008

	Other	255 (100)	0 (0)	255 (100)	-	-	-
	Total	2399 (98.40)	39 (1.60)	2438 (100)			
Malignancy type	Haematological	391 (98.49)	6 (1.51)	397 (100)	1.00		
	Oncological	285 (96.28)	11 (3.72)	296 (100)	2.47	0.924-6.606	0.071
	Total	676 (97.55)	17 (2.45)	693 (100)			

PICC= peripherally inserted central catheter; CVAD= central venous access device; ¥Based on log binomial generalized linear model; CI=confidence interval; RR=relative risk; ^As per treatment request

Most PICCs were inserted in the basilic vein in the right arm and required one needling attempt (table 3). Nearly equal numbers of single lumen (4Fr) and double lumen (5 Fr) PICCs were used. Most PICCs were verified using electrocardiogram (ECG), using a combination of securement devices and were inserted by staff with 3-5 years of experience. The infusion of chemotherapy was associated with nearly four times the risk of thrombosis.

Table 3: PICC insertion factors and risk of thrombosis

Characteristic		Venous thrombosis			Univariate analysis		
		No (n=2399)	Yes (n= 39)	Total (n= 2438)			
		n (%)	n (%)	n (%)	RR	95% CI	Sig¥
Arm	Left	491 (97.61)	12 (2.39)	503 (100)	1.71	0.871-3.347	0.119
	Right	1906 (98.60)	27 (1.40)	1933 (100)	1.00		
	Total	2397 (98.40)	39 (1.60)	2436 (100)			
Vein	Basilic	1861 (98.52)	28 (1.48)	1889 (100)	1.00		
	Brachial	403 (97.58)	10 (2.42)	413 (100)	1.63	0.800-3.336	0.178
	Cephalic	130 (99.24)	1 (0.76)	131 (100)	0.51	0.071-3.755	0.513
	Total	2394 (98.40)	39 (1.60)	2433 (100)			
Needling attempts	1	2029 (98.50)	31 (1.50)	2060 (100)	1.00		
	2	203 (98.54)	3 (1.46)	206 (100)	0.97	0.298-3.138	0.956
	3+	65 (100)	0 (0)	65 (100)			
	Total	2297 (98.54)	34 (1.46)	2331 (100)			
Catheter size (Fr) and lumen	4 (Single lumen)	1251 (98.82)	15 (1.18)	1266 (100)	1.00		
	5 (Double lumen)	1136 (97.93)	24 (2.07)	1160 (100)	1.75	0 .920-3.312	0.088
	6 (Triple lumen)	12 (100)	0 (0)	12 (100)	-	-	-
	Total	2399 (98.40)	39 (1.60)	2438 (100)			
Tip confirmation method	CXR	101 (98.06)	2 (1.94)	103 (100)	1.00		
	ECG	1480 (98.40)	24 (1.60)	1504 (100)	0.82	0.197-3.429	0.788
	Both	817 (98.43)	13 (1.57)	830 (100)	0.98	0.185-3.524	0.775
	Total	2398 (98.40)	39 (1.60)	2437 (100)			
Securement device	Adhesive	895 (98.35)	15 (1.65)	910 (100)	1.00		
	Subcutaneous	521 (97.75)	12 (2.25)	533 (100)	1.37	0.644-2.895	0.416
	Combination	977 (98.79)	12 (1.21)	989 (100)	0.73	0.346-1.564	0.426
	Other∩	5 (100)	0 (0)	5 (100)	-	-	-
	Total	2398 (98.40)	39 (1.60)	2437 (100)			
Staff years of experience	0	40 (100)	0 (0)	40 (100)	1.00		
	1-2	898 (98.25)	16 (1.75)	914 (100)	1.58	0.530-4.680	0.413
	3-5	1103 (98.31)	19 (1.69)	1122 (100)	1.52	0.522-4.450	0.441
	6+	356 (98.89)	4 (1.11)	360 (100)	-	-	-
	Total	2397 (98.40)	39(1.60)	2436 (100)			
Infusion^							
	Antibiotics/Antivirals	976 (99.29)	7 (0.71)	983 (100)	1.00		

Chemotherapy	1011 (97.31)	28 (2.69)	1039 (100)	3.78	1.660-8.623	0.002
Blood products	29 (100)	0 (0)	29 (100)	-	-	-
TPN	216 (99.08)	2 (0.92)	218 (100)	1.28	0.269- 6.159	0.751
Other[#]	167 (98.82)	2 (1.18)	169 (100)	1.66	0.348- 7.932	0.524
Total	2399 (98.40)	39 (1.60)	2438 (100)			

PICC= peripherally inserted central catheter; ¥Based on log binomial generalized linear model; CI=confidence interval; RR=relative risk; CXR=chest x-ray; ECG=electrocardiogram [∩] suture or glue; TPN=total parenteral nutrition [#]intravenous therapy, electrolytes, difficult access, frequent blood draws; ^As per treatment request, participants often had more than one listed, coded as chemotherapy if this was included in list

Cases of thrombosis

There were 39 cases of confirmed thrombosis, a rate of 1.6% (95% CI 1.14% - 2.19%). These comprised 13 cases of SVT (33%), 5 cases of DVT (13%) and 21 cases involving both the superficial and deep venous system (54%).

Catheter to vein ratio

Based on ROC analysis, the CVR was not an effective diagnostic variable when treated as a continuous variable. The area under the curve was close to 0.5 when the ROC analysis was performed using the entire sample and according to diagnostic group. As the models lacked diagnostic ability, we analysed the association between risk of thrombosis and CVR cut-offs commonly used in clinical practice.

All participants

As per table 4, a CVR cut-off of 33% did not appear to be associated with risk of thrombus, whereas, a 45% cut-off (≤45% versus ≥46%) was predictive, with those with a higher ratio having more than twice the risk of thrombus (RR 2.30; 95% CI 1.202-4.383; p=0.01).

The analysis was repeated with participants who didn't have the tapered portion of the PICC inserted that is, PICCs with an external length ≤6cm were excluded (table 5). This comprised 1,098 cases or 45% of the sample. Use of a CVR greater than 45% remained associated with more than twice the risk of thrombosis. When a 33% CVR cut-off was analysed, the use of a CVR higher than 34% appeared protective of thrombosis. However, neither of these results were statistically significant.

Table 4: Catheter to vein ratio and risk of thrombosis according to diagnosis in patients with a PICC

		All PICCs					
		Venous thrombosis			Univariate analysis		
	Catheter to vein ratio	No (n=2399)	Yes (n= 39)	Total (n= 2438)	RR	95% CI	Sig¥
		n (%)	n (%)	n (%)			
All participants	≤33%	914 (98.39)	15 (1.61)	929 (100)	1.00		
	≥34%	1485 (98.41)	24 (1.59)	1509 (100)	0.99	0.519-1.867	0.963
	Total	2399 (98.40)	39 (1.60)	2438 (100)			
	≤45%	1935 (98.72)	25 (1.28)	1960 (100)	1.00		
	≥46%	464 (97.07)	14 (2.93)	478 (100)	2.30	1.202-4.383	0.012
	Total	2399 (98.40)	39 (1.60)	2438 (100)			
		No (n=1285)	**Yes (n= 32)**	**Total (n=1317)**			
		n (%)	n (%)	n (%)			
Cancer diagnosis	≤33%	361 (97.57)	9 (2.43)	370 (100)	1.00		
	≥34%	924 (97.57)	23 (2.43)	947 (100)	0.99	0.466-2.138	0.997
	Total	1285 (97.57)	32 (2.43)	1317 (100)			
	≤45%	943 (98.13)	18 (1.87)	961 (100)	1.00		
	≥46%	342 (96.07)	14 (3.93)	356 (100)	2.10	1.055-4.177	0.035
	Total	1285 (97.57)	32 (2.43)	1317 (100)			
		No (n=391)	**Yes (n=6)**	**Total (n=397)***			
		n (%)	n (%)	n (%)			
Haematological cancer diagnosis	≤33%	75 (98.68)	1 (1.32)	76 (100)	1.00		
	≥34%	316 (98.44)	5 (1.56)	321 (100)	1.18	0.140-9.986	0.877
	Total	391 (98.49)	6 (1.51)	397 (100)			
	≤45%	241 (99.18)	2 (0.82)	243 (100)	1.00		
	≥46%	150 (97.40)	4 (2.60)	154 (100)	3.16	0.585-17.023	0.181
	Total	391 (98.49)	6 (1.51)	397 (100)			
		No (n=285)	**Yes (n=11)**	**Total (n=296)***			
		n (%)	n (%)	n (%)			
Oncological cancer diagnosis	≤33%	51 (91.07)	5 (8.93)	56 (100)	1.00		
	≥34%	234 (97.50)	6 (2.50)	240 (100)	0.28	0.089-0.885	0.030
	Total	285 (96.28)	11 (3.72)	296 (100)			
	≤45%	169 (96.57)	6 (3.43)	175 (100)	1.00		
	≥46%	116 (95.87)	5 (4.13)	121 (100)	1.21	0.376-3.860	0.753
	Total	285 (96.28)	11 (3.72)	296 (100)			
		No (n=1114)	**Yes (n= 7)**	**Total (n=1121)**			
		n (%)	n (%)	n (%)			
Infection and other diagnoses^	≤33%	553 (98.93)	6 (1.07)	559 (100)	1.00		
	≥34%	561 (99.82)	1 (0.18)	562 (100)	0.17	0.020-1.372	0.096
	Total	1114 (99.38)	7 (0.62)	1121 (100)			
	≤45%	992 (99.3)	7 (0.7)	999 (100)	1.00		
	≥46%	122 (100)	0 (0)	122 (100)	-	-	-
	Total	1114 (99.38)	7 (0.62)	1121 (100)			

