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Risk Factors of Catheter-Related Thrombosis (CRT) in Cancer Patients: A Patient-Level Data (IPD) Meta-Analysis of Clinical Trials and Prospective Studies

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Running Head: CRT in Adult Cancer Patients.

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SUMMARY

Background: Knowledge of independent, baseline risk factors of catheter-related thrombosis (CRT) may help select adult cancer patients at high risk to receive thromboprophylaxis.

Objectives: We conducted a meta-analysis of individual patient-level data to identify these baseline risk factors.

Patients/Methods: MEDLINE, EMBASE, CINAHL, CENTRAL, DARE, Grey literature databases were searched in all languages from 1995-2008.

Prospective studies and randomized controlled trials (RCTs) were eligible. Studies were included if original patient-level data were provided by the investigators and if CRT was objectively confirmed with valid imaging.

Multivariate logistic regression analysis of 17 prespecified baseline characteristics was conducted. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were estimated.

Results: A total sample of 5636 subjects from 5 RCTs and 7 prospective studies was included in the analysis. Among these subjects, 425 CRT events were observed. In multivariate logistic regression, the use of implanted ports as compared with peripherally implanted central venous catheters (PICC), decreased CRT risk (OR = 0.43; 95% CI, 0.23-0.80), whereas past history of deep vein thrombosis (DVT) (OR = 2.03; 95% CI, 1.05-3.92), subclavian venipuncture insertion technique (OR = 2.16; 95% CI, 1.07-4.34), and improper catheter tip location (OR = 1.92; 95% CI, 1.22-3.02), increased CRT risk.

Conclusions: CRT risk is increased with using PICC catheters, previous history of DVT, subclavian venipuncture insertion technique and improper positioning of the catheter tip. These factors may be useful for risk stratifying patients to select those for thromboprophylaxis. Prospective studies are needed to validate these findings.

Keywords: Catheter-related thrombosis; risk factors; meta-analysis; cancer; thromboprophylaxis; adults.

INTRODUCTION

Indwelling central venous catheters (CVCs) are widely used to facilitate treatment in cancer patients. It is estimated that in the United States more than 5 million CVCs are inserted annually, with a significant proportion being used in cancer patients[1, 2]. These devices have revolutionized clinical practice and resulted in major improvements in the quality of care. Importantly, CVCs allow administration of intravenous therapy at home, thereby improving patients' quality of life and reducing health care costs. However, these benefits come with a price. Many complications have been associated with the use of these devices, including catheter-related thrombosis (CRT), infection and other serious consequences[1, 3].

The event rate of symptomatic CRT varies widely among studies, with earlier studies reporting risk as high as 28%, while more recent studies report a much lower risk, generally 5% or less[4-10]. It is estimated that symptomatic CRT represents only one third of all CRT events; the clinical significance of asymptomatic CRT remains uncertain[1]. CRT can delay the administration of chemotherapy, increase the risk of systemic infections, and lead to pulmonary embolism (PE)[11-15]. Treatment of CRT exposes patients to the hazards of anticoagulant therapy.

Observational studies have attempted to elucidate risk factors of CRT. However, the data have often been limited by small sample sizes, and heterogeneity in their outcomes definitions as well as in the patient populations studied[16]. Furthermore, the use of prophylaxis is often unspecified and uncontrolled in these studies, leading to more uncertainty about the true incidence of CRT and the true benefits of anticoagulant prophylaxis.

Although some early studies showed dramatic reductions in CRT with low dose warfarin or low molecular weight heparin (LMWH) [7, 17, 18], recent clinical trials [4, 5, 10, 19] did not show any benefit in terms of reducing symptomatic or asymptomatic events. Reasons for this discrepancy may include differences in catheter materials and design, outcome ascertainment and lack of statistical power[16].

Identifying independent risk factors of CRT would provide a basis for individualized therapy. For example, anticoagulant prophylaxis could be limited to patients with a high risk of thrombosis, thereby sparing those with a low risk the potential harm associated with anticoagulation. We performed a meta-analysis using individual patient-level data from prospective studies to identify clinical baseline risk factors that would be useful in risk stratifying patients for development of CRT.

METHODS

Data Sources and Searches

We searched the following databases: MEDLINE, EMBASE, CINAHL (Cumulative Index to Nursing and Allied Health), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), and the Grey literature databases (The New York Academy of Medicine-Grey Literature Report; MetaLib; Scientific meetings databases, which include American Society of Hematology and American Society of Clinical Oncology; and Google scholar). We also consulted experts in the field to identify additional studies.

