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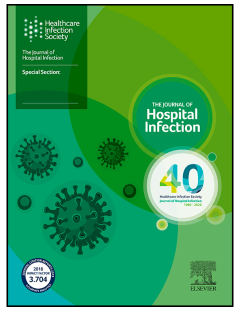

Decreased Mortality among Patients with Catheter-Related Bloodstream Infections at Catalan Hospitals (2010-2019)

Laia Badia-Cebada, Judith Peñafiel, Joaquin Lopez-Contreras, Virginia Pomar, Jose Antonio Martínez, Germina Santana, Jordi Cuquet, Maria M. Montero, Carlota Hidalgo-López, Marta Andrés, Montserrat Gimenez, María Dolores Quesada, Montserrat Vaqué, Simona Iftimie, Carlota Gudiol, Rafel Perez, Anna Coloma, Anna Marrón, Pilar Barrufet, Marilo Marimon, Ana Lérida, Mercè Clarós, Maria Fernanda Ramírez-Hidalgo, Graciano Garcia Pardo, M. Jesus Martinez, Elena Lourdes Chamarro, Emili Jiménez-Martínez, Ana Hornero, Enric Limón, Maria López, Esther Calbo, Miquel Pujol, Oriol Gasch, on behalf of the Surveillance of health-care associated infections in Catalonia (VINCat)

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SUMMARY

Background: The incidence of catheter-related bloodstream infections (CRBSI) has fallen over the last decade, especially in intensive care units (ICUs). **Aim:** to assess the existence of concomitant trends in outcomes and to analyse the current risk factors for mortality.

Methods: A multicentre retrospective cohort study was conducted at 24 Catalan hospitals participating in the Surveillance of healthcare associated infections in Catalonia (VINCat). All hospital-acquired CRBSI episodes diagnosed from January 2010 to December 2019 were included. A common protocol including epidemiological, clinical and microbiological data was prospectively completed. Mortality at 30 days after bacteraemia onset was analysed using the Cox regression model.

Findings: Over the study period, 4,795 episodes of CRBSI were diagnosed. Among them, 75% were acquired in conventional wards and central venous catheters were the most frequently involved (61%). The 30-day mortality rate was 13.8%, presenting a significant downward trend over the study period: from 17.9% in 2010 to 10.6% in 2019 (HR 0.95 [0.92-0.98]). The multivariate analysis identified age (HR 1.03 [1.02-1.04]), femoral catheter (HR 1.78 [1.33-2.38]), medical ward acquisition (HR 2.07 [1.62-2.65] and ICU acquisition (HR 3.45 [2.7-4.41]), *S. aureus* (HR 1.59 [1.27-1.99]) and *Candida sp.* (HR 2.19 [1.64-2.94]) as risk factors for mortality while the mortality rate associated with episodes originating in peripheral catheters was significantly lower (HR 0.69 [0.54-0.88]).

Conclusions: Mortality associated with CRBSI has fallen in recent years but remains high. Intervention programs should focus especially on ICUs and medical wards, where incidence and mortality rates are highest.

Key words: Mortality, Healthcare-associated infection, Catheter-related bloodstream infections, Intervention program.

INTRODUCTION

Catheter-related bloodstream infections (CRBSI) represent around 15% of healthcare associated infections and are a frequent cause of nosocomial bacteraemia, accounting for between 25% and 43% of all episodes[1–4]. Over the past few years CRBSI incidence rates have fallen, especially the episodes associated with central venous catheters [5]. This is mainly due to the implementation of infection prevention programs in intensive care units (ICUs) [6]. In hospitals belonging to the VINCat, 'Bacteremia Zero Program' started in 2009, showing a reduction in the risk of CRBSI of 50% [7] by the application of bundles of preventive measures that included hand hygiene, use of chlorhexidine alcohol solution for skin antisepsis, full barrier precautions, daily review of need for catheterization and femoral site avoidance. A similar intervention was implemented in 11 hospitals of VinCat during the same year, including all catheters inserted in conventional wards [8]. These interventions, together with the initiation of benchmarking between hospital results in 2007 had a direct impact on CRBSI incidence, as was previously described [5].