PICC= peripherally inserted central catheter; ¥Based on log binomial generalized linear model; CI=confidence interval; RR=relative risk;
^ infection requiring intravenous antibiotics or other non-cancer diagnosis with difficult venous access requiring patient controlled analgesia, intravenous fluid etc.* does not add up to total number due to missing data about cancer diagnosis

Effect of diagnosis on risk of thrombosis

Cancer

When only participants with cancer were included in the analysis, a 45% CVR cut-off was associated with twice the risk of thrombosis (RR 2.10; 95% CI 1.055-4.177; p=0.035), whilst the use of a 33% CVR cut-off was not associated with risk (table 4). Although not statistically significant, when analysis was repeated with participants without the tapered portion of the PICC inserted, a CVR of 34% or greater appeared protective and the use of a CVR more than 45% was also associated with increased risk of thrombosis (table 5).

We then separated those with malignancy according to cancer type (693 participants had this information recorded) and repeated the analysis. For those with a haematological diagnosis, a CVR greater than 34% was associated with slightly higher risk whilst a CVR greater than 45% was associated with more than 3 times the risk of thrombosis, although both results did not reach statistical significance. This analysis couldn't be repeated for those without the tapered portion of the PICC inserted in this group as there were no cases of thrombosis.

For those with a solid tumour, a CVR greater than 33% was associated with reduced risk of thrombosis and a CVR greater than 45% was associated with slightly elevated increased risk although the latter finding was not statistically significant. When the analysis was repeated for those who did not have the tapered portion of the PICC inserted, a CVR greater than 33% appeared protective, whilst a CVR higher than 45% was associated with more than 4 times increased risk, although the results did not reach statistical significance (table 5).

Infection

In participants with an infection or other non-cancer diagnosis, the association between a 45% cut-off and risk of thrombosis could not be analysed as none of the participants with a ratio of 46% and above developed thrombus (table 4). A 33% CVR cut-off appeared to be protective in this cohort, with those with a CVR higher than 34% having less risk of thrombosis, although this was not statistically significant. Similar results were found when only non-tapered PICCs were included in the analysis (table 5).

Table 5: Catheter to vein ratio and risk of thrombosis in non-tapered PICCs

		Venous thrombosis			Univariate analysis		
	Catheter to vein ratio	**No (n=1085)** n (%)	**Yes (n=13)** n (%)	**Total (n=1098)** n (%)	RR	95% CI	Sig¥
All participants	≤33%	563 (98.43)	9 (1.57)	572 (100)	1.00		
	≥34%	522 (99.24)	4 (0.76)	526 (100)	0.48	0.150-1.560	0.224
	Total	1085 (98.82)	13 (1.18)	1098 (100)			

	≤45%	1021 (98.93)	11 (1.07)	1032 (100)	1.00		
	≥46%	64 (96.97)	2 (3.03)	66 (100)	2.84	0.643-12.563	0.168
	Total	1085 (98.82)	13 (1.18)	1098 (100)			
		No (n=479) n (%)	**Yes (n=8)** n (%)	**Total (n=487)** n (%)			
Cancer diagnosis	≤33%	210 (97.67)	5 (2.33)	215 (100)	1.00		
	≥34%	269 (98.90)	3 (1.10)	272 (100)	0.47	0.115-1.962	0.303
	Total	479 (98.36)	8 (1.64)	487 (100)			
	≤45%	445 (98.67)	6 (1.33)	451 (100)	1.00		
	≥46%	34 (94.44)	2 (5.56)	36 (100)	4.18	0.874- 19.950	0.073
	Total	479 (98.36)	8 (1.64)	487 (100)			
		No (n=39) n (%)	**Yes (n=0)** n (%)	**Total (n=39)** n (%)			
Haematological cancer diagnosis	≤33%	19 (100)	0 (100)	19 (100)	1.00		
	≥34%	20 (100)	0 (100)	20 (100)	-	-	-
	Total	39 (100)	0 (100)	39 (100)			
	≤45%	38 (100)	0 (100)	38 (100)	1.00		
	≥46%	1 (100)	0 (100)	1 (100)	-	-	-
	Total	39 (100)	0 (100)	39 (100)			
		No (n=16) n (%)	**Yes (n=3)** n (%)	**Total (n=19)** n (%)			
Oncological cancer diagnosis	≤33%	6 (75)	2 (25)	8 (100)	1.00		
	≥34%	10 (90.91)	1 (9.09)	11 (100)	0.36	0.039-3.351	0.372
	Total	16 (84.21)	3 (15.79)	19 (100)			
	≤45%	15 (88.24)	2 (11.76)	17 (100)	1.00		
	≥46%	1 (50)	1 (50)	2 (100)	4.25	0.635-28.456	0.136
	Total	16 (84.21)	3 (15.79)	19 (100)			
		No (n=606) n (%)	**Yes (n=5)** n (%)	**Total (n=611)** n (%)			
Infection and other diagnoses^	≤33%	353 (98.88)	4 (1.12)	357 (100)	1.00		
	≥34%	253 (99.61)	1 (0.39)	254 (100)	0.35	0.040-3.125	0.348
	Total	606 (99.18)	5 (0.82)	611 (100)			
	≤45%	576 (99.14)	5 (0.86)	581 (100)	1.00		
	≥46%	30 (100)	0 (0)	30 (100)	-	-	-
	Total	606 (99.18)	5 (0.82)	611 (100)			

PICC= peripherally inserted central catheter; ¥Based on log binomial generalized linear model; CI=confidence interval; RR=relative risk;^ infection requiring intravenous antibiotics or other non-cancer diagnosis with difficult venous access requiring patient controlled analgesia, intravenous fluid etc; 1 participant had missing external length

DISCUSSION

We aimed to identify an optimal CVR cut-off for PICC insertion to prevent the risk of thrombosis. However, ROC analysis demonstrated that the CVR as a continuous measure was not an effective diagnostic variable overall, probably due to the low number of cases with higher CVRs. Hence, we analysed the risk of thrombosis associated with CVR cut-offs used in clinical practice.

A CVR greater than 45% was associated with twice the risk of PICC associated thrombosis when all participants were included in the analysis. When this analysis was performed according to diagnostic group, similar results were found in those with cancer. For those participants with malignancy, a CVR 45% cut-off was associated with more than twice the risk of thrombosis (RR 2.10; 95% CI 1.055-4.177; p=0.035). Although not statistically significant, this pattern continued when this was reanalysed with participants who did not have the reverse taper portion of the PICC inserted. Whereas none of the results for the 33% CVR cut-off were statistically significant in these cohorts.

