

# Incidence and Potential Risk Factors of Catheter Associated Thrombosis in Solid Tumors

Francisco José Pelegrín Mateo (✉ [fpelegrin.m@gmail.com](mailto:fpelegrin.m@gmail.com))

Hospital General Universitario de Elche <https://orcid.org/0000-0002-4340-9493>

Asia Ferrández Arias

Hospital General Universitario de Elche

Lucía Gómez González

Hospital General Universitario de Elche

Teresa Quintanar Verdúguez

Hospital General Universitario de Elche

Irene Belmonte Heredia

Hospital General Universitario de Elche

Jaime Belmonte Justamante

Hospital General Universitario de Elche

Pilar Calderón Gómez

Hospital General Universitario de Elche

María Carmen García García

Hospital General Universitario de Elche

Matilde Miguel Manzanera

Hospital General Universitario de Elche

Álvaro Rodríguez Lescure

Hospital General Universitario de Elche

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## Research Article

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# Abstract

## Purpose

Central venous catheters (CVCs) have become common practice in oncology. Besides their benefits, as an invasive procedure, several complications are associated with them. Catheter associated thrombosis (CAT) is one of the most relevant due to their impact in quality of life and mortality, but the prothrombotic risk factors implied have been poorly assessed.

The aim of the study is to evaluate the incidence of upper extremity deep vein thrombosis (UEDVT) associated to catheter use in patients with solid tumors. Secondary endpoints are to describe the population using CVCs and to evaluate potential risk factors of CAT.

## Methods

Patients diagnosed of solid tumors assisted at a tertiary level hospital between 2016 and 2019, and using CVCs were included.

## Results

455 patients were enrolled. The incidence of CAT was 5.49% (25) in the whole population. 5.05% (23) was associated with PICC while 0.44% (2) was due to PORT use. Among the factors included in the univariate and multivariate regression models, age  $\geq 50$  years and PORT use were identified as protective factors related to the development of CAT.

## Conclusion

CVCs remains a safe approach for the delivering of treatments in patients with solid tumors. Age  $\leq 50$  and use of PICC are risk factors for developing CAT. Larger prospective studies are needed to identify additional risk factors of CAT.

# Introduction

Central venous catheters (CVCs) are widely used in oncology for the administration of chemotherapy, blood products or parenteral nutrition. Their use reduces the need for frequent peripheral venipunctures for blood sampling. Evidence from the literature indicates that besides its benefits, using these devices carries some complications such as thrombosis, infection, or migration, among others.

One of the most diagnosed complications is catheter – associated thrombosis (CAT). Several risk factors associated with CAT have been identified: underlying malignancy (finding different incidences depending on the primary tumor), patients' comorbidities (abnormal renal function, obesity, coagulopathies), treatment – related [1] (use of blood transfusions, erythropoiesis or granulopoiesis-stimulating agents,

chemotherapy, directed therapies and combinations), type of catheter [2, 3] and the material [4] they are made of.

There is no unique definition of CAT. The most accepted is the formation of the clot in the vein where the catheter is placed [5]. Other proposed definitions are the formation of a clot on the tip of the catheter, the formation of a fibrin sleeve, the occlusion of the lumen or a superficial thrombosis of the vein used. While the latter definitions imply a less severe complications, the first one may develop pulmonary embolism or superior cava vein syndrome among others[6, 7].

In daily practice, the CVCs most used for cancer patients are peripherally inserted central catheters (PICCs) and totally implantable venous access ports (PORTs). Insertion of PORTs requires surgery, which is sometimes associated with major complications such as pneumothorax or hemorrhage following arterial malpuncture. PICCs are generally more accessible due to the possibility of insertion by trained nurses [8, 9] and lower cost, although literature addressing comparison between the two devices is scarce. A systematic review [3] evaluating differences between PICCs and other CVCs devices in general population, found no high-quality studies, only two with medium quality, and the results showed an increased incidence of deep vein thrombosis (DVT) in patients using PICCs, with decreased risk for catheter occlusion. Chopra et al [2] also found in their systematic review and meta – analysis an elevated risk of DVP when PICCs are used compared with other CVCs in the general population, especially when placed in patients with critical illness or cancer. Following this line, some studies have compared PICCs and PORTs in cancer patients and have found that PICCs are associated with an elevated risk of complications [10, 11], especially thrombosis but also occlusion, infection or mechanical problems, with no differences in cost [10].

