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Catheter associated blood stream infection in patients with cancer: comparison of left and right-sided insertions

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Summary

Background: There is limited research on the relationship between side of insertion of central venous catheters (CVAD) and bloodstream infection risk in patients with cancer.

Aim: To conduct an exploratory analysis of data from a randomized trial (RCT) and data from a prospective cohort study to compare infection rates for right and left-sided insertions.

Methods: The study populations were patients aged > 14 years with cancer from two tertiary hospitals in Brisbane, Australia. The primary endpoint was catheter-associated bloodstream infection (CA-BSI) adjudicated by blinded assessors. For the RCT we conducted randomized intention-to-treat comparisons between left and right-side allocated insertion for early (≤ 14 days) and late infection (> 14 days) using Cox proportional hazards regression. We also combined the RCT data with cohort study data collected from one of the hospitals prior to the RCT and conducted non-randomized comparisons between left and right-sided insertions.

Results: In 634 randomly allocated CVADs there were 141 CA-BSI. Analysis showed strong evidence of right-side allocated insertions having an increased risk of early infection by 2.5 times (95% CI: 1.3-4.7) however there was no evidence of increased risk for late infection (hazard ratio [HR]: 1.06, 95% CI: 0.71-1.59). Results from analysis of the RCT and cohort study data combined (2,786 CVAD insertions and 385 CA-BSI) were similar.

Conclusion: Study findings suggest an increased risk of catheter-associated bloodstream infection in patients with cancer for CVAD inserted into the right-side for around 2 weeks after line insertion. The mechanism underpinning the increased risk is unknown.

Introduction

In a prospective cohort study of 723 adult patients with cancer (1127 CVADs), risk of catheter-associated bloodstream infection was found to be associated with: type of central venous access device (CVAD); patient diagnosis; number of previous insertions; and, somewhat surprisingly, side of insertion. Multivariable analysis showed right-sided insertion was associated with a statistically significant 60% increased risk of infection[1]. This unexpected finding led to speculation of a possible mechanism that could explain the observed increased risk. It was thought it may relate to the handedness of patients being predominantly right, and right-sided insertions in these patients leading to increased movement and possibly greater bacterial contamination of the catheterized arm. This hypothesis was subsequently tested in a clinical trial of 640 CVADs randomized to catheter insertion into the dominant or non-dominant arm[2].

Results from the trial suggested the hypothesized mechanism is probably incorrect with no difference in infection rate observed between the dominant and non-dominant arms (hazard ratio [HR] 0.91, 95% confidence interval [CI]: 0.65-1.28, P=0.60). Other possible mechanisms include anatomical differences between right and left; and difference in the level of difficulty with left compared to right-sided insertion. If the latter mechanism is true, then we could expect a stronger association with early compared to late infection. In the prospective cohort study, analysis of early infection (within 14 days) and late infection (>14 days), suggested the association for early infection may be stronger (HR 1.75 vs 1.35) although the difference between early and late estimates of association was not statistically significant[1]. Further, characteristics of the catheter inserter may play a role.

To further investigate potential mechanisms that could explain an association between side of insertion and infection risk, we conducted further exploratory analyses of the trial and observational data to estimate the association between side of insertion and early infection, late infection, and all infection. The role of handedness of the catheter inserter was also explored.

Methods

Our exploratory analyses are conducted in two parts. In part 1 we have conducted analyses using the RCT data only. In part 2 we have combined the RCT data with prospective cohort study data and conducted an individual patient data (IPD) meta-analysis. The cohort data included CVADs inserted at Princess Alexandra Hospital between 1 January 2004 and 31 December 2009. The trial was conducted at Princess Alexandra Hospital and Royal Brisbane and Women's Hospital and included CVADs inserted between 19 February 2013 and 15 March 2016. For the cohort study, some infection control practices did change over the study period. We used different dressings and changed the central line bungs and central line brands over this time. Other aspects of infection control (hand hygiene, chlorhexidine skin antisepsis, strict aseptic technique, line and insertion site monitoring, blood culture practice, central line insertional location and practice) were constant throughout the study period. For the RCT, line care was standardized throughout the study at both hospitals.