Neither the 33% or 45% CVR cut-off produced statistically significant results in those with infection or other non-malignant conditions. We found a thrombosis rate of only 0.8% in this cohort and the analysis of thrombosis risk for each CVR was limited by a low number of cases of thrombosis. It is difficult to compare our results to previous research as most includes a mixed cohort (with cancer patients who have increased risk of thrombosis) and don't report results separately. Where research does examine only those receiving a PICC for the treatment of infection, with no underlying malignancy, insertion decisions such as the CVR are not documented. Whilst the optimal CVR is not available for these patients, we still recommend that a CVR limit is used until a more accurate estimate of risk is established.

The results from the present study suggest that the use of a CVR ≤45% is an important component of the strategies used during PICC insertion to reduce the risk of thrombosis in cancer patients requiring a PICC [16]. Thrombosis is a significant adverse event in patients with cancer and is associated with increased morbidity and mortality. [17, 18] Factors such as the selection of an appropriate sized vein are especially important in the cancer patient cohort as larger, multi-lumen PICCs may be required which exacerbates thrombosis risk. These results support the use of a 45% CVR cut-off as advocated in the Infusion Nurses Society clinical guidelines (2016) and previous research that used ROC analysis to determine the optimal CVR cut-off. [15]

Our analysis of the risk associated with the CVRs used in clinical practice of those with haematological and oncological cancers separately should be interpreted with caution due to the

low numbers of cases. However, it may be that cancer type may influence risk. Previous research has found that those with a haematological cancer (Hodgkin lymphoma) experienced higher rates of PICC associated thrombosis than those with solid tumours [19] Further research is required to determine PICC associated thrombosis risk according to cancer type generally and may consider investigating risk according to specific diagnosis. A more nuanced understanding of the risk of PICC associated thrombosis for individual consumers would allow clinicians to provided targeted interventions for those most at risk.

IMPLICATIONS FOR CLINICAL PRACTICE

This study indicates that the CVR should not exceed 45% for those with a cancer diagnosis. Whilst the optimal CVR for those with infection and other non-malignant conditions is inconclusive, the low thrombosis rate found in the present study supports the use of minimum vein size strategy for all patients requiring a PICC. The minimum vein diameters needed to achieve ≤45% CVR are detailed in table 6. Many health consumers requiring a PICC will have a vein large enough for clinicians to adhere to these recommendations (we found that 80% of participants had a CVR ≤45%, which demonstrates that adherence to the INS recommendations is feasible in most cases).

However, some health consumers will require a larger multi-lumen device and may not have an appropriate vein to accommodate the larger catheter. This is problematic, especially in those with cancer who are at higher risk and the use of thromboprophylaxis may be considered. Some evidence suggests that thromboprophylaxis reduces the risk of symptomatic CVAD associated thrombosis in patients with cancer. A Cochrane review [20], found that thromboprophylaxis (low-molecular-weight heparin) halved the risk of thrombosis in patients with a CVAD (RR 0.43, 95% CI 0.22- 0.81). This meta-analysis was comprised of RCTs that included patients with mostly solid tumours. Further research is needed in those with haematological malignancies. The use of thromboprophylaxis in patients with haematological cancers also needs to be weighed against bleeding risk [21]. Yet, thromboprophylaxis is used in some haematological cancer groups e.g. multiple myeloma patients taking thalidomide [22]. An alternative vascular access device may also be considered for those most at risk. Research in cancer patients that has compared thrombosis risk according to different CVADs has found that PICCs were associated with more than 7 times the risk of thrombosis (HR 7.48, 95% CI 1.03-54.1, p=0.046) when compared to other non-tunnelled vascular access devices (central venous catheters), whilst implanted ports were associated with half the risk (HR 0.47 95% CI 0.03-7.90 p=0.597). [23] Although insertion decisions such as the CVR

are not documented in this research, perhaps large CVRs account for increased risk of thrombosis for those with a PICC.

Table 6:Minimum vein sizes to achieve ≤45% CVR

PICC size (fr)	Minimum vein size
4Fr	2.96 mm
5Fr	3.70 mm
6Fr	4.44mm

CVR=catheter to vein ratio

CVR with a tapered PICC

Our results indicate that clinicians who use a reverse taper PICC should be aware of the increased diameter of the taper and depending on vein size, increased risk of thrombosis should the taper be advanced into the vein. It is important to recognise the significant impact that the taper has on PICC diameter. For example, a 6Fr longer tapered PICC would be 8Fr at the hub or 2.67mm so to meet the 45% CVR cut-off, a vein would need to be 5.8mm in diameter rather than 4.5mm if it was inserted to the hub. To improve the accuracy of the PICC diameter for tapered PICCs when determining the CVR in clinical practice, clinicians could use the external length to determine the additional taper diameter as detailed in this study.

Alternatively, clinicians may avoid the use of the tapered part of the PICC by avoiding insertion of the taper. This will leave an external length of ≥7cm. Whilst increased external length may be thought to increase dislodgement rates, anecdotally, this has not been the case with clinicians in this study. Some sites have introduced a sub-cutaneous device to fix the PICC in place which provides additional security for those with longer external lengths.

LIMITATIONS

A limitation with this study was the inclusion of PICCs with reverse taper design and resulting imprecise diameter to inform the CVR. Whilst we developed an equation to determine the adjusted PICC diameter based on the external length this did not allow for the impact of subcutaneous tissue on this measurement. However, we expected this to have minimal impact on the overall CVR. Furthermore, we also presented analysis which only included non-tapered PICCs. There is a possibility that some participants presented to a regional hospital rather than the major

hospitals in this study with symptoms of thrombus, hence, we would miss cases of thrombus. However, we expected this to be unlikely as most would be managed by their treating team at the specialist centres in the hospitals where the study was conducted. A further limitation, as with all retrospective studies is the reliance on existing data which in this study was evident in problems with missing data. Although participants were allowed into the dataset more than once, missing data meant that clustering could not be allowed for. However, we expected this to be a small proportion of patients and the impact of clustering to be minimal.

CONCLUSION

The use of an appropriate vein size for PICC insertion is an important strategy to reduce PICC associated thrombosis in clinical practice. A CVR cut-off of 33% was not useful in predicting PICC-associated thrombosis in cancer patients or those with other diagnoses. Our findings suggest that, in participants with cancer, the CVR should not exceed 45%, although further prospective studies are required to make definitive conclusions. This cut-off was not associated with risk of thrombosis for those with an infection and other non-cancer diagnosis. Whilst further research is needed to determine the optimal CVR for those with infection, it is still recommended that the CVR is limited to reduce the risk of thrombosis.

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Author statement

RS: contributions to conception and design, literature search, data analysis and interpretation, writing, final approval of the version to be published
PC, GJ: contributions to conception and design, data interpretation, writing, final approval of the version to be published.
AS, MY, TF, CK : contributions to conception and design, acquisition of data, data interpretation, writing, final approval of the version to be published.
AE, JC: contributions to conception and design, data analysis and interpretation, writing, final approval of the version to be published.

Funding statement
This work was supported by a Pathfinder grant from the University of South Australia, Adelaide, Australia (School of Nursing and Midwifery). Award/Grant number is not applicable. There was no conflict of interest, activities or potential for influencing this work by the funders. The grant organisation had no financial interest or role in the design, conduct, analysis or manuscript preparation for this project.

Competing interests
The authors declare that they have no competing interests

Data sharing statement
Data are available upon reasonable request from the corresponding author.