We used the following search terms: *Central venous catheterization (text and MeSH) AND thrombosis, thromboembolism (text and MeSH) NOT haemodialysis, renal dialysis, hemodialysis, dialysis (text and MeSH) AND cohort studies clinical trials, longitudinal studies, prospective studies (text, MeSH, Publication type) AND 1995-2008.*

The MEDLINE electronic component of the search was updated on a daily basis between May 2007 and March 2008.

Study Selection

The title and abstract were used to select for articles to be invited for participation. A study was eligible for the analysis if it met all the following inclusion criteria: (1) an observational prospective cohort study or randomized clinical trial; and (2) published between 1995 and March 1, 2008. Studies were excluded if they met any one of the following exclusion criteria: (1) conducted mainly in children < = 18 years of age; (2) dealt mainly with fibrin sheath formation, or intraluminal thrombosis of CVCs, and not with catheter-related deep vein thrombosis (DVT); (3) included mainly non-cancer patient populations

(e.g. hemodialysis patients); (4) enrolled less than a total of 100 subjects; (5) did not use objective testing to confirm a diagnosis of CRT; (6) were duplicate publications containing data reported in later studies. Once the study selection was complete, authors of the publications were invited to collaborate and forward primary data for analysis. A study was not included in the analysis if a response was not received after two reminders were sent to the investigator.

Data Extraction and Verification

The investigators were asked to provide primary data on the following baseline variables on each subject: Age, sex, type of cancer, cancer stage, type of cancer therapy given, type of catheter, insertion side, insertion site, number of lumen, size of catheter, location of catheter tip, prophylactic anticoagulation use, number of attempts or a grade of difficulty of insertion, baseline platelet count, history of previous thrombosis, previous catheter insertion, and estrogen exposure in the form of oral contraceptive pills or hormone replacement therapy at the time of catheter insertion, and whether CRT developed or not.

We collected data from the publications on the following variables: duration of follow-up in each study, type of radiographic evaluation used to detect CRT in each study, and whether the study was designed to evaluate only symptomatic CRT vs. total CRT (symptomatic and asymptomatic).

One author (W.S.) evaluated the data from each study and compared the data with the publication for completion. Any discrepancy was resolved through discussion with the investigator.

Quality Assessment

Two authors (W.S. and T.M.) independently and in duplicate evaluated the methodological quality of the different studies using criteria described by Jadad et al. [20] for randomized clinical trials, and using the Newcastle-Ottawa Scale by Wells et al. [21] for nonrandomized prospective cohort studies. This quality assessment was not used to weigh the studies differently during the analyses.

Data Synthesis and Analysis

For subjects who received more than one catheter during the course of any of the studies [8, 22, 23], only outcomes observed while they had their first device in place were evaluated in this project. If the

study had data on cancer and non-cancer subjects[24], we only used the data reported on the cancer subjects.

CRT was treated as a binary outcome. All the risk factors were treated as categorical and dummy variables were created for each category. A separate category was created for missing data for each variable, and a dummy variable was created for this category and was included in the regression analyses. This category [missing data category] was never chosen to be the referent group for any of the analyses.

We conducted an unconditional multivariate logistic regression including all the prespecified baseline factors. We were unable to conduct a conditional logistic regression because some studies did not collect data on several variables that we adjusted for. The risks for CRT were expressed as odds ratios (OR), with corresponding 95% confidence intervals (CI).

For any risk factor that was significantly associated with CRT in the multivariate model, we assessed whether the association between this risk factor and CRT varied significantly between studies; this was accomplished by creating an interaction term between the risk factor and a variable that indicated study membership. Univariate logistic regression was employed for this analysis.

We plotted a freedom from CRT survival curve for the entire sample using the Kaplan-Meier method. Survival data were lacking from several studies, so we were unable to account for potential competing risks.

All statistical tests were two sided, and *P* values less than .05 were considered statistically significant. All analyses were conducted using SAS version 9.1.

IRB Approval

This project was submitted to the University of Wisconsin Institutional Review Board and was exempted from full review. The contributing co-authors obtained approval from their local IRBs in accordance with their local guidelines.