Detailed methods used for the trial are reported elsewhere[2]. In summary, this randomized trial recruited inpatients and outpatients aged > 14 years with cancer from two tertiary hospitals. Patients with contraindication to CVAD insertion on one side of the body; implantable ports; and peripheral venous catheters were excluded. The majority of CVADs were inserted with ultrasound guidance by trained operators and managed according to a standardized nursing policy[3, 4]. The primary endpoint was catheter-associated blood stream infection (CA-BSI), defined according to the

Australian Infection Control Association[5-7] and adjudicated by two independent medical practitioners who were blinded to treatment group allocated. Any disagreements were resolved by discussion. CA-BSI were identified when: (a) the patient had a recognized pathogen isolated from one or more blood cultures (e.g. Staphylococcus aureus, Streptococcus pneumoniae, Escherichia coli, Klebsiella species, Proteus species, Candida albicans); or (b) the patient had at least one of the following signs and symptoms within 24 hours of a positive blood culture being collected (fever > 38^{o}C, chills, rigors, hypotension), and at least one of the following: isolation of a common skin commensal (e.g. diptheroids, coagulase negative staphylococci, Micrococcus sp, Propionbacterium species, Bacillus species) from two or more blood culture sets drawn on separate occasions within a 48 hour period; or isolation of a common skin contaminant from a single blood culture and appropriate antimicrobial therapy is commenced. In addition to (a) and (b) above, the CVAD must have been present within 48 hours of the event and the organism must not be related to an infection at another site. Secondary endpoints were the more strictly defined catheter-related blood stream infection (CR-BSI)[8, 9]; and clinical suspicion of infection. Follow-up was until infection, until the line was removed, or until 3 months after the last patient was randomized.

Due to the design of the trial, randomized comparisons addressing our study aims could be performed. The rationale is as follows. In the trial, patients were randomized to insertion of CVAD into either the dominant, or the non-dominant arm. Therefore, if we consider left-handed and right-handed patients separately, we can perform randomized comparisons between allocated insertion into the right and allocated insertion into the left side by performing a stratified analysis where the strata are left-handed and right-handed patients (Figure 1). These are intention-to-treat (ITT) comparisons. We also conducted “as-inserted” comparisons by comparing left and right-sided insertions.

Cox proportional hazards regression was used for analysis of survival outcomes using SAS, version 9.4 for Windows (SAS Institute Inc., Cary, NC). To estimate hazard ratios for early and late infection outcomes we used a single Cox model but added an additional explanatory exposure parameter after 14 days to estimate and test the change in hazard ratio for late infections compared to early infections. Interaction between inserter handedness and allocated side of insertion was tested. Variables included in adjusted analyses for “as-inserted” comparisons were line type and patient diagnosis. These variables were shown in the prospective cohort study to be associated with infection risk[1]. As the unit of analysis was lines within patients, cluster robust variances were estimated to account for the small number of patients included more than once in the trial.

Individual patient data (IPD) meta-analysis was conducted using a combined dataset of individual patient line insertions from the RCT and the cohort study. Cox proportional hazards regression was used for analysis of time to CA-BSI stratified by study type (trial or cohort study), line type (tunnelled, non-tunnelled, PICC) and broad patient diagnosis (intensive haematology, other haematology, oesophageal/rectal/colon cancer, other solid tumour). Subgroup analysis was conducted by line type and hospital. All meta-analyses involved “as-inserted” comparisons, i.e. left-side insertions were compared to right-sided insertions. Detailed methods used for the prospective cohort study are previously published [1]. The main differences between the RCT and the cohort study methods were that: implantable ports (n=24) were included in the cohort study but not in the RCT; handedness of inserters was not collected in the cohort study; and patients with contraindication to CVAD insertion on one side of the body were included in the cohort study.

Results

Part 1: RCT exploratory data analysis

Participants

There were 1225 patients assessed for eligibility with 585 excluded largely due to either refusal (n=244) or not meeting inclusion criteria (n=273). Notably only 1 patient with breast cancer was randomized with most excluded due to a contraindication to having a CVAD inserted into one side of the body. This resulted in 640 CVADs randomized in the study however six were subsequently excluded due to: withdrawal of consent (n=2); randomization error (n=2); Port-a-Cath insertion (n=1); and failure to insert any line (n=1). Characteristics of the included patients stratified by allocated left and right sided insertions are presented in Table 1. Of note, the percentage of patients who did not have a line inserted as randomly allocated was 8%. Reasons included: patient refusal (n=10); unsuitable venous anatomy (n=29); failed insertion on randomized side (n=5); and other (n=8). These patients are included in their allocated group for intention-to-treat analyses whereas for "as-inserted" analyses they are grouped according to the actual side of insertion. Number of insertion attempts had a similar distribution for allocated left and right-sided insertions.