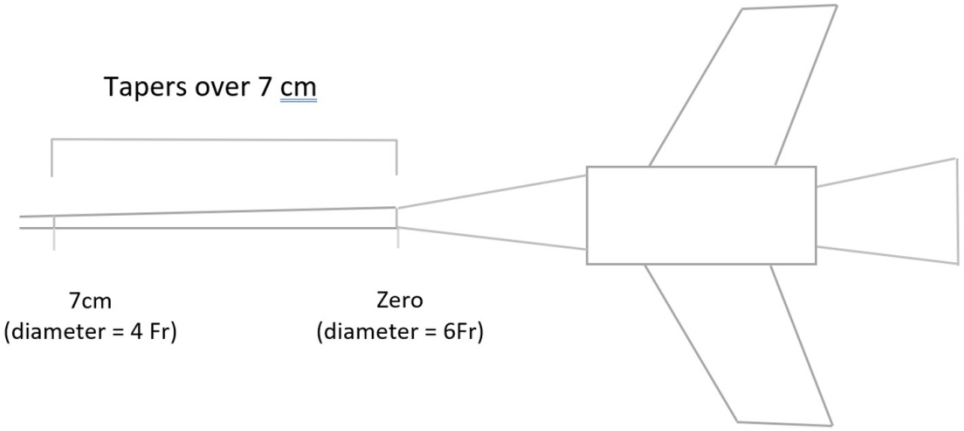

Figure 1: 4 Fr reverse taper PICC
(image author's own)

391x180mm (96 x 96 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4-5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-5
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5-6
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6-7
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	Report numbers of outcome events or summary measures over time	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-10
		(*b*) Report category boundaries when continuous variables were categorized	7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-12
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The catheter to vein ratio and risk of peripherally inserted central catheter (PICC) associated thrombosis according to diagnostic group: a retrospective cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-045895.R2
Article Type:	Original research
Date Submitted by the Author:	08-Jun-2021
Complete List of Authors:	Sharp, Rebecca; University of South Australia, Clinical and Health Sciences/Rosemary Bryant AO Research Centre Carr, Peter; National University of Ireland Galway, School of Nursing and Midwifery; Griffith University, Alliance for Vascular Access Teaching and Research (AVATAR) Childs, Jessie; University of South Australia, Clinical & Health Sciences Scullion, Andrew; Calvary Mater Hospital, Vascular Access Team Young, Mark; St Vincent's Hospital Sydney, Peri-Operative Services Flynn, Tanya; St George Hospital, Cancer Services Kirker, Carolyn; Capital and Coast District Health Board, Department of Anaesthesia and Pain Management Jackson, Gavin; Fiona Stanley Hospital, Medical Imaging Esterman, Adrian; University of South Australia, Clinical & Health Sciences
Primary Subject Heading:	Nursing
Secondary Subject Heading:	Oncology, Infectious diseases, Radiology and imaging
Keywords:	RADIOLOGY & IMAGING, Interventional radiology < RADIOLOGY & IMAGING, Adult oncology < ONCOLOGY

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Title page

The catheter to vein ratio and risk of peripherally inserted central catheter (PICC) associated thrombosis according to diagnostic group: a retrospective cohort study

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Word count

3001 words

Keywords

Peripherally inserted central catheter (PICC), thrombosis, central venous access device

Abstract:

Objectives: determine the effect of the catheter to vein ratio (CVR) on rates of symptomatic thrombosis in individuals with a peripherally inserted central catheter (PICC) and identify the optimal CVR cut-off point according to diagnostic group
Design: retrospective cohort study
Setting: 4 tertiary hospitals in Australia and New Zealand
Participants: adults who had undergone PICC insertion
Primary outcome measure: symptomatic thrombus of the limb in which the PICC was inserted
Results: 2,438 PICC insertions were included with 39 cases of thrombosis (1.6%; 95% CI 1.14% - 2.19%). Receiver operator characteristic (ROC) analysis was unable to be performed to determine the optimal CVR overall or according to diagnosis. The association between

risk of thrombosis and CVR cut-offs commonly used in clinical practice were analysed. A 45% cut-off (≤45% versus ≥46%) was predictive of thrombosis, with those with a higher ratio having more than twice the risk (RR 2.30; 95% CI 1.202-4.383; p=0.01). This pattern continued when only those with malignancy were included in the analysis, those with cancer had twice the risk of thrombosis with a CVR greater than 45%. Whereas the 33% CVR cut-off was not associated with statistically significant results overall or in those with malignancy. Neither the 33% or 45% CVR cut-off produced statistically significant results in those with infection or other non-malignant conditions.

Conclusions: Adherence to CVR cut-offs are an important component of PICC insertion clinical decision-making to reduce the risk of thrombosis. These results suggest that in individuals with cancer, the use of a CVR ≤45% should be considered to minimise risk of thrombosis. Further research is needed to determine the risk of thrombosis according to malignancy type and the optimal CVR for those with a non-malignant diagnosis.

ARTICLE SUMMARY

Strengths and limitations of this study

- Large, multi-site study with 2,438 peripherally inserted central catheters (PICCs)
- First study to analyse risk of thrombosis associated with the 33% and 45% catheter to vein ratio (CVR) cut-off recommendations commonly used in clinical practice for PICC insertion
- Analysed risk of thrombosis associated with CVRs according to diagnostic group
- Unable to perform planned analysis (receiver operator characteristic analysis) to determine the optimal catheter to vein ratio to prevent thrombosis in individuals with a PICC
- The use of a tapered PICC impacted the accuracy of the PICC diameter and hence CVR for those participants that had the tapered portion inserted.

INTRODUCTION

Peripherally inserted central catheter (PICC) associated thrombosis is often uncomfortable, may result in loss of intravenous access for treatment and damage to the vasculature limiting further PICC insertions. In some cases, PICC associated thrombosis precipitates pulmonary embolism and post thrombotic syndrome. [1, 2] Approximately 2% of individuals receiving antimicrobials as part of outpatient parenteral therapy (OPAT) develop thrombosis. [3, 4] Whilst those receiving cancer treatment suffer much higher rates, with 4-6% of consumers with a haematological malignancy and 2-5% of those with a solid tumour developing PICC associated thrombosis. [3, 5-7]

This adverse event can be explained using mechanisms related to Virchow's triad (stasis, endothelial damage and hypercoagulable state of the patient). PICCs may have a large impact on the interruption of blood flow (stasis). In a mechanical model, Nifong and McDevitt (2011) demonstrated that blood flow was dependant on the size of the catheter and cylinder (or vein) size and PICCs commonly used in clinical practice may impede blood flow up to 80%. [8]

PICC insertion decisions such as the use of an appropriate catheter to vein ratio (CVR) affect PICC associated thrombosis rates. [3] Contemporary insertion approaches include measurement of the target vein diameter using ultrasound and limiting the CVR to reduce the risk of thrombosis. [9] Different CVR cut-offs are used in clinical practice, many sites use a 33% CVR limit, that is only one third of the vein should be occupied by the catheter. [7, 10-13] Other sites use a 45% CVR limit as advocated by the Infusion Therapy Standards of Practice (Infusion Nurses Society 2016). [14] However, there is a lack of research investigating safe CVRs to use for PICC insertion. Previous research in an adult population that used receiver operator characteristic (ROC) analysis found that a 45% CVR was the optimal cut-off to reduce the risk of thrombus. [15] Participants with a CVR of more than 45% were 13 times more likely to suffer from thrombosis. Yet these findings were based on just four cases and all participants with this adverse event had a haematological malignancy.

Most of the research investigating thrombosis rates associated with CVR cut-offs focus on individuals with cancer. [5, 7, 11, 13] This is problematic as many consumers with an infection (without an underlying malignancy diagnosis) receive a PICC for antimicrobial

treatment and it is unknown whether the CVR cut-off may differ according to diagnosis. There is a need to investigate the association between the CVR and PICC-associated thrombosis in a larger sample and to determine a safe CVR cut-off in individuals with both malignant and non-malignant health conditions. This study aimed to determine the effect of the CVR on rates of symptomatic thrombosis in individuals with a PICC, identify the optimal CVR cut-off point and determine if the CVR cut-off is the same for those with malignant and non-malignant disease.

METHOD

This was a retrospective cohort study set at hospitals in Australia (Calvary Mater Hospital, Newcastle, St Vincent's Hospital, Sydney and St George Hospital, Sydney) and New Zealand (Capital & Coast District Health Board, Wellington). Clinicians from PICC services at each site used an existing PICC database and hospital information systems to populate a standardised spreadsheet. Data regarding PICC insertion from 2015-2018 was included.

Inclusion criteria: adultswho had undergone PICC insertion that terminated in the superior vena cava/right atrium junction.

Exclusion criteria: cases where diagnosis, PICC size (Fr), external length and vein diameter measurement were missing.