Therefore, we conducted a retrospective single – centre cohort to describe CAT incidence in patients with solid tumors and the potential risk factors implicated.

## **Material & Methods**

The aim of this study is to evaluate the incidence of upper extremity deep vein thrombosis (UEDVT) associated to catheter use in patients with solid tumors. Secondary endpoints of our research are to describe the population treated using implantable devices and to explore risk factors of catheter associated thrombosis.

Patients with solid tumors attended at Elche's General Hospital and PICC or PORT carriers were included between January 1st, 2016 and December 31st, 2019. Variables included are summarized in 'Appendix 1'.

PICC were implanted by trained nurses within the Oncology Department, while PORTs were implanted by trained physicians from the ICU Department. Polyurethane was the material used. The diameters used for PICC were 4F and 5F depending on the caliber of the vein. The correct placement at the inferior third of the superior cava vein was checked by electrocardiography. The definition used for catheter associated thrombosis was the diagnose by image of the clot in the vessel where the catheter was placed.

A first analysis of missing data was performed. In addition, we conducted an analysis with logical, range and consistency tests to rule out errors in the variables collected.

We conducted a descriptive analysis stratifying by type of device. Proportions were used for the analysis of categorical data, while mean and standard deviation were calculated to describe quantitative variables. To detect differences in basal characteristics between groups,  $\chi^2$ , Fisher's exact and t – student tests were used as indicated. For the exploratory analysis of the potential risk factors, a logistic regression model was performed. Any clinical factors with a p value < 0.05 in the univariate analysis were included in the multivariate regression model. Statistical analysis was done using STATA version 14 (StataCorp LLC. Texas, USA).

The present research has been developed according to the Declaration of Helsinki (Fortaleza, Brasil, October 2013) and the Spanish Organic Law of Personal Data Protection (Ley Orgánica 3/2018, de 5 de diciembre, BOE 2018; 294, 6 de diciembre: 119788–119857).

## Results

A total of 455 patients were included, 292 PICCs and 163 PORTs. 64.18% (292) patients were women, while 35.82% (163) were men. Localized disease represented 50.77% (231) of cases, for the 48.57% (221) of advanced disease (3 patients missing). A full descriptive analysis of the total cohort is summarized in 'Table 1'.

Table 1  
Descriptive analysis by group of catheter used.

	Catheter	
	PICC	Port – a - Cath
<b>Edad (Md, SD)</b>	58.5 (12.9)	61.3 (11.8)
<b>Sex</b>		
Male	96 (21.1%)	83 (18.24%)
Female	196 (43.08%)	80 (17.58%)
<b>Use of catheter</b>		
Citotoxic Chemotherapy	222 (48.79%)	142 (31.21%)
Directed Therapy	5 (1.1%)	2 (0.44%)
Combination Chemotherapy – Directed Therapy	39 (8.57%)	13 (2.86%)
Nutrition	7 (1.54%)	0
Missing	19 (4.18%)	6 (1.32%)
<b>Smoking habit</b>		
Yes	97 (21.32%)	72 (15.82%)
No	190 (41.76%)	90 (19.78%)
Missing	5 (1.1%)	1 (0.22%)
<b>BMI (kg/m<sup>2</sup>)</b>		
Underweight (< 18.5)	7 (1.54%)	4 (0.88%)
Normal weight (18.5–24.9)	105 (23.08%)	56 (12.31%)
Overweight (25–29.9)	80 (17.58%)	64 (14.07%)
Obese (30–39.9)	65 (14.29%)	29 (6.37%)
Severe obesity (≥ 40)	6 (1.32%)	2 (0.44%)
Missing	29 (6.37%)	8 (1.76%)
<b>Previous thrombotic event</b>		
Yes	15 (3.3%)	10 (2.2%)
No	276 (60.66%)	153 (33.63%)
Missing	1 (0.22%)	0