Impact of line type, side of line insertion and inserter handedness on early and late CA-BSI

There were 141 CA-BSI in total with the overall rate of CABSI being 3.58 per 1000 line-days. Of these 141 CA-BSI, 46 were early infections and 95 were late infections. There were only 16 events for the stricter CR-BSI outcome observed hence further analysis of these data was not undertaken. The organisms cultured from episodes of CA-BSI and CR-BSI are reported in Table II of the main RCT publication[2].

Previously,[2] we demonstrated that patients with tunnelled lines had a higher risk of infection than did patients with PICC lines (HR 2.05, 95% CI: 1.45-2.91). However, when considered in terms of the timing of infection, this difference is predominantly due to an increased risk of early infections with tunnelled lines as there is little difference between PICC lines and tunnelled lines for late infections (Figure 2). Non-tunnelled lines are not shown because they were inserted for short durations with all recorded infections occurring within 20 days.

In terms of the impact of side of line insertion, Cox regression analysis provided weak evidence of a 38% higher risk of CA-BSI for right-sided allocated insertions compared to left-sided allocated insertions based on intention-to-treat analysis (HR 1.38, 95% CI: 0.98-1.92). As inserted adjusted analysis resulted in a similar finding (HR 1.40, 95% CI: 0.99-1.97). Results from intention-to-treat Cox-regression analysis showed evidence of increased risk of early infection in right-sided allocated insertions compared to left-sided allocated insertions but not for late infection. Further, there was some evidence that the hazard ratios for early and late infections are different (P=0.02). As inserted analyses provided similar results (Table 2). Kaplan-Meier failure rate of CA-BSI by left versus right side allocated insertions illustrates the difference between groups occurs in the first 15 days with a steeper increase for the right sided compared to the left sided allocated insertions over this period (Figure 3).

The handedness of the CVAD inserter was associated with CA-BSI risk; with left-handed inserters having more than double the risk of right-handed inserters (HR 2.22, 95% CI: 1.35-3.70, P=0.002). Further analysis showed weak evidence of an interaction between handedness of inserter and side of insertion (P=0.053) suggesting the hazard ratio (for right vs left-sided allocated insertion) may be larger for left-handed inserters than right-handed inserters (HR 3.31, 95% CI: 1.09-10.0 vs 1.21, 0.85-1.73, respectively). Hazard ratios for early infection were larger than those for late infection

although there was insufficient evidence to conclude the hazard ratios were statistically different (Table 2).

Part 2: Individual patient meta-analysis

A total of 2,786 CVAD insertions (1,130 [41%] into the left side) were included in the meta-analysis: 2,152 collected prior to the trial (of which 1,127 were previously published[1]). There were 385 CA-BSI events in total (244 from the cohort study) with 150 early infections and 235 late infections. The organisms cultured from the episodes of CA-BSI (and CR-BSI) of the previously published cohort study are reported in Table II of the original publication[1]. Overall, there was an increased risk of CA-BSI for right-sided insertions by 42% (95% CI: 1.13-1.79). Further analysis showed a large increased risk of early infection for right-sided insertions (HR 2.18, 95% CI: 1.41-3.36) but insufficient evidence of a difference for late infection (HR 1.16, 95% CI: 0.88-1.53) and strong evidence that these two hazard ratios are different (P=0.004). Results of subgroup analysis by hospital and line type are shown in Table 3.

Discussion

Results indicate CVAD insertion into the right-hand side of patients is associated with more than double the early infection risk compared to CVAD insertion into the left-hand side of patients. No association was found for late infections. There was no evidence of difference in infection risk between dominant and non-dominant sides of insertion for either early or late infections[2]. These findings provide evidence of an increased risk of infection for right side insertions initiated at line insertion and lasting for around 2 weeks. Taken over the entire follow up period there appears to be an approximate 40% increased risk of infection. Further, left-handed inserters are associated with greater risk of infection compared to right-handed inserters, although this result is based on small numbers for left-handed inserters.