Participants were allowed in the study more than once. PICCs were inserted as per usual clinical practice at each site. The anteroposterior diameter of the relevant vein (basilic, brachial or cephalic) was measured using ultrasound at the insertion point. No tourniquet was used during the measurement process to reflect the natural vein diameter. Veins were measured using a linear transducer angled at 90 degrees to the vein and from hypoechoic inner wall to inner wall of the vein excluding the echogenic rim of the vein. The measurement was conducted using inbuilt callipers in a Site~Rite® 8 Ultrasound System (C. R. Bard, Salt Lake City, UT) at Australian sites and a Sonosite micromax and SII at the New Zealand site (SonoSite, Bothell, WA).

A polyurethane, reverse taper PICC design was used by all sites (figure 1).

This catheter increases in diameter toward the hub (tapers 2Fr over 7cm). So that a 4Fr PICC is 4Fr (1.33mm) at 7cm and 6Fr (2mm) at zero (near the hub). This is an increase in 0.67mm over 7cm toward the hub or 0.10mm per cm. For those participants with an external length ≤6cm, the external length (measured from insertion site to zero at sites) was used to determine the additional taper diameter for those PICCs (table 1). This measurement was added to the diameter of the PICC (Fr) as stated in the manufacturer information (outer diameter). For example, if a participant had a 4Fr PICC (1.33 mm) with an external length of 3cm, the additional taper diameter would be 0.4mm and the overall PICC diameter would be 1.733mm. For participants with an external length ≥7cm (tapered part of the PICC not inserted), manufacturer information was used to determine the PICC diameter.

Table 1: Taper diameter as per external length

External length (cm)	Additional taper diameter (mm)
0	0.7
1	0.6
2	0.5
3	0.4
4	0.3
5	0.2
6	0.1

The participant medical record number was used to access hospital information systems for sonography reports performed on the same upper extremity as the site of PICC insertion. De-identified reports were copied by clinicians at each site and these reports were reviewed by two members of the project team at the University of South Australia (one an accredited medical Sonographer) to determine cases of thrombus.

Patient and Public Involvement

Patients and the public were not involved in any way in this study.

Outcome measure

The primary outcome measure was symptomatic thrombus of the limb in which the PICC was inserted, which included thrombus that occurred in the superficial (SVT) or deep venous system (DVT) post PICC insertion. SVT was defined as occlusive thrombus in a superficial vein in which the PICC was inserted (basilic or cephalic veins). DVT included occlusive thrombus in the vein the PICC was inserted (if brachial) or if it extended into adjacent deep vasculature (axillary or subclavian veins). All cases were confirmed using ultrasound after clinical signs and symptoms triggered diagnostic testing whilst the PICC was still in situ or within 8 weeks of removal.

Ethical considerations

Ethics approval was obtained from the South Eastern Sydney Local Health District, Australia (HREC/17/POWH/174), Northern A Health and Disability Ethics Committee, New Zealand (17/NTA/264) and the University of South Australia (20026) Human Research Ethics Committees.

Power analysis:

A power analysis using PASS 11 (NCSS, UT, USA) determined that to achieve 80% power and 0.05 significance level, 2,140 participants were required. A test of two independent proportions was based on an expected increased risk of thrombus (RR=2.0) where 80% have a catheter to vein ratio ≤45% and are considered low risk with a 3% thrombus rate and 20% a ratio of ≥46% will be high risk with a 6% thrombus rate. That is 1,712 in the low risk group and 428 in the high risk group. These thrombus rates are based on previous research. [15] It was possible for a patient to be in the study more than once (PICC reinsertion/exchange).However, we expected this to be a small proportion of participants and the impact of clustering to be minimal.

Statistical Analysis Plan

Descriptive statistics were used to present information about the study population. CVRs were determined by dividing PICC diameter (stated diameter or tapered diameter) by vein diameter and multiplying by 100 to generate a percentage. The association between the CVR and the risk of thrombus was analysed using a log binomial generalised linear model. This analysis was performed with all participants and according to diagnostic group. The

same PICC design, with reverse taper capability was used in this study, but not all participants had the reverse taper portion inserted. As we were unsure about the accuracy of the PICC diameter (and hence CVR) of those with the tapered portion of the PICC inserted, analysis was repeated for those who didn't have the tapered portion of the PICC inserted. Receiver operator characteristic (ROC) analysis was used to plot the sensitivity and specificity of each ratio measurement using MedCalc for Windows, version 12.5 (MedCalc Software, Ostend, Belgium). The area under the curve (AUC) was used to identify the ideal CVR cut-off point with the aim to maximize sensitivity and specificity. All results with $p \leq 0.05$ were considered statistically significant.

RESULTS

There were 2,475 cases available, 37 were excluded due to missing data (11 with missing vein diameter and 26 missing diagnosis), leaving 2,438 PICC insertions in the analysis. Nearly equal numbers of participants were male and female (table 2), with a mean age of 59 years old (SD 17.09). Most participants did not have a history of central venous access device (CVAD) insertion and had a cancer diagnosis. Participants with a cancer diagnosis had three times the risk of thrombosis than those with an infection as an underlying diagnosis. Those with a solid tumour appeared to have higher risk of thrombosis than those with a haematological malignancy, however this was not statistically significant.

Table 2: Participant factors and risk of thrombosis in individuals with a PICC

Characteristic		Venous thrombosis			Univariate analysis		
		No (n=2399) n (%)	Yes (n= 39) n (%)	Total (n= 2438) n (%)	RR	95% CI	Sig¥
Gender	Female	1104 (98.13)	21 (1.87)	1125 (100)	1.00		
	Male	1294 (98.63)	18 (1.37)	1312 (100)	0.73	0.394-1.372	0.334
	Total	2398 (98.40)	39 (1.60)	2437 (100)			
Age (years)	19-45	457 (97.86)	10 (2.14)	467 (100)	1.00		
	46-65	946 (98.54)	14 (1.46)	960 (100)	0.68	0.304-1.521	0.349
	66-79	773 (98.35)	13 (1.65)	786 (100)	0.77	0.341-1.747	0.535
	80+	189 (98.95)	2 (1.05)	191 (100)	0.49	0.108- 2.210	0.353
	Total	2365 (98.38)	39 (1.62)	2404 (100)			
Previous CVAD	Y	718 (97.82)	16 (2.18)	734 (100)	1.61	0.858 -3.038	0.137
	N	1681 (98.65)	23 (1.35)	1704 (100)	1.00		
	Total	2399 (98.40)	39 (1.60)	2438 (100)			
Number of previous CVAD	0	1688 (98.48)	26 (1.52)	1714 (100)	1.00		
	1	534 (98.16)	10 (1.84)	544 (100)	1.21	0.588-2.496	0.602
	≥2	168 (98.25)	3 (1.75)	171 (100)	1.16	0.528-5.597	0.810
	Total	2390 (98.39)	39 (1.61)	2429 (100)			
Primary diagnosis^	Infection	859 (99.19)	7 (0.81)	866 (100)	1.00		
	Cancer	1285 (97.57)	32 (2.43)	1317 (100)	3.01	1.332- 6.779	0.008

	Other	255 (100)	0 (0)	255 (100)	-	-	-
	Total	2399 (98.40)	39 (1.60)	2438 (100)			
Malignancy type	Haematological	391 (98.49)	6 (1.51)	397 (100)	1.00		
	Oncological	285 (96.28)	11 (3.72)	296 (100)	2.47	0.924-6.606	0.071
	Total	676 (97.55)	17 (2.45)	693 (100)			

PICC= peripherally inserted central catheter; CVAD= central venous access device; ¥Based on log binomial generalized linear model; CI=confidence interval; RR=relative risk; ^As per treatment request

Most PICCs were inserted in the basilic vein in the right arm and required one needling attempt (table 3). Nearly equal numbers of single lumen (4Fr) and double lumen (5 Fr) PICCs were used. Most PICCs were verified using electrocardiogram (ECG), using a combination of securement devices and were inserted by staff with 3-5 years of experience. The infusion of chemotherapy was associated with nearly four times the risk of thrombosis.