The clinical presentation of CRBSI ranges from mild systemic inflammatory response syndrome to septic thrombophlebitis or systemic complications such as endocarditis or endophthalmitis[9]. Therefore, the associated mortality may be as high as 15-30% [10–14]. Inpatient costs are significant [15], and in fact central-line bloodstream infections have been considered one of the costliest healthcare-associated infections of all [16].

Although previous studies have reported risk factors for CRBSI-associated mortality, their conclusions often present significant differences. Advanced age, specific comorbidities, clinical severity, and C*andida* and *Staphylococcus aureus* aetiologies are usually among the predictors of worse outcomes [10-11,13-14,17].

The possible link between the recent epidemiological variations, lower incidence rates and changes in CRBSI prognostic factors has not been definitively established. The objective of this multicentre study is to describe CRBSI mortality over a long period and to analyse the current prognostic factors for mortality.

METHODS

Setting and study design

A retrospective cohort study conducted in 24 Catalan hospitals participating in the Surveillance of health-care associated infections in Catalonia (VINCat program). All nosocomial CRBSI episodes diagnosed at each hospital from January 2010 to December 2019 were prospectively recorded in accordance with the Surveillance of health-care associated infections in Catalonia (VINCat) recommendations [18].

The 24 Catalan hospitals participating in this study are classified into three categories according to the number of beds and complexity available for hospitalization: 500 beds or more (Group I, 7 hospitals), 200 to 499 beds (Group II, 14 hospitals), and fewer than 200 beds (Group III, 1 hospital). Among them, 5 centres are provided with transplantation program; 16 are university teaching hospitals and one is a monographic onco-haematological hospital. Twenty hospitals are provided with intensive-care units.

The Infection Control Teams prospectively follow all episodes of CRBSI identified at the microbiology laboratories and complete a protocol with the most relevant characteristics of the episode, including epidemiological and demographic information, catheter use and placement, aetiology, and outcomes.

Patients under the age of 18, patients in whom CRBSI was detected in outpatient care and those with a hospital stay of less than 48 hours at the time of bacteraemia detection were not included in the study. Patients admitted to palliative care and psychiatry Departments were not included, either.

Definitions

Catheter-related bloodstream infection was diagnosed when bacterial growth was detected in patients carrying a venous catheter, with at least one set of blood cultures obtained from a peripheral vein and two sets in the case of habitual skin-colonizing microorganisms (coagulase-negative staphylococci, Micrococcus sp., Propionibacterium acnes, Bacillus sp. and Corynebacterium sp.). These cultures must be accompanied by one of the following: (1) isolation of the same microorganism in the catheter tip and in the peripheral blood culture; (2) a proportion of 3:1 in the quantitative blood culture through the catheter hub and in peripheral blood; (3) growth of the blood culture from the catheter hub at least 2 hours before the peripheral culture; (4) exclusion of any other source of bacteraemia with clinical signs of infection at the site of catheter insertion; or (5) resolution of clinical signs and symptoms after catheter withdrawal, with or without appropriate antibiotic treatment [19].

Catheters were divided into three categories: peripheral, central, and peripherally-inserted central catheter (PICC). The annual incidence rate of catheter-related bloodstream infections diagnosed per 1,000 patient-days was obtained as the total number of bloodstream infections detected in one year x 1,000 divided by the total year hospital stays. Mortality was defined as death occurring within 30 days of bacteraemia onset.

Microbiology

Two sets of two blood samples were obtained from all patients with a suspected BSI. An additional blood sample obtained through the catheter was also collected if the vascular catheter was the suspected origin of BSI. When possible, the catheter tip was cultured after removal. Blood samples were processed at the microbiology laboratories of each centre in accordance with standard operating procedures. Each microorganism was identified using the standard microbiological techniques at each centre.

Statistical analysis

Nominal categorical variables were described by the number of cases and the percentage of the total by category. Continuous variables following a normal distribution were described with mean and standard deviation; those that were not normally distributed were described by the mean and first and third quartiles. 95% confidence intervals of mortality incidence at 30 days after bacteraemia onset were calculated with the Exact Binomial Test.

To compare the adjusted mortality rate at 30 days from bacteraemia onset among hospitals, two Frailty Cox regression models were estimated. The first model was adjusted by age, gender, type of ward, aetiological microorganism, year, type of catheter and hospital as a frailty term. The second model was adjusted by the same factors, except changing type of catheter to catheter location. To visualize supplier unit comparisons, a funnel plot on the ratio of observed and expected deaths was used.