Meta-analysis provided similar estimates as for the trial itself for the association between side of insertion and overall risk of infection as well as separately for early and late infections. The increased power of this analysis due to inclusion of more lines and infections has resulted in increased precision of estimates and smaller p-values for the statistically significant results. Subgroup analysis has shown evidence of stronger associations between side of insertion and infection rates for early compared to late infection at each of the two hospitals and for PICCs however results are inconclusive for other line types. This latter point possibly relates to insufficient numbers.

Review of the findings from this study in the context of previous research is limited by the paucity of prior research examining side of insertion as a risk factor for blood stream infection. A summary of research in the field of hematology suggests *site* of insertion has not been shown to be an independent factor in the development of catheter-related bloodstream infections[10] however it appears, apart from one prospective study which showed an increased risk for right-sided insertions[1], there are no adequately powered studies comparing left and right-sided insertions for risk of infection. Previous studies have compared left and right-sided insertions for other outcomes such as malposition of catheter with two studies reporting right-side insertions are at higher risk compared to left-sided insertions[11, 12]. Malposition can be identified via x-ray and typically this will lead to re-insertion of the catheter. A recent trial of 202 cancer and non-cancer patients showed

a 40% lower risk of complications associated with right-sided insertions of PICCs however there were only four bloodstream infections in total confirmed[13].

The mechanism underpinning the apparent increased risk of early infection found in this study is unknown, although it is unlikely to be related to movement of the catheterized arm. The increased risk is observed for early infection only, suggesting it may be related to line insertion. Greater difficulty could be an explanation for the increased risk found for left-handed inserters compared to right-handed inserters, however, the cause of the increased right sided infection rate requires further study. The increased risk for tunnelled lines compared to PICCs is most likely related to tunnelled lines involving more traumatic insertion or the neck having higher organism load.

Strengths of this study include the prospective design, independent outcome assessment and the consistency of the results across different hospitals and subgroups of patients. Our analyses, however, were exploratory as they were not prespecified in the study protocol although they were based on previously reported analyses conducted on a prospective cohort of cancer patients[1]. A further limitation is the lack of previous studies that have reported on side of insertion in the context of catheter-associated or related bloodstream infection. Given the lack of previous studies and the unknown mechanism for the finding of a higher risk of infection in the right side within the first 2 weeks of insertion we do not believe our results can be generalized to other patient groups until further studies have been conducted.

Conclusion

Our study has shown evidence of a higher risk of catheter-associated bloodstream infection in adult cancer patients for catheters inserted into the right side that appears to last for around 2 weeks after line insertion. The mechanism underpinning the apparent increased risk is unknown. Further research is needed to determine whether this finding can be replicated in other cohorts of patients and to explore possible explanations.

Acknowledgements

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Declaration of competing interest

None declared.

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Table 1. Characteristics of the RCT patients stratified by allocated left and right sided insertion

Variable	No. (%)		
	Left	Right	Total
Gender			
Female	99 (31.8)	117 (36.2)	216 (34.1)
Male	212 (68.2)	206 (63.8)	418 (65.9)
Age			
Mean (SD)	55.6 (13.8)	56.1 (13.7)	55.9 (13.7)
Patient diagnosis			
Intensive haematology	167 (53.7)	178 (55.1)	345 (54.4)
Other haematology	21 (6.7)	14 (4.3)	35 (5.5)
Oesophageal/rectal/colon cancer	81 (26.0)	75 (23.2)	156 (24.6)
Other solid tumour	42 (13.5)	56 (17.3)	98 (15.5)
Centre			
PAH	207 (66.6)	208 (64.4)	415 (65.5)
RBWH	104 (33.4)	115 (35.6)	219 (34.5)
Line type			
Tunnelled	70 (22.5)	74 (22.9)	144 (22.7)
Non-tunnelled	28 (9.0)	38 (11.8)	66 (10.4)
PICC	213 (68.5)	211 (65.3)	424 (66.9)
No. of prior lines			
0	279 (89.7)	297 (91.9)	576 (90.9)
1	27 (8.7)	26 (8.1)	53 (8.4)
2	5 (1.6)	0 (0.0)	5 (0.8)
Lumens			
Single	5 (1.6)	4 (1.2)	9 (1.4)
Double	264 (84.9)	277 (85.8)	541 (85.3)
Triple	42 (13.5)	42 (13.0)	84 (13.3)
Number of insertion attempts			
1	284 (91.3)	299 (92.6)	583 (92.0)
2	18 (5.8)	21 (6.5)	39 (6.2)
3+	9 (2.9)	3 (0.9)	12 (1.8)
Inserter's dominant hand			
Left	28 (9.0)	30 (9.3)	58 (9.2)