Results

Studies that were identified

Our search identified two hundred and forty one references in MEDLINE, eight references in EMBASE, and ten abstracts. Forty four references (40 papers and 4 abstracts) met our eligibility criteria (Figure 1). Twenty-two investigators in 7 countries agreed to participate. We were not able to use data from 5 of the studies because of various technical difficulties (missing data code for 2 studies; obsolete software for 3 studies). We received the data for one study[25] after closure of the database and completion of the analysis; therefore, results from this study were not included in the current analysis. Three reports were based on the same participants; data from one of these three reports were used. Data for 2 studies could not be retrieved. Hence, the current results represent the pooled data from 12 studies [4, 8-10, 19, 22-24, 26-29].

Baseline characteristics of the Studies and Patient Sample

Table 1s (online only) summarizes some of the key features of the 12 studies. Five were randomized clinical trials and seven were prospective cohort studies. Nine studies included subjects with solid as well as hematologic malignancies; whereas in three studies only subjects with either solid or hematologic malignancies were included. Only five studies included all three types of central venous catheters. The primary outcome in 8 studies was clinically overt, symptomatic CRT. In most studies no routine screening for thrombosis was performed. Median duration of follow up among 11 studies ranged between 15 days and 237 days; one study reported a maximum duration of follow up of 530 days. Ultrasonography and venography were the diagnostic modalities most frequently used to confirm a diagnosis of CRT. The sample sizes ranged between 100 and 1533 subjects.

Table 1 summarizes the main characteristics of the patient sample used for the analysis. By pooling all 12 studies, a total of 5636 subjects with 425 CRT events were observed. The median age was 59 years (interquartile range [IQR] 50-67). There were roughly equal proportions of men and women. The most frequent type of catheter used was the chest wall external central venous catheter (including tunneled and non-tunneled), followed by implanted ports; PICC catheters were the least frequent type

used (15%). Most (60%) subjects did not have a history of deep vein thrombosis. Single lumen catheters were placed in 76% of patients and 55% of the insertions placed the catheter tip at the junction between superior vena cava and right atrium. The majority (80%) of patients had solid tumors, 60% had advanced disease and 75% were receiving chemotherapy. The proportion of the subjects who received any form of thromboprophylaxis was roughly equal to the proportion who did not receive any form of thromboprophylaxis, at 45%. Data were not available in 50% or more of patients for the following variables: site of insertion; difficulty of the insertion procedure; history of catheter placement; baseline platelet count; and use of estrogen products. The main reason for missing data was that not all of the studies collected data on all of the seventeen variables that were examined in this analysis.

Assessment of the Quality of Studies

Table 2s (online only) summarizes the independent assessment of the quality of the 12 studies. Overall, the quality of the randomized clinical trials ranged from very good to excellent with no study having a JADAD score of less than 3.

For the cohort studies, two studies had relatively short follow-up duration [23, 24] and one study did not report on the adequacy of follow-up [28]. Otherwise, all the studies met the assessment criteria for non-randomized cohort design.

Results of the Multivariate Logistic Regression Analysis

Table 2 summarizes the results of the multivariate logistic regression analysis. All 17 prespecified risk factors were included in the multivariate model. The following variables were significantly associated with a higher CRT risk: (1) Subclavian vein insertions compared to upper arm veins insertions (OR 2.16; 95% CI 1.07-4.34); (2) previous history of deep vein thrombosis (OR 2.03; 95% CI 1.05-3.92); (3) catheter tip positioned more proximal than the junction between SVC and RA (OR 1.92; 95% CI 1.22-3.02). Only one variable was significantly associated with lower CRT risk: implanted ports when compared to PICC catheters were associated with a roughly 60% relative risk reduction (RRR) (OR 0.43; 95% CI 0.23-0.80). Chest wall external CVCs were also associated with 40% RRR as compared with PICC catheters, but this failed to reach statistical significance (OR 0.60; 95% CI 0.33-1.10).

A number of risk factors were associated with a higher risk of CRT, but none reached statistical significance. These include: (1) higher lumen number; (2) technically difficult procedures; (3) lack of thromboprophylaxis; (4) estrogen exposure; and (5) left sided insertions; see also Table 3s (online only).

Heterogeneity Assessment

Table 4s (online only) summarizes the results of the analysis of heterogeneity of the associations between catheter type, proper catheter positioning, prior history of deep vein thrombosis, site of insertion, and CRT. The only association that varied significantly between studies was the association between proper catheter positioning and risk of CRT.