	<b>Catheter</b>	
<b>Previous anticoagulation</b>		
Yes	26 (5.71%)	21 (4.62%)
No	265 (58.24%)	142 (31.21%)
Missing	1 (0.22)	0
<b>Type of anticoagulation</b>		
Acenocumarol	3 (6.38%)	3 (6.38%)
Warfarin	1 (2.13%)	0
Low – Molecular – Weight Heparin (LMWH)	19 (40.43%)	15 (31.91%)
Direct – Action Oral Anticoagulation	2 (4.26%)	2 (4.26%)
Missing	1 (2.13%)	1 (2.13%)
<b>Previous antiaggregation</b>		
Yes	16 (3.52%)	15 (3.3%)
No	275 (60.44%)	148 (32.53%)
Missing	1 (0.22%)	0
<b>Stage of disease</b>		
Localized	167 (36.7%)	64 (14.07%)
Advanced	122 (26.81%)	99 (21.76%)
Missing	3 (0.66%)	0
<b>Performance status (ECOG)</b>		
ECOG 1	83 (18.4%)	26 (5.71%)
ECOG 2	161 (35.38%)	113 (24.84%)
ECOG 3	13 (2.86%)	3 (0.66%)
ECOG 4	1 (0.22%)	0
Missing	3 (0.66%)	2 (0.44%)
<b>Concurrent use of GSCF</b>		
Yes	110 (24.18%)	60 (13.19%)
No	176 (38.68%)	98 (21.54%)
Missing	6 (1.32%)	5 (1.1%)

	Catheter	
<b>Concurrent radiotherapy</b>		
Yes	122 (26.81%)	25 (5.49%)
No	163 (35.82%)	135 (29.67%)
Missing	7 (1.54%)	3 (0.66%)
<b>Concurrent hormonal therapy</b>		
Yes	82 (18.02%)	8 (1.76%)
No	202 (44.4%)	149 (32.75%)
Missing	8 (1.76%)	6 (1.32%)
<b>Second cancer</b>		
Yes	24 (5.27%)	14 (3.08%)
No	253 (55.6%)	140 (30.77%)
Missing	15 (3.3%)	9 (1.98%)

The basal characteristics of the population were unbalanced for age, sex, use of catheter, smoking habit, cancer stage, concomitant radiotherapy, and concomitant hormonotherapy. The most represented cancers were breast cancer (24.84%), gastrointestinal (9.67%), lung (8.35%) and genitourinary (8.35%) for the PICCs' group, and gastrointestinal (27.47%) and breast cancers (4.18%) for the PORTs' group. Detailed information on the distribution by cancer location according to the type of device implanted is described in 'Figure 1' and 'Figure 2'.

Thromboembolic events were observed in 5.49% (25) of all patients. 5.05% (23) was associated with PICC while 0.44% (2) was due to PORT use. Low Molecular Weight Heparin (LMWH) was the first option to treat a thromboembolic event.

Regarding other complications of the use of central devices, 0.66% (3) of PICC presented with a dislodgement during their use. No dislodgement issues were observed with the use of PORTs. Infectious complications were observed in 2.2% (10) of the whole cohort, being more frequent with PICC (1.54% (7)) than with PORTs (0.66% (3)). The most frequently isolated microorganism was *staphylococcus epidermidis* (33.3%). *Staphylococcus aureus met icilin resistant* (16,7%), *meticilin sensible* (16.67%), *haemolyticus* (16.67%) and *hominis* (16.67%) were other microorganisms documented. No other complications derived from the use of PICCs or PORTs were documented.

The mean duration of use was 4.76 months (SD 3.75) for PICC and 19.45 months (SD 20.3) for PORTs. End of antineoplastic treatment was the most frequent reason to remove them (31.43%). Own initiative (0.88%), thrombosis (0.66%), migration (0.66%), infection (0.44%), unrelated fever (0.44%), phlebitis

(0.44%) and painful point of access (0.44%) were other causes of removal, whereas the majority of patients retain the catheters at the time of the present analysis.

Logistic regression model of potential risk factors is displayed in 'Table 2'. Both in the univariate and multivariate analyses age  $\geq$  50 and PORT were observed to have less risk of developing a thromboembolic event.