Right	283 (91.0)	293 (90.7)	576 (90.8)
Patient's dominant hand			
Left	28 (9.0)	31 (9.6)	59 (9.3)
Right	283 (91.0)	292 (90.4)	575 (90.7)
Inserted as randomized			
Yes	281 (90.4)	301 (93.2)	582 (91.8)
No	30 (9.6)	22 (6.8)	52 (8.2)

PICC, peripherally inserted central venous catheter

Table 2. RCT analysis of association between side of insertion and early and late CA-BSI, overall and according to inserted handedness

	CA-BSI	
Timing (subgroup)	HR (95% CI)	^P-value (interaction)
Early infection (all)		0.02
Left	1.00	
Right	2.48 (1.31-4.68)*	
Late infection (all)		
Left	1.00	
Right	1.06 (0.71-1.59)#	
Early infection (inserter left-handed)		0.11
Left	1.00	
Right	3.99 (0.86-18.6)	
Late infection (inserter left-handed)		
Left	1.00	
Right	2.71 (0.49-13.8)	
Early infection (inserter right-handed)		0.085
Left	1.00	
Right	2.21 (1.09-4.45)	
Late infection (inserter right-handed)		
Left	1.00	
Right	0.96 (0.65-1.46)	

*HR 2.14 (95% CI: 1.13-4.03) in “as inserted” adjusted analysis
#HR 1.16 (95% CI: 0.77-1.75) in “as inserted” adjusted analysis
^Based on statistical comparison of HRs for early and late infection

Table 3: Subgroup meta-analysis of association between side of insertion and early and late CA-BSI by line type and hospital

Subgroup	Timing	HR (95% CI) (Right vs Left (ref))	^P-value (interaction)
PA Hospital	Early	1.88 (1.19-2.97)	0.014
(n=2,567)	Late	1.21 (0.87-1.69)	
RBWH	Early	6.50 (1.52-27.8)	0.041
(n=219)	Late	1.05 (0.64-1.72)	
Tunnelled	Early	1.56 (0.77-3.15)	0.25
(n=474)	Late	1.35 (0.79-2.30)	
Non-tunnelled	Early	2.02 (0.32-12.8)	NA*
(n=366)	Late	NA*	
PICC	Early	2.74 (1.56-4.80)	0.0019
(n=1,922)	Late	1.07 (0.77-1.50)	