Table 3: PICC insertion factors and risk of thrombosis

Characteristic		Venous thrombosis			Univariate analysis		
		No (n=2399)	Yes (n= 39)	Total (n= 2438)			
		n (%)	n (%)	n (%)	RR	95% CI	Sig¥
Arm	Left	491 (97.61)	12 (2.39)	503 (100)	1.71	0.871-3.347	0.119
	Right	1906 (98.60)	27 (1.40)	1933 (100)	1.00		
	Total	2397 (98.40)	39 (1.60)	2436 (100)			
Vein	Basilic	1861 (98.52)	28 (1.48)	1889 (100)	1.00		
	Brachial	403 (97.58)	10 (2.42)	413 (100)	1.63	0.800-3.336	0.178
	Cephalic	130 (99.24)	1 (0.76)	131 (100)	0.51	0.071-3.755	0.513
	Total	2394 (98.40)	39 (1.60)	2433 (100)			
Needling attempts	1	2029 (98.50)	31 (1.50)	2060 (100)	1.00		
	2	203 (98.54)	3 (1.46)	206 (100)	0.97	0.298-3.138	0.956
	3+	65 (100)	0 (0)	65 (100)			
	Total	2297 (98.54)	34 (1.46)	2331 (100)			
Catheter size (Fr) and lumen	4 (Single lumen)	1251 (98.82)	15 (1.18)	1266 (100)	1.00		
	5 (Double lumen)	1136 (97.93)	24 (2.07)	1160 (100)	1.75	0 .920-3.312	0.088
	6 (Triple lumen)	12 (100)	0 (0)	12 (100)	-	-	-
	Total	2399 (98.40)	39 (1.60)	2438 (100)			
Tip confirmation method	CXR	101 (98.06)	2 (1.94)	103 (100)	1.00		
	ECG	1480 (98.40)	24 (1.60)	1504 (100)	0.82	0.197-3.429	0.788
	Both	817 (98.43)	13 (1.57)	830 (100)	0.98	0.185-3.524	0.775
	Total	2398 (98.40)	39 (1.60)	2437 (100)			
Securement device	Adhesive	895 (98.35)	15 (1.65)	910 (100)	1.00		
	Subcutaneous	521 (97.75)	12 (2.25)	533 (100)	1.37	0.644-2.895	0.416
	Combination	977 (98.79)	12 (1.21)	989 (100)	0.73	0.346-1.564	0.426
	Other∩	5 (100)	0 (0)	5 (100)	-	-	-
	Total	2398 (98.40)	39 (1.60)	2437 (100)			
Staff years of experience	0	40 (100)	0 (0)	40 (100)	1.00		
	1-2	898 (98.25)	16 (1.75)	914 (100)	1.58	0.530-4.680	0.413
	3-5	1103 (98.31)	19 (1.69)	1122 (100)	1.52	0.522-4.450	0.441
	6+	356 (98.89)	4 (1.11)	360 (100)	-	-	-
	Total	2397 (98.40)	39(1.60)	2436 (100)			
Infusion^							
	Antibiotics/Antivirals	976 (99.29)	7 (0.71)	983 (100)	1.00		

Chemotherapy	1011 (97.31)	28 (2.69)	1039 (100)	3.78	1.660-8.623	0.002
Blood products	29 (100)	0 (0)	29 (100)	-	-	-
TPN	216 (99.08)	2 (0.92)	218 (100)	1.28	0.269- 6.159	0.751
Other[#]	167 (98.82)	2 (1.18)	169 (100)	1.66	0.348- 7.932	0.524
Total	2399 (98.40)	39 (1.60)	2438 (100)			

PICC= peripherally inserted central catheter; ¥Based on log binomial generalized linear model; CI=confidence interval; RR=relative risk; CXR=chest x-ray; ECG=electrocardiogram [∩] suture or glue; TPN=total parenteral nutrition [#]intravenous therapy, electrolytes, difficult access, frequent blood draws; ^As per treatment request, participants often had more than one listed, coded as chemotherapy if this was included in list

Cases of thrombosis

There were 39 cases of confirmed thrombosis, a rate of 1.6% (95% CI 1.14% - 2.19%). These comprised 13 cases of SVT (33%), 5 cases of DVT (13%) and 21 cases involving both the superficial and deep venous system (54%).

Catheter to vein ratio

Based on ROC analysis, the CVR was not an effective diagnostic variable when treated as a continuous variable. The area under the curve was close to 0.5 when the ROC analysis was performed using the entire sample and according to diagnostic group. As the models lacked diagnostic ability, we analysed the association between risk of thrombosis and CVR cut-offs commonly used in clinical practice.

All participants

As per table 4, a CVR cut-off of 33% did not appear to be associated with risk of thrombosis, whereas, a 45% cut-off (≤45% versus ≥46%) was predictive, with those with a higher ratio having more than twice the risk of thrombus (RR 2.30; 95% CI 1.202-4.383; p=0.01).

The analysis was repeated with participants who didn't have the tapered portion of the PICC inserted, that is, PICCs with an external length ≤6cm were excluded (table 5). This comprised 1,098 cases or 45% of the sample. Use of a CVR greater than 45% remained associated with more than twice the risk of thrombosis. When a 33% CVR cut-off was analysed, the use of a CVR higher than 34% appeared protective of thrombosis. However, neither of these results were statistically significant.

Table 4: Catheter to vein ratio and risk of thrombosis according to diagnosis in individuals with a PICC

		All PICCs					
		Venous thrombosis			Univariate analysis		
	Catheter to vein ratio	No (n=2399)	Yes (n= 39)	Total (n= 2438)	RR	95% CI	Sig¥
		n (%)	n (%)	n (%)			
All participants	≤33%	914 (98.39)	15 (1.61)	929 (100)	1.00		
	≥34%	1485 (98.41)	24 (1.59)	1509 (100)	0.99	0.519-1.867	0.963
	Total	2399 (98.40)	39 (1.60)	2438 (100)			
	≤45%	1935 (98.72)	25 (1.28)	1960 (100)	1.00		
	≥46%	464 (97.07)	14 (2.93)	478 (100)	2.30	1.202-4.383	0.012
	Total	2399 (98.40)	39 (1.60)	2438 (100)			
		No (n=1285)	**Yes (n= 32)**	**Total (n=1317)**			
		n (%)	n (%)	n (%)			
Cancer diagnosis	≤33%	361 (97.57)	9 (2.43)	370 (100)	1.00		
	≥34%	924 (97.57)	23 (2.43)	947 (100)	0.99	0.466-2.138	0.997
	Total	1285 (97.57)	32 (2.43)	1317 (100)			
	≤45%	943 (98.13)	18 (1.87)	961 (100)	1.00		
	≥46%	342 (96.07)	14 (3.93)	356 (100)	2.10	1.055-4.177	0.035
	Total	1285 (97.57)	32 (2.43)	1317 (100)			
		No (n=391)	**Yes (n=6)**	**Total (n=397)***			
		n (%)	n (%)	n (%)			
Haematological cancer diagnosis	≤33%	75 (98.68)	1 (1.32)	76 (100)	1.00		
	≥34%	316 (98.44)	5 (1.56)	321 (100)	1.18	0.140-9.986	0.877
	Total	391 (98.49)	6 (1.51)	397 (100)			
	≤45%	241 (99.18)	2 (0.82)	243 (100)	1.00		
	≥46%	150 (97.40)	4 (2.60)	154 (100)	3.16	0.585-17.023	0.181
	Total	391 (98.49)	6 (1.51)	397 (100)			
		No (n=285)	**Yes (n=11)**	**Total (n=296)***			
		n (%)	n (%)	n (%)			
Oncological cancer diagnosis	≤33%	51 (91.07)	5 (8.93)	56 (100)	1.00		
	≥34%	234 (97.50)	6 (2.50)	240 (100)	0.28	0.089-0.885	0.030
	Total	285 (96.28)	11 (3.72)	296 (100)			
	≤45%	169 (96.57)	6 (3.43)	175 (100)	1.00		
	≥46%	116 (95.87)	5 (4.13)	121 (100)	1.21	0.376-3.860	0.753
	Total	285 (96.28)	11 (3.72)	296 (100)			
		No (n=1114)	**Yes (n= 7)**	**Total (n=1121)**			
		n (%)	n (%)	n (%)			
Infection and other diagnoses^	≤33%	553 (98.93)	6 (1.07)	559 (100)	1.00		
	≥34%	561 (99.82)	1 (0.18)	562 (100)	0.17	0.020-1.372	0.096
	Total	1114 (99.38)	7 (0.62)	1121 (100)			
	≤45%	992 (99.3)	7 (0.7)	999 (100)	1.00		
	≥46%	122 (100)	0 (0)	122 (100)	-	-	-
	Total	1114 (99.38)	7 (0.62)	1121 (100)			