Kaplan-Meier Survival Analysis of CRT

Figure 2 displays the freedom from CRT survival curve based on the Kaplan-Meier method. The median duration of follow up of CRT-free subjects was 133 days (interquartile range (IQR), 51-248 days). Most events occurred during the first 100 days of follow up. The cumulative incidence of CRT is 8.5% at 6 months, 10% at 1 year, and 12% at 2 years. The median number of days between catheter insertion and CRT was 15 days (IQR, 8-47).

Discussion and Conclusions

This study is the first individual patient-level data meta-analysis designed to identify baseline patient- and catheter-related risk factors of CRT in patients with cancer. Based on prospectively collected data on 5636 patients with 425 CRT events in 12 studies conducted between 1995 and 2008, we found that a history of deep vein thrombosis, subclavian venipuncture site, and improper catheter tip location increased the risk of CRT. Furthermore, the risk of CRT was higher in patients with PICC catheters than in those with implanted port devices.

Because CRT is an important complication of indwelling central venous catheters, prophylaxis with anticoagulants has been recommended previously. However, contemporary randomized controlled trials evaluating warfarin and low molecular weight heparin prophylaxis have failed to show a reduction in symptomatic events [4, 5, 10, 19]. Furthermore, given that the rate of symptomatic CRT is low at 5%[1], the most recent American College of Chest Physicians Consensus Guidelines in 2008 advised

against the routine use of anticoagulant prophylaxis to prevent CRT[30, 31]. It seems likely, however, that selecting patients at higher risk of CRT to receive prophylaxis would be beneficial and useful. Unfortunately, previous studies have lacked the power to identify risk factors with certainty because of low event rates and small sample sizes, among other limitations. Individual patient-level data meta-analysis offers an opportunity to enhance statistical power using information that is already available. This is particularly efficient for studying uncommon events.

Our findings confirm those in previous studies. A history of venous thrombosis has been reported to predict for future episodes of thrombosis; this may indicate the patient is predisposed because of familial or acquired thrombophilia [1, 16, 24]. Subclavian venipuncture site has been associated with a higher risk of CRT in a number of papers [16]. This may be due to anatomical or technical factors. Improper position of the catheter tip has also been associated with increased risk of CRT [1, 16]. Having the tip at the junction of the SVC and right atrium may be protective because of a greater dilutional effect when vasculotoxic agents are infused, or because there is a lower likelihood that the tip of the catheter will be in direct contact with the endothelium. Finally, implanted port devices may be associated with a lower risk of CRT than PICC because of a lower incidence of infection (which in turn can lead to thrombosis), or because the shorter catheter track with port devices reduces endothelial trauma. A retrospective study in patients with hematologic malignancies demonstrated in multivariate analysis that CRT risk was higher with the use of PICC catheters as compared with centrally inserted catheters[32]. Whether bedside insertion of PICC, a frequent practice at most centers, leads to more complications than insertion of devices under radiologic imaging guidance has not been established. The potential mechanisms proposed here warrant study and validation.

Our project has several strengths. Our search strategy was comprehensive. Our sample is large and widely representative and increases the external validity of our results. We excluded studies published prior to 1995 because changes in catheter design, material, insertion techniques, post-insertion catheter care, and diagnostic imaging accuracy would likely introduce significant heterogeneity and the results would not be relevant for contemporary practice. We excluded studies with fewer than 100

patients due to the limited number of CRT events in each study. We included asymptomatic cases if they were objectively confirmed because the risk factors are likely the same for symptomatic and asymptomatic events. Given that we only had 4 studies that included symptomatic and asymptomatic events, a sensitivity analysis that is restricted to this group would have been extremely limited with regard to its sample size and power; therefore, this analysis was not conducted.