*Insufficient late infections for estimation of HR

^Based on statistical comparison of HRs for early and late infection

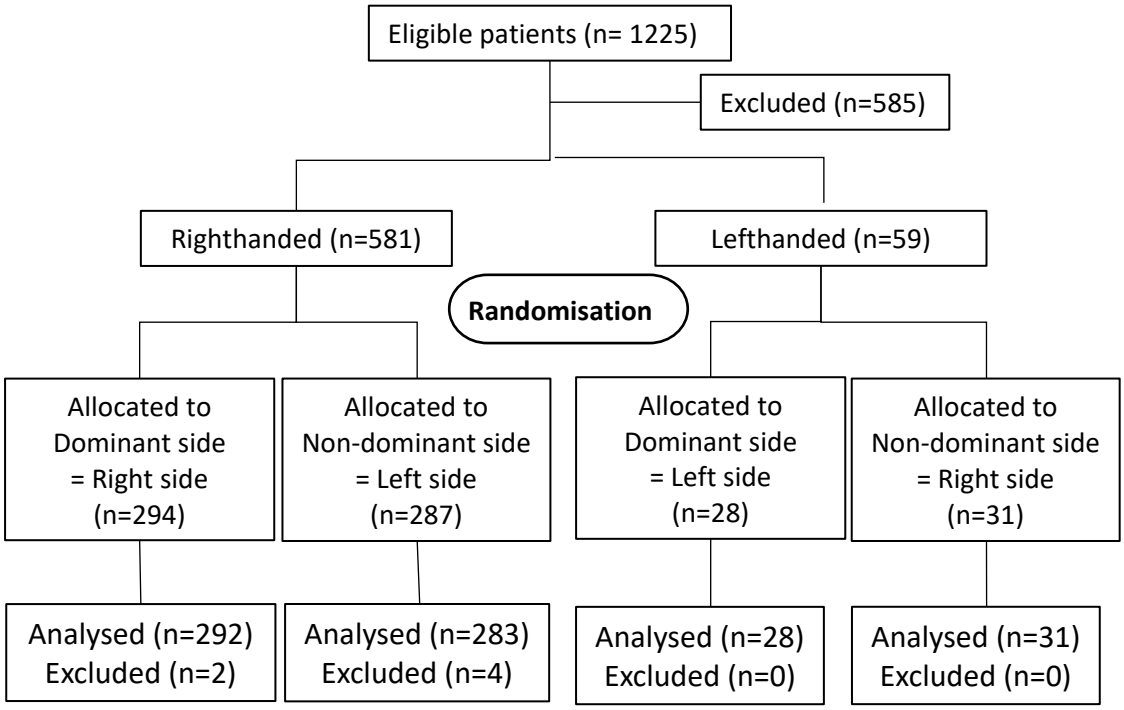

Figure 1. Flow chart of the trial stratified by dominant hands of patients