PICC= peripherally inserted central catheter; ¥Based on log binomial generalized linear model; CI=confidence interval; RR=relative risk;
^ infection requiring intravenous antibiotics or other non-cancer diagnosis with difficult venous access requiring patient controlled analgesia, intravenous fluid etc.* does not add up to total number due to missing data about cancer diagnosis

Effect of diagnosis on risk of thrombosis

Cancer

When only participants with cancer were included in the analysis, a 45% CVR cut-off was associated with twice the risk of thrombosis (RR 2.10; 95% CI 1.055-4.177; p=0.035), whilst the use of a 33% CVR cut-off was not associated with risk (table 4). Although not statistically significant, when analysis was repeated with participants without the tapered portion of the PICC inserted, a CVR of 34% or greater appeared protective and the use of a CVR more than 45% was also associated with increased risk of thrombosis (table 5).

We then separated those with malignancy according to cancer type (693 participants had this information recorded) and repeated the analysis. For those with a haematological diagnosis, a CVR greater than 34% was associated with slightly higher risk whilst a CVR greater than 45% was associated with more than 3 times the risk of thrombosis, although both results did not reach statistical significance. This analysis couldn't be repeated for those without the tapered portion of the PICC inserted in this group as there were no cases of thrombosis.

For those with a solid tumour, a CVR greater than 33% was associated with reduced risk of thrombosis and a CVR greater than 45% was associated with slightly elevated increased risk although the latter finding was not statistically significant. When the analysis was repeated for those who did not have the tapered portion of the PICC inserted, a CVR greater than 33% appeared protective, whilst a CVR higher than 45% was associated with more than 4 times increased risk, although the results did not reach statistical significance (table 5).

Infection

In participants with an infection or other non-cancer diagnosis, the association between a 45% cut-off and risk of thrombosis could not be analysed as none of the participants with a ratio of 46% and above developed thrombus (table 4). A 33% CVR cut-off appeared to be protective in this cohort, with those with a CVR higher than 34% having less risk of thrombosis, although this was not statistically significant. Similar results were found when only non-tapered PICCs were included in the analysis (table 5).

Table 5: Catheter to vein ratio and risk of thrombosis in non-tapered PICCs

		Venous thrombosis			Univariate analysis		
	Catheter to vein ratio	**No (n=1085)** n (%)	**Yes (n=13)** n (%)	**Total (n=1098)** n (%)	RR	95% CI	Sig¥
All participants	≤33%	563 (98.43)	9 (1.57)	572 (100)	1.00		
	≥34%	522 (99.24)	4 (0.76)	526 (100)	0.48	0.150-1.560	0.224
	Total	1085 (98.82)	13 (1.18)	1098 (100)			

	≤45%	1021 (98.93)	11 (1.07)	1032 (100)	1.00		
	≥46%	64 (96.97)	2 (3.03)	66 (100)	2.84	0.643-12.563	0.168
	Total	1085 (98.82)	13 (1.18)	1098 (100)			
		No (n=479) n (%)	**Yes (n=8)** n (%)	**Total (n=487)** n (%)			
Cancer diagnosis	≤33%	210 (97.67)	5 (2.33)	215 (100)	1.00		
	≥34%	269 (98.90)	3 (1.10)	272 (100)	0.47	0.115-1.962	0.303
	Total	479 (98.36)	8 (1.64)	487 (100)			
	≤45%	445 (98.67)	6 (1.33)	451 (100)	1.00		
	≥46%	34 (94.44)	2 (5.56)	36 (100)	4.18	0.874- 19.950	0.073
	Total	479 (98.36)	8 (1.64)	487 (100)			
		No (n=39) n (%)	**Yes (n=0)** n (%)	**Total (n=39)** n (%)			
Haematological cancer diagnosis	≤33%	19 (100)	0 (100)	19 (100)	1.00		
	≥34%	20 (100)	0 (100)	20 (100)	-	-	-
	Total	39 (100)	0 (100)	39 (100)			
	≤45%	38 (100)	0 (100)	38 (100)	1.00		
	≥46%	1 (100)	0 (100)	1 (100)	-	-	-
	Total	39 (100)	0 (100)	39 (100)			
		No (n=16) n (%)	**Yes (n=3)** n (%)	**Total (n=19)** n (%)			
Oncological cancer diagnosis	≤33%	6 (75)	2 (25)	8 (100)	1.00		
	≥34%	10 (90.91)	1 (9.09)	11 (100)	0.36	0.039-3.351	0.372
	Total	16 (84.21)	3 (15.79)	19 (100)			
	≤45%	15 (88.24)	2 (11.76)	17 (100)	1.00		
	≥46%	1 (50)	1 (50)	2 (100)	4.25	0.635-28.456	0.136
	Total	16 (84.21)	3 (15.79)	19 (100)			
		No (n=606) n (%)	**Yes (n=5)** n (%)	**Total (n=611)** n (%)			
Infection and other diagnoses^	≤33%	353 (98.88)	4 (1.12)	357 (100)	1.00		
	≥34%	253 (99.61)	1 (0.39)	254 (100)	0.35	0.040-3.125	0.348
	Total	606 (99.18)	5 (0.82)	611 (100)			
	≤45%	576 (99.14)	5 (0.86)	581 (100)	1.00		
	≥46%	30 (100)	0 (0)	30 (100)	-	-	-
	Total	606 (99.18)	5 (0.82)	611 (100)			

PICC= peripherally inserted central catheter; ¥Based on log binomial generalized linear model; CI=confidence interval; RR=relative risk;^ infection requiring intravenous antibiotics or other non-cancer diagnosis with difficult venous access requiring patient controlled analgesia, intravenous fluid etc; 1 participant had missing external length

DISCUSSION

We aimed to identify an optimal CVR cut-off for PICC insertion to prevent the risk of thrombosis. However, ROC analysis demonstrated that the CVR as a continuous measure was not an effective diagnostic variable overall, probably due to the low number of cases with higher CVRs. Hence, we analysed the risk of thrombosis associated with CVR cut-offs used in clinical practice.

A CVR greater than 45% was associated with twice the risk of PICC associated thrombosis when all participants were included in the analysis. When this analysis was performed according to diagnostic group, similar results were found in those with cancer. For those participants with malignancy, a CVR 45% cut-off was associated with more than twice the risk of thrombosis (RR 2.10; 95% CI 1.055-4.177; p=0.035). Although not statistically significant, this pattern continued when this was reanalysed with participants who did not have the reverse taper portion of the PICC inserted. Whereas the results for the 33% CVR cut-off were not statistically significant in these cohorts.

Neither the 33% or 45% CVR cut-off produced statistically significant results in those with infection or other non-malignant conditions. We found a thrombosis rate of only 0.8% in this cohort and the analysis of thrombosis risk for each CVR was limited by a low number of cases of thrombosis. It is difficult to compare our results to previous research as most includes a mixed cohort (with consumers with cancer who have increased risk of thrombosis) and don't report results separately. Where research does examine only those receiving a PICC for the treatment of infection, with no underlying malignancy, insertion decisions such as the CVR are not documented. Whilst the optimal CVR is not available for this cohort, we still recommend that a CVR limit is used until a more accurate estimate of risk is established.