Our data should be interpreted in the context of the following limitations. First, several variables had large amount of missing data. Second, the low 1-year and 2-year event rates limited our ability to assess heterogeneity. Third, although we adjusted for many confounders, there are other potential confounders that were not controlled for **due to lack of data**; for e.g., we did not have data on the use of certain well known prothrombotic antineoplastic agents (e.g., lenalidomide and thalidomide [33]), nor did we have detailed data on the schedule of chemotherapy (e.g. infusion or blous) or the type of chemotherapy that was used (e.g. sclerosing vs. nonsclerosing); the latter property was shown to be an important predictor of CRT[7]. Similarly, we were unable to adjust for exact type of cancer (only whether it was solid or hematologic), or the presence of familial thrombophilia (it has been reported that factor V Leiden and prothrombin G20210A mutation status are significant predictors of CRT[24, 34, 35]). Fourth, variable duration of follow up and inconsistent reporting of survival data limited our ability to account for competing events and may have limited our ability to accurately estimate the true incidence of CRT over time. Fifth, inability to obtain primary data from all studies that met our eligibility criteria. Due to the limitations listed above, our findings should be viewed as exploratory and require validation.

In conclusion, we identified four independent risk factors of CRT using individual patient level data from prospective studies. Validation of the results could lead to the development of risk stratification models that will help to tailor prophylaxis therapy in cancer patients with indwelling central venous catheters.

Authorship Addendum:

All of the following authors provided patient-level data, assisted in study design, revised and approved the manuscript:

M. Verso, G. Agnelli, S. Couban, A. Young, M. De Cicco, R. Biffi, C. J. van Rooden, M. V. Huisman, D. Fagnani, C. Cimminiello, M. Moia, M. Magagnoli, S. P. Povoski, S. Malak.

E. C. Williams and T. Moua assisted in the study design, data collection, and manuscript writing.

W. Saber and A. Y. Lee conceived the idea of the project, designed the study, performed the statistical analyses, and wrote the manuscript. A.Y. Lee also provided patient-level data.

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Table 1. Baseline characteristics of all participants and according to their CRT status.

Variable	All Participants	According to CRT status	
		No CRT	With CRT
Age, yr			
Median (IQR)	59 (50-67)		
Age, yr – no. (%)*			
< 60 yr	2877 (51)	2641 (51)	236 (56)
≥ 60 yr	2757 (49)	2568 (49)	189 (44)
Missing	2	2	0
Sex – no. (%)*			
Male	2881 (51)	2675 (51)	206 (48)
Female	2747 (49)	2528 (49)	219 (52)
Missing	8	8 (0.15)	0
Type of Catheter – no. (%)*			
PICC	875 (15)	836 (16)	39 (9)
CVC†	2523 (45)	2304 (44)	219 (52)
Implanted Ports	1904 (34)	1788 (34)	116 (27)
Missing	334 (6)	283 (5)	51 (12)
Insertion Site – no. (%)*			
Upper arm Veins	808 (14)	772 (15)	36 (8)
Subclavian Vein	1447 (26)	1210 (23)	237 (56)
Internal Jugular Vein	413 (7)	389 (7)	24 (6)
Others	22 (0.4)	22 (0.4)	0 (0)
Missing	2946 (52)	2818 (54)	128 (30)
Past Medical History of DVT			
Present	131 (2)	117 (2)	14 (3)
Absent	3387 (60)	3096 (59)	291 (68)
Missing	2118 (38)	1998 (38)	120 (28)
Catheter Size – no (%)*			
< 6.5 French	1946 (35)	1849 (35)	97 (23)
≥ 6.5 French	1871 (33)	1625 (31)	246 (58)
Missing	1819 (32)	1737 (33)	82 (19)
Lumen Number – no. (%)*			
Triple	33 (0.59)	31 (0.6)	2 (0.5)
Double	570 (10)	531 (10)	39 (9)
Single	4310 (76)	4028 (77)	282 (66)
Missing	723 (13)	621 (12)	102 (24)

Table 1. Continued.

Variable	All Participants	According to CRT status	
		No CRT	With CRT
Grading of technical difficulties during Catherer insertion – no. (%)*			
Easy	1300 (23)	1256 (24)	44 (10)
Difficult	213 (4)	203 (4)	10 (2)
Missing	4123 (73)	3752 (72)	371 (87)
Past History of Catheter Insertion – no. (%)*			
Present	171 (3)	149 (3)	22 (5)
Absent	1716 (30)	1466 (28)	250 (59)
Missing	3749 (67)	3596 (69)	153 (36)
Baseline Platelet Count – no (%)*			
< 100 K/uL	219 (4)	212 (4)	7 (2)
100-499 L/uL	1863 (33)	1642 (32)	221 (52)
≥ 500 K/uL	99 (2)	91 (2)	8 (2)
Missing	3455 (61)	3266 (63)	189 (44)
Catheter Tip Location at the Junction between SVC and RA or in RA – no. (%)*			
Yes	3082 (55)	2846 (55)	236 (56)
No	547 (10)	511 (10)	36 (8)
Missing	2007 (36)	1854 (36)	153 (36)
Any form of Thromboprophylaxis given – no. (%)‡			
Yes	2545 (45)	2337 (45)	208 (49)
No	2460 (44)	2270 (44)	190 (45)
Missing	631 (11)	604 (12)	27 (6)
Current or Recent Exposure to Estrogen (OCP or HRT) – no. (%)*			
Yes	30 (1)	22 (0.4)	8 (2)
No	410 (7)	360 (7)	50 (12)
Missing	5196 (92)	4829 (93)	367 (86)