The Kaplan-Meier method was used to estimate the cumulative incidence of death by place of acquisition and by catheter use in CRBSI.

The conditions of application were evaluated in all models. The 95% confidence interval was calculated for each estimator. The level of statistical significance was arbitrarily set at 5%. The analysis was performed with the statistical package R version 4.1.0. for Windows.

Ethical considerations

Participation in the VINCat Program is voluntary and data confidentiality is guaranteed by VINCat. This study was evaluated and approved by the Parc Taulí Hospital Research Ethics Committee (2021/5069).

RESULTS

During the study period, 4,795 episodes of CRBSI were detected. Patients' mean age was 64.5 years, and 35.7% were female. Almost two thirds of CRBSI episodes originated in central venous catheters (60.4%), PVC represented 24.2% and PCVC 15.3%. Most episodes occurred in medical wards (44.4%). A quarter of the catheters were used for parenteral nutrition, 4.9% for haemodialysis and the rest for serum and medical infusions. CRBSI were diagnosed 10 days (IQR 6-18) after catheter insertion (central catheters 13 days [IQR 8.00-21], peripheral catheters 5 days [IQR 3- 7], and peripherally-inserted cental catheters 12 days [IQR 7-21]). The most frequently involved microorganisms were coagulase-negative staphylococci (37.4%) and *S. aureus* (24.1%). Gram-negative bacilli were the cause of 26.3% of the episodes, being *Klebsiella pneumoniae* 408 (33%) followed by *Pseudomonas aeruginosa* 268 (21%), *Enterobacter cloacae* 132 (10%) and *Escherichia coli* 93 (7.5%) the most frequent.

The overall 30-day mortality rate was 13.8%, falling significantly over the study period from 17.9% in 2010 to 10.6% in 2019 [HR 0.95 95% CI (0.92-0.98)] (Figure 1). Death occurred a median of 11 days (IQR 5-19) after CRBSI onset. The catheters associated with higher cumulative incidence of patient death were carried by patients admitted at ICUs for haemodialysis (incidence 0.42 95% CI [0.29-0.52]), parenteral nutrition (incidence 0.21 95% CI [0.15-0.26]), and other uses (incidence 0.2 95% CI [0.18-0.23]), followed by catheters carried by patients admitted in medical wards for parenteral nutrition (incidence 0.19 95% CI [0.14-0.23]). Regardless of their use, the catheters associated with the lowest risk of patient death were those carried by patients admitted in surgical units (incidence 0.07 95% CI [0.06-0.09]). (Figure 2).

The multivariate analysis identified age (HR 1.03 95% CI [1.02-1.04]), femoral catheter (HR 1.78 95% CI [1.33-2.38]), medical ward (HR 2.07 95% CI [1.62-2.65]) and ICU acquisition [HR 3.45 95% CI (2.7-4.41]), *Staphylococcus aureus* (HR 1.59 95% CI [1.27-1.99]) and *Candida sp.* (HR 2.19 95% CI [1.64-2.94]) as risk factors for mortality. Mortality associated with peripheral vascular catheters was significantly lower (HR 0.69 95% CI [0.54-0.88]) in a second multivariate model that included catheter type instead of catheter location as a potential predictor of mortality (Table I).

Adjusting by catheter type, 30-day mortality was associated with age in episodes associated with all three types of catheter, while medical ward and intensive care unit acquisitions, and *Candida sp.* were independent risk factors for mortality in both episodes associated with CVC and PICC. Last, *S.aureus* and other microorganisms were identified as independent risk factors for death only in episodes associated to CVC (Table 2).

Differences in mortality between hospitals were assessed adjusting for age, gender, days since admission, year, type of ward, aetiological microorganism and catheter use. At four centres, being one of them an onco-haematological referal hospital, the number of deaths was significantly higher than expected ([observed/expected deaths (99% CI): 1.73 (1.07-2.6), 1.56 [0.54-3.34], 1.41 [0.9-2.08] and 1.24 [0.97-1.56], respectively), while at three other hospitals, belonging all of them to group 1, mortality rates were significantly lower than expected (ratio observed/expected deaths (99%CI): 0.84 [0.5-1.3], 0.81 [0.59-1.07] and 0.77 [0.39-1.32], respectively) (Figure 3).