The results from the present study suggest that the use of a CVR ≤45% is an important component in the strategies used during PICC insertion to reduce the risk of thrombosis in individuals with cancer requiring a PICC [16]. Thrombosis is a significant adverse event in consumers with cancer and is associated with increased morbidity and mortality. [17, 18] Factors such as the selection of an appropriate sized vein are especially important in the cancer patient cohort as larger, multi-lumen PICCs may be required which exacerbates thrombosis risk. These results support the use of a 45% CVR cut-off as advocated in the Infusion Nurses Society clinical guidelines (2016) and previous research that used ROC analysis to determine the optimal CVR cut-off. [15]

Our analysis of the risk associated with the CVRs used in clinical practice of those with haematological and oncological cancers separately should be interpreted with caution due to the

low numbers of cases. However, it may be that cancer type may influence risk. Previous research has found that those with a haematological cancer (Hodgkin lymphoma) experienced higher rates of PICC associated thrombosis than those with solid tumours. [19] Further research is required to determine PICC associated thrombosis risk according to cancer type generally and may consider investigating risk according to specific diagnosis. A more nuanced understanding of the risk of PICC associated thrombosis for individual consumers would allow clinicians to provided targeted interventions for those most at risk.

IMPLICATIONS FOR CLINICAL PRACTICE

This study indicates that the CVR should not exceed 45% for those with a cancer diagnosis. Whilst the optimal CVR for those with infection and other non-malignant conditions is inconclusive, the low thrombosis rate found in the present study supports the use of minimum vein size strategy for all individuals requiring a PICC. The minimum vein diameters needed to achieve ≤45% CVR are detailed in table 6. Many health consumers requiring a PICC will have a vein large enough for clinicians to adhere to these recommendations (we found that 80% of participants had a CVR ≤45%, which demonstrates that adherence to the INS recommendations is feasible in most cases).

However, some health consumers will require a larger multi-lumen device and may not have an appropriate vein to accommodate the larger catheter. This is problematic, especially in those with cancer who are at higher risk and the use of thromboprophylaxis may be considered. Some evidence suggests that thromboprophylaxis reduces the risk of symptomatic CVAD associated thrombosis in individuals with cancer. A Cochrane review [20], found that thromboprophylaxis (low-molecular-weight heparin) halved the risk of thrombosis for those with a CVAD (RR 0.43, 95% CI 0.22- 0.81). This meta-analysis was comprised of RCTs that included individuals with mostly solid tumours. Further research is needed in those with haematological malignancies. The use of thromboprophylaxis in individuals with haematological cancers also needs to be weighed against bleeding risk [21]. Yet, thromboprophylaxis is used in some haematological cancer groups e.g. consumers with multiple myeloma taking thalidomide [22]. An alternative vascular access device may also be considered for those most at risk. Research in individuals with cancer that has compared thrombosis risk according to different CVADs has found that PICCs were associated with more than 7 times the risk of thrombosis (HR 7.48, 95% CI 1.03-54.1, p=0.046) when compared to other non-tunnelled vascular access devices (central venous catheters), whilst implanted ports were associated with half the risk (HR 0.47 95% CI 0.03-7.90 p=0.597). [23] Although insertion

decisions such as the CVR are not documented in this research, perhaps large CVRs account for increased risk of thrombosis for those with a PICC.

Table 6:Minimum vein sizes to achieve ≤45% CVR

PICC size (fr)	Minimum vein size
4Fr	2.96 mm
5Fr	3.70 mm
6Fr	4.44mm

CVR=catheter to vein ratio

CVR with a tapered PICC

Our results indicate that clinicians who use a reverse taper PICC should be aware of the increased diameter of the taper and depending on vein size, increased risk of thrombosis should the taper be advanced into the vein. It is important to recognise the significant impact that the taper has on PICC diameter. For example, a 6Fr longer tapered PICC would be 8Fr at the hub or 2.67mm so to meet the 45% CVR cut-off, a vein would need to be 5.8mm in diameter rather than 4.5mm if it was inserted to the hub. To improve the accuracy of the PICC diameter for tapered PICCs when determining the CVR in clinical practice, clinicians could use the external length to determine the additional taper diameter as detailed in this study.

Alternatively, clinicians may avoid the use of the tapered part of the PICC by avoiding insertion of the taper. This will leave an external length of ≥7cm. Whilst increased external length may be thought to increase dislodgement rates, anecdotally, this has not been the case with clinicians in this study. Some sites have introduced a sub-cutaneous device to fix the PICC in place which provides additional security for those with longer external lengths.

LIMITATIONS

A limitation with this study was the inclusion of PICCs with reverse taper design and resulting imprecise diameter to inform the CVR. Whilst we developed an equation to determine the adjusted PICC diameter based on the external length this did not allow for the impact of subcutaneous tissue on this measurement. However, we expected this to have minimal impact on the overall CVR. Furthermore, we also presented analysis which only included non-tapered PICCs. There is a possibility that some participants presented to a regional hospital rather than the major

hospitals in this study with symptoms of thrombosis, hence, we would miss cases of thrombosis. However, we expected this to be unlikely as most would be managed by their treating team at the specialist centres in the hospitals where the study was conducted. A further limitation, as with all retrospective studies is the reliance on existing data which in this study was evident in problems with missing data. For example, although participants were allowed into the dataset more than once, missing data meant that clustering could not be allowed for. However, we expected this to be a small proportion of participants and the impact of clustering to be minimal.

CONCLUSION

This large study with over 2000 PICC insertions found a low rate of thrombosis which supports the use of this device to provide treatment for individuals with cancer and infection. The use of an appropriate vein size for PICC insertion is an important strategy to reduce PICC associated thrombosis in clinical practice. A CVR cut-off of 33% was not useful in predicting PICC-associated thrombosis in participants with cancer or other diagnoses. Our findings suggest that, in individuals with cancer, the CVR should not exceed 45%, although further prospective studies are required to make definitive conclusions. This cut-off was not associated with risk of thrombosis for those with an infection and other non-cancer diagnosis. Whilst further research is needed to determine the optimal CVR for those with infection, it is still recommended that the CVR is limited to reduce the risk of thrombosis.

Figure 1: 4 Fr reverse taper PICC (image author's own)

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Author statement

RS: contributions to conception and design, literature search, data analysis and interpretation, writing, final approval of the version to be published
PC, GJ: contributions to conception and design, data interpretation, writing, final approval of the version to be published.
AS, MY, TF, CK : contributions to conception and design, acquisition of data, data interpretation, writing, final approval of the version to be published.
AE, JC: contributions to conception and design, data analysis and interpretation, writing, final approval of the version to be published.

Funding statement
This work was supported by a Pathfinder grant from the University of South Australia, Adelaide, Australia (School of Nursing and Midwifery). Award/Grant number is not applicable. There was no conflict of interest, activities or potential for influencing this work by the funders. The grant organisation had no financial interest or role in the design, conduct, analysis or manuscript preparation for this project.

Competing interests
The authors declare that they have no competing interests

Data sharing statement
Data are available upon reasonable request from the corresponding author.

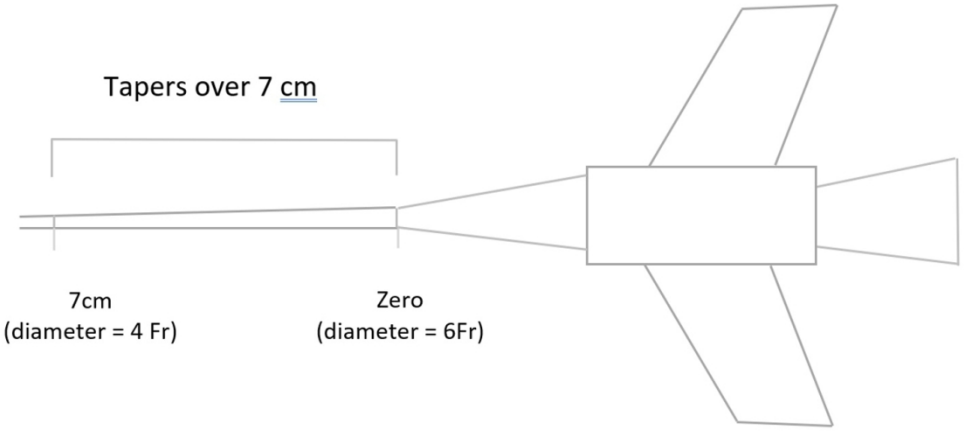

Figure 1: 4 Fr reverse taper PICC
(image author's own)

391x180mm (96 x 96 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4-5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-5
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5-6
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6-7
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	Report numbers of outcome events or summary measures over time	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-10
		(*b*) Report category boundaries when continuous variables were categorized	7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-12
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.