Table 1. Continued.

Variable	All Participants	According to CRT status	
		No CRT	With CRT
Cancer Stage – no. (%)			
Early	1381(24.5)	1257 (24)	124 (29)
Advanced	3448 (61)	3214 (62)	234 (55)
Missing	807 (14)	740 (14)	67 (16)
Anticancer Therapy – no. (%)*			
Only Chemotherapy	3981 (71)	3663 (70)	318 (75)
Combined Chemoradiotherapy	234 (4)	222 (4)	12 (3)
Only Radiotherapy	80 (1)	79 (2)	1 (0.2)
No therapy	718 (13)	693 (13)	25 (6)
Missing	623 (11)	554 (11)	69 (16)
Disease Type – no. (%)*			
Hematologic Cancers	937 (17)	864 (17)	73 (17)
Solid Cancers	4561 (81)	4218 (81)	343 (81)
Others	37 (0.6)	35 (1)	2 (0.4)
Missing	101 (2)	94 (2)	7 (2)
Side of Catheter Insertion – no. (%)*			
Right	2272 (40)	2030 (39)	242 (57)
Left	1097 (19)	981 (19)	116 (27)
Missing	2267 (40)	2200 (42)	67 (16)
Total – no (%)*	**5636 (100)**	**5211 (92.46)**	**425 (7.54)**

Abbreviations: CRT, catheter-related thrombosis; IQR, interquartile range; PICC, peripherally implanted central catheter; CVC, central venous catheter; DVT, deep vein thrombosis; SVC, superior vena cava; RA, right atrium; OCP, oral contraceptive pills; HRT, hormone replacement therapy.

* The sum of the percentages may not equal 100 percent due to rounding errors.

†Include Hickman catheters and non-tunneled catheters.

‡Include Antiplatelet agents; prophylactic doses of unfractionated heparin and low molecular weight heparin, minidose warfarin (1 mg daily) and dose adjusted warfarin (target International Normalized Ratio (INR), 1.5-2).

Table 2. Adjusted Odds Ratios of Risk Factors of CRT.*

Variable	Multivariate Analysis	
	Odds Ratio (95% CI)	**P Value**
Type of Catheter		
PICC	1 [Reference]†	
Chest wall external CVC	0.60 (0.33-1.10)	.10
Implanted Port	**0.43 (0.23-0.80)**	**.008**
Insertion Site		
Upper arm Veins	1 [Reference]†	
Subclavian Veins	**2.16 (1.07-4.34)**	**.029**
Internal Jugular Vein	1.56 (0.71-3.40)	.26
Past Medical History of DVT		
Absent	1 [Reference]†	
Present	**2.03 (1.05-3.92)**	**.034**
Catheter Tip Location at the Junction between SVC and RA, or in RA		
Yes	1 [Reference]†	
No	**1.92 (1.22-3.02)**	**.004**
Lumen Number		
Single	1 [Reference]†	
Double	1.34 (0.87-2.04)	.17
Triple	3.79 (0.75-19.21)	.10
Grading of technical difficulties during Catheter insertion		
Easy	1 [Reference]†	
Difficult	1.78 (0.79-4.00)	.16
Any form of Thromboprophylaxis given‡		
No	1 [Reference]†	
Yes	0.80 (0.63-1.03)	.09
Current or Recent Exposure to Estrogen (OCP or HRT)		
No	1 [Reference]†	
Yes	1.65 (0.64-4.23)	.29
Side of Catheter Insertion		
Right	1 [Reference]†	
Left	1.28 (0.97-1.70)	.079