Table 2  
Univariate and multivariate regression models of risk factors.

	Univariable analysis		Multivariable analysis	
	Odds ratio	p	Odds ratio	p
<b>Age</b>				
< 50	1 (reference)		1 (reference)	
≥ 50	0.29	0.004	0.21	0.006
<b>Type of catheter</b>				
PICC	1 (reference)		1 (reference)	
Port – a – Cath	0.14	0.009	0.068	0.012
<b>Sex</b>				
Female	1 (reference)			
Male	0.86	0.726		
<b>Use of catheter</b>				
Citotoxic chemotherapy	1 (reference)			
Directed therapy	3.02	0.317		
Combination	1.51	0.468		
Nutrition	1			
<b>Smoking habit</b>				
No	1 (reference)			
Yes	1.31	0.512		
<b>BMI (kg/m<sup>2</sup>)</b>				
< 25	1 (reference)			
≥ 25	0.685	0.370		
<b>Creatinine</b>				
Cr < 1	1 (reference)			
Cr ≥ 1	0.54	0.405		
<b>Fibrinogen</b>				

**Appendix 1 – Variables included.**

	Univariable analysis	Multivariable analysis
< 500	1 (reference)	
≥ 500	0.87	0.778
<b>Leucocytes</b>		
< 11 000	1 (reference)	
≥ 11 000	0.351	0.312
<b>Platelets</b>		
< 450 000	1 (reference)	
≥ 450 000	1.03	0.969
<b>Stage of disease</b>		
Localized	1 (reference)	
Advanced	0.68	0.351
<b>Performance status (ECOG)</b>		
ECOG < 2	1 (reference)	
ECOG ≥ 2	0.77	0.674
<b>Use of GCSF</b>		
No	1 (reference)	
Yes	1.38	0.441
<b>Appendix 1 – Variables included.</b>		

## Discussion

Despite incidence of UEDVT in cancer patients using implantable devices has been reported from 0.3–28.3% [12, 13], there is a lack of data regarding this population [3]. In our study the incidence of UEDVT was 5.49% in the overall population, being 5.05% and 0.44% for PICC and Port – a – Cath, respectively. All the detected UEDVT were symptomatic at the time of diagnosis. These results are in accordance to the published literature.

Regarding the baseline characteristics of our population, the younger age of the patients in the PICC group might have confounded the association between age and increased risk of CAT. Being aware of the limitations of our study, the higher rate of concurrent radiotherapy or hormone therapy in the PICC group did not translate, as expected, into an increased risk of CAT. On the contrary, the lower proportion of non – smokers among PICC users could have diluted the effect of smoking as a risk factor for thrombosis.

Features related to the type and treatment of the disease have been identified as risk factors, such as lymphoma, metastatic disease and use of chemotherapy, radiotherapy or erythropoiesis – stimulating agents[14–18]. None of them reached statistical significance on our univariate or multivariate regression models. Due to a small sample size and to the inaccuracy it would have implied, we did not analyze the impact of each type of cancer on the primary endpoint. There were no differences in the type of treatment administered through the catheter. To our knowledge, this is the first study in exploring the relation between non – cytotoxic therapy and CAT.

Malposition, hospitalization, infection, body mass index > 25 and therapeutic dose anticoagulation also have been reported as increased risk factors to develop UEDVT in patients with cancer using PICC[15, 17–20]. This was not appreciated in our research. Of note, as a retrospective study, an ultrasound doppler to detect malposition was not performed regularly in the follow – up, as it is not a standard in daily practice.

There are several limitations with our study. It is a retrospective single – center study, so the results may not be applicable to other institutions. The retrospective character of the study difficulted the access to the complete information of the variables assessed. Due to the small sample size we were not able to evaluate the association with the type of cancer or chemotherapy scheme, as it would not have been assessable. The higher proportion of breast cancer in the PICC group, added to the lower age of this population, might have translated into confounding results. Finally, the diagnosis of asymptomatic UEDVT might have been underestimated because a regular ultrasound at the time of removal was not performed.