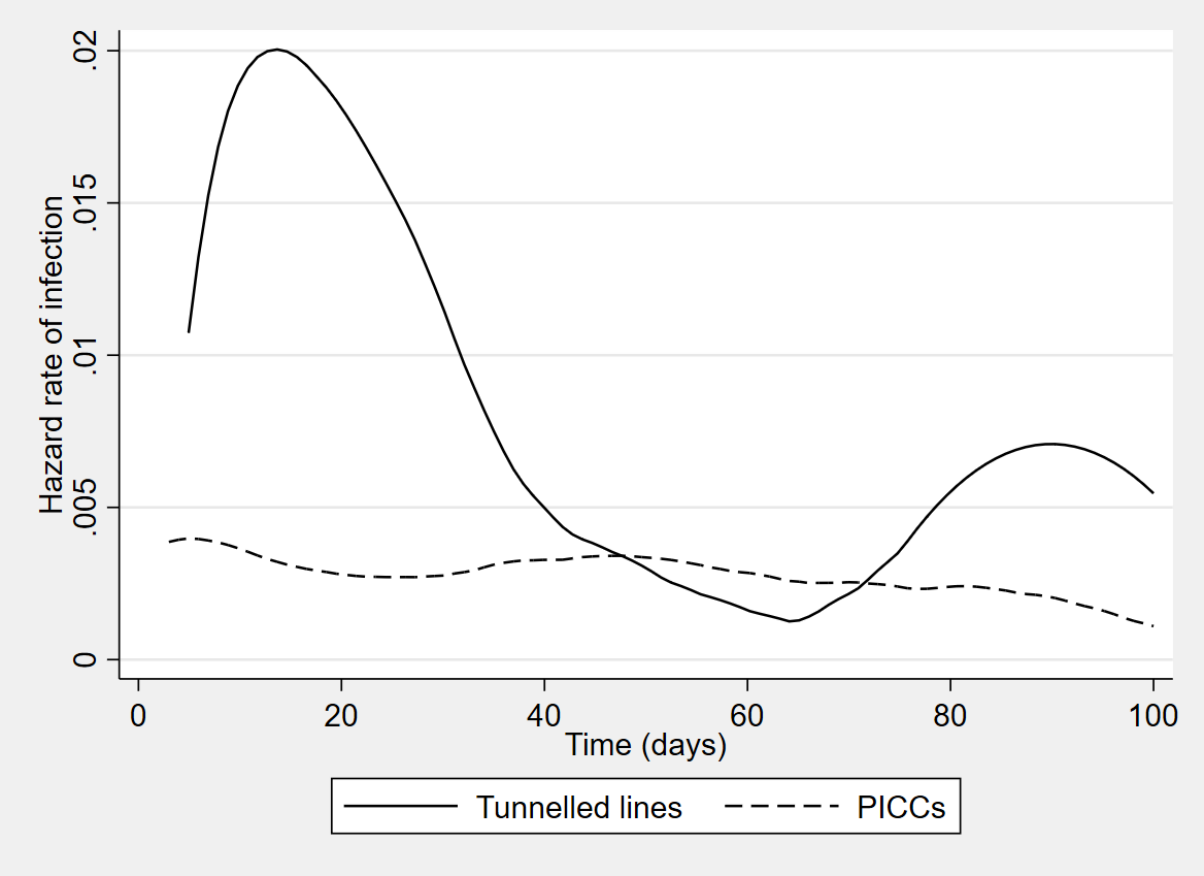

Figure 2. The smoothed hazard function of CA-BSI for PICCs and tunnelled lines in the RCT

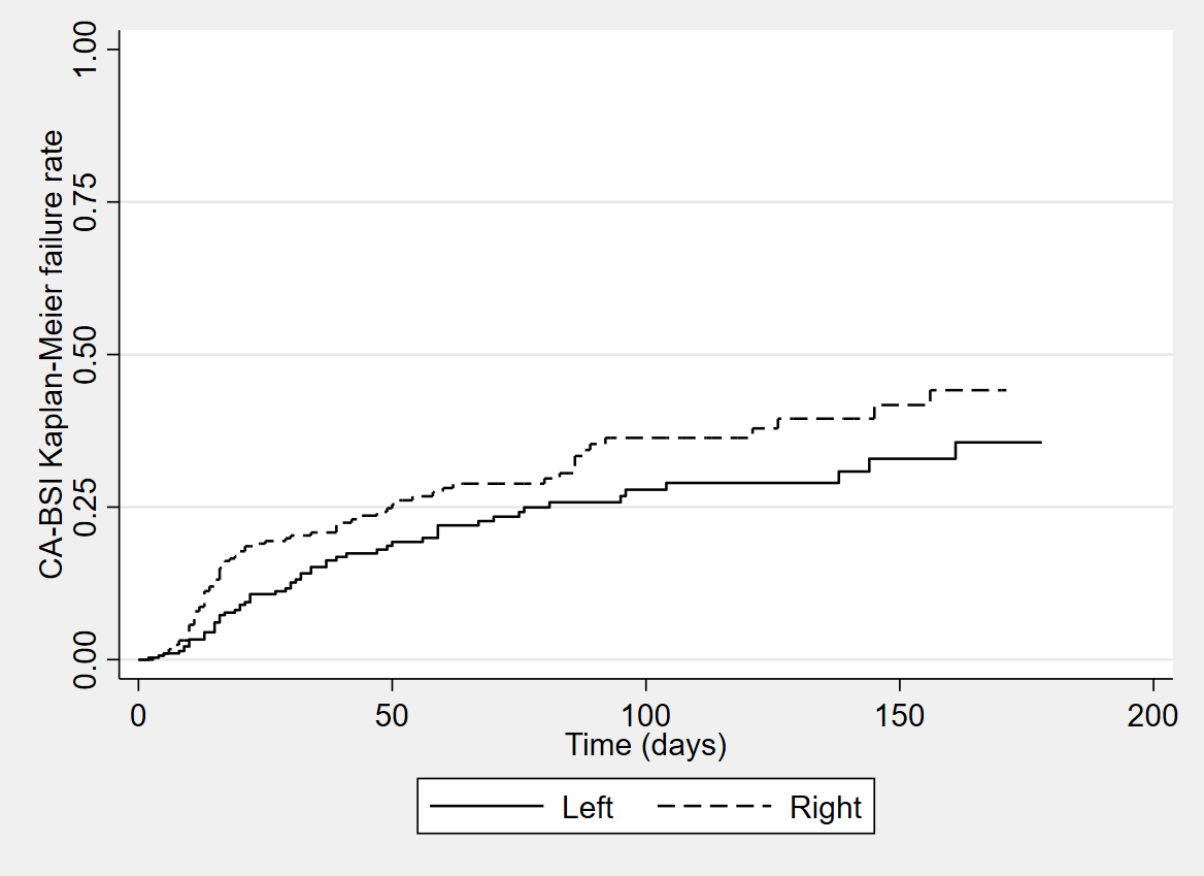

Figure 3. The Kaplan-Meier failure rate of CA-BSI by allocated group in the RCT