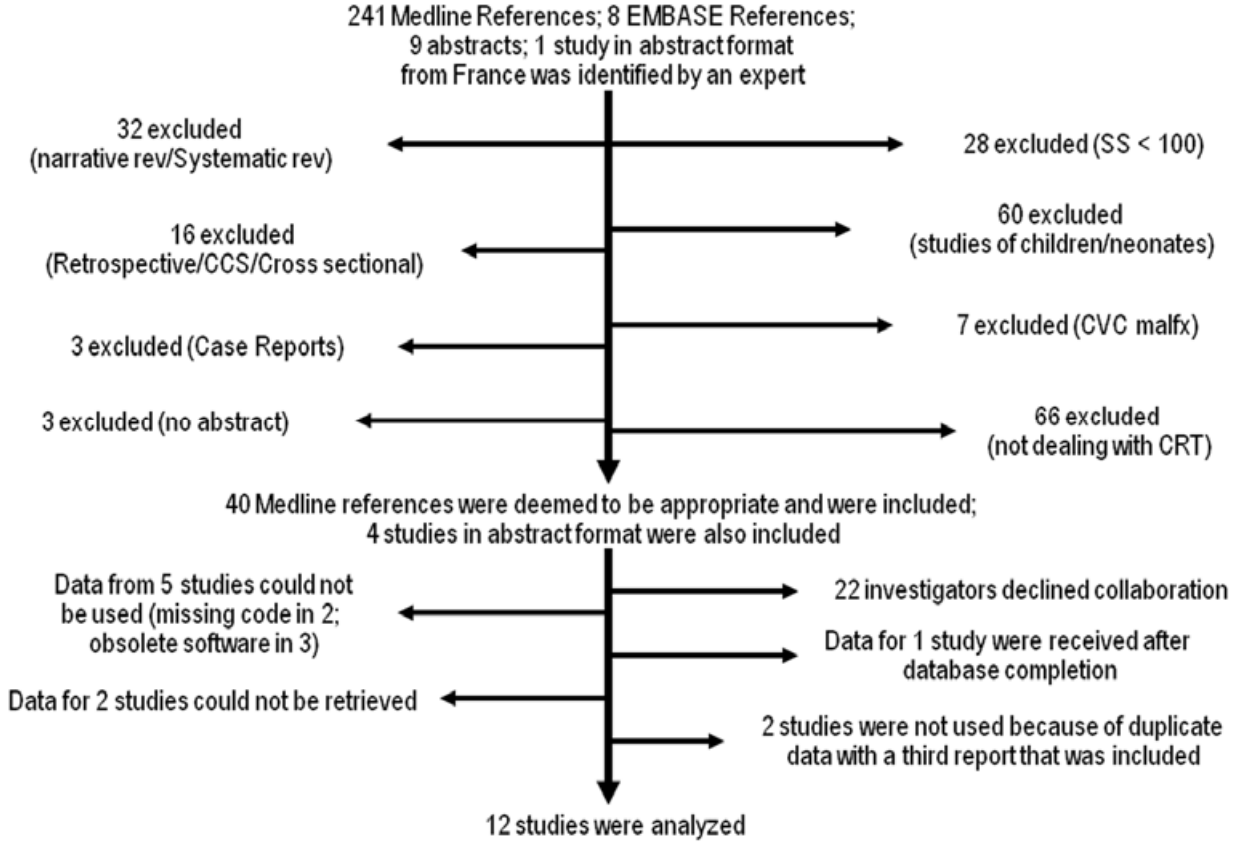
Abbreviations: CRT, catheter-related thrombosis; CI, confidence interval; CVC, central venous catheter; PICC, peripherally implanted central catheter; DVT, deep vein thrombosis; SVC, superior vena cava; RA, right atrium; OCP, oral contraceptive pills; HRT, hormone replacement therapy.

*Odds ratios and 95% CI are not shown for Missing data category.

†Reference group for the logistic regression analysis.

‡Include antiplatelets; prophylactic dosages of heparin (unfractionated and low molecular weight heparin); minidose warfarin (1mg daily) and dose adjusted warfarin (target International Normalized Ratio, 1.5-2).

Figure 1. Flow diagram of studies that were identified by our search.



Abbreviations: malfx, malfunction; CCS, case-control studies; CRT, catheter-related thrombosis; SS, sample size.

Figure 2: Freedom from CRT