In conclusion, the use of PICC in patients with solid cancers implies an elevated risk of catheter associated thrombosis compared to Port – a – Cath. Overall, it remains a safe approach for delivering treatment to this population. There is an unmet need to identify the risk factors associated to it.

## **Declarations**

### **Conflict of Interest**

None declared.

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**Conflicts of interest/Competing interests.** None.

**Availability of data and material.** Not applicable.

**Code availability.** Not applicable.

**Authors' contributions.** All authors affirm that they have contributed substantially to the design of the study, acquisition, analysis and interpretation of data, as well as the elaboration of the manuscript. All

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**Ethics approval.** Approval from Clinical Research Ethics Committee of General University Hospital of Elche.

**Consent to participate.** Approval from Clinical Research Ethics Committee of General University Hospital of Elche for exemption of the consent to participate due to the retrospective character of the study and the high death rate of the population included.

**Consent for publication.** Approval from Clinical Research Ethics Committee of General University Hospital of Elche.

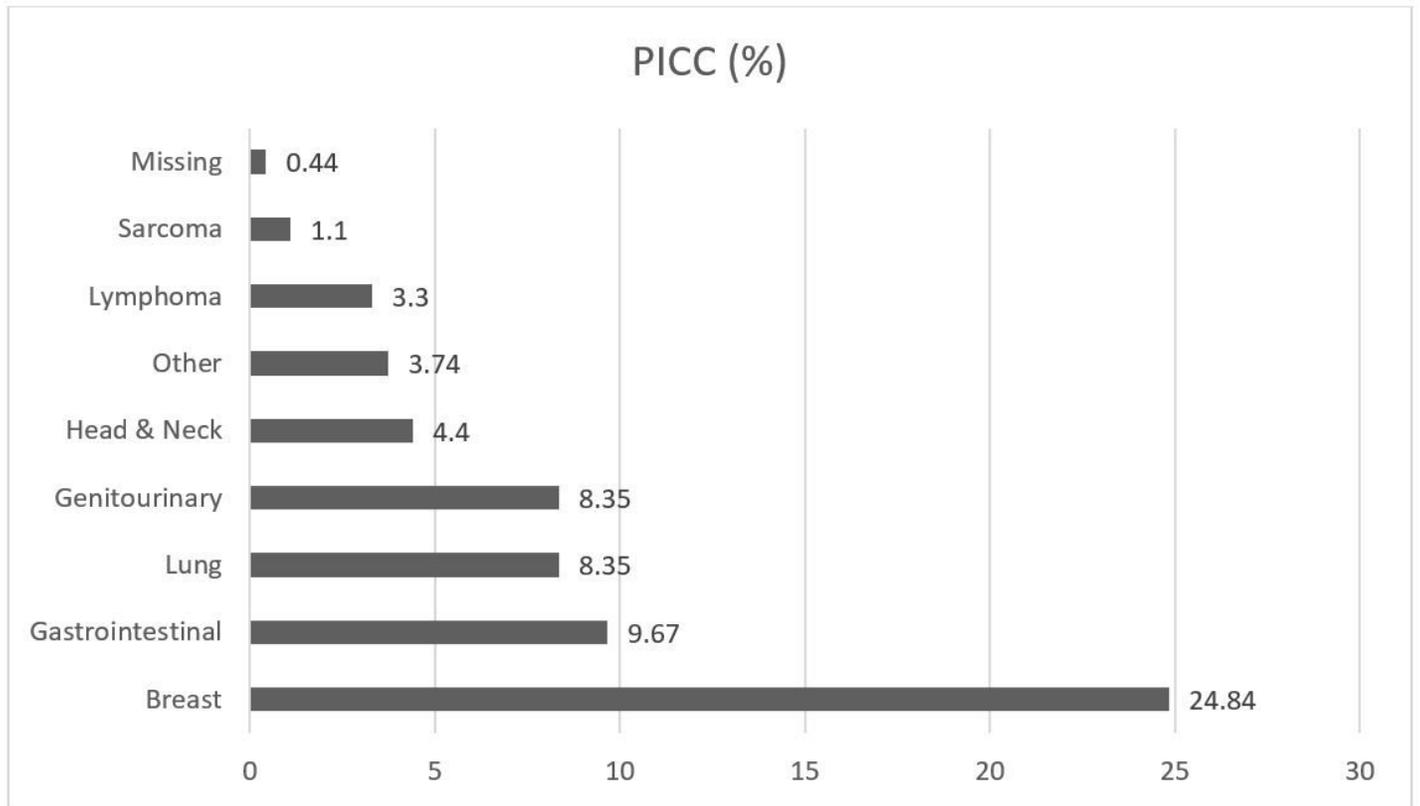
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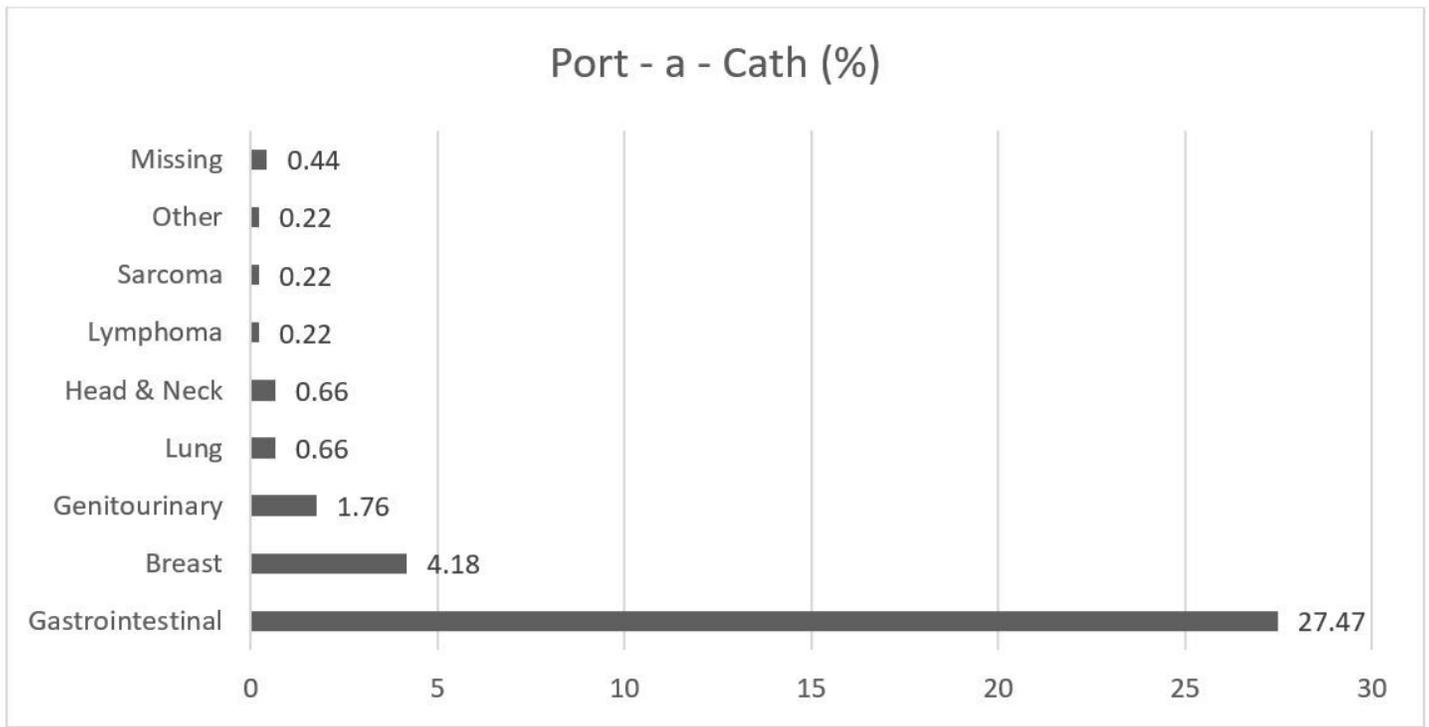
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## Figures



**Figure 1**

Distribution by cancer location in PICC's patients group.



**Figure 2**

Distribution by cancer location in Port – a – Cath’s patients group.