DISCUSSION

Thanks to the coordinated active surveillance program in place at Catalan hospitals, the present study was able to identify a downward trend in CRBSI-associated mortality and to analyse the current risk factors for death in a cohort of almost 5,000 episodes.

Notably, some other studies [14,20] based on codified data instead of prospective surveillance information had previously reported a progressive decline in mortality rates associated with CRBSI over recent years. There may be different complementary explanations for this decrease. The lower mortality rates may be associated with improvements in medical therapeutic response, the use of new antibiotics, and early catheter withdrawal when CRBSI is suspected [21,22]. Nevertheless, it is quite probable that intervention programs implemented to reduce CRBSI incidence in recent years have had an additional impact on mortality. Such preventive programs might be associated not just with the reduction in incidence rates, but also with better outcomes. These programs have been frequently implemented in different settings after their great impact on CRBSI incidence in the ICUs was first demonstrated (6). They were based on the application of bundles including evidence-based measures such as hand washing, using full-barrier precautions, cleaning the skin with chlorhexidine, avoiding the femoral site if possible, and removing unnecessary catheters [7,23].

In our setting, different interventions were carried out: First, since 2007, the results of CRBSI VINCat surveillance are diffused to professionals involved in the care of vascular catheters[18,24]. Benchmarking between centres is essential to analyse incidence rates and to guide targeted preventive measures, but also to compare clinical results and analyse them if they are worse than expected [25]. In this regard, differences between hospital fatality rates were also assessed in this study. After adjusting for clinically important variables, four of the 24 participating hospitals had significantly higher mortality rates. In one hospital, an onco-haematological centre, these worse outcomes were to be expected, given the shorter life expectancy of the patients admitted [26,27]. A second intervention called Bacteremia Zero Program is being implemented since 2009 to reduce the incidence rate of CRBSI in the VINCat hospitals ICUs [7]. Last, in 2010 a similar intervention was conducted in conventional wards of 11 hospitals participating in the VinCat program [8].

As previously shown in other settings, some of these preventive interventions reduced the rate of CRBSI episodes acquired in ICUs, those associated with central venous catheters [28], and/or those caused by more virulent pathogens such as *Staphylococcus aureus* [29]. Similarly, we recently described a downward trend in the episodes of CRBSI acquired in the ICUs, and those associated with central venous catheters at hospitals participating in the VINCat program [5].

Therefore, some of the risk factors for death identified in this study and others [10,11,15] were specially affected by the implemented preventive programs. Recognition of risk factors for death is highly valuable since it identifies the most vulnerable populations after an episode of CRBSI, and who are therefore potential targets for specific preventive actions. Concretely, we found that age, central venous catheters, certain more virulent pathogens and ICU acquisition were risk factors for death. Notably, infections due to catheters used for haemodialysis in ICUs had by far the worst prognosis. Other studies focused on catheters used for haemodialysis also observed high mortality rates associated with this use [12,30].

The main limitations of this study are its retrospective design and the lack of information on patients' comorbidities. However, the common definitions used at all participating hospitals and the inclusion of a large number of episodes allowed us to present some interesting conclusions regarding CRBSI outcomes. Specifically, a downward trend in CRBSI-associated mortality was identified, probably favoured by the implementation of preventive interventions, especially in the ICUs. Preventive programs should also be implemented in medical wards, especially targeted at patients at higher risk of death.

Our group is currently leading an intervention in conventional wards in Catalan hospitals (Spanish Ministry of Economics and Competitiveness. Health Institute Carlos III Expedient: PI20/01563). to assess whether any impact on mortality rates is observed in this setting.

CONCLUSIONS

Mortality related to catheter-related bloodstream infections has experienced a downward trend over the 10 year study period, but it is still high. Age, femoral location, ICU and conventional wards acquisition and *S. aureus* and *Candida sp* aetiology were identified as significant risk factors for death. The recognition of these risk factors allows to identify the most vulnerable populations that would benefit from specific preventive actions.

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CONFLICT OF INTEREST STATEMENT

None of the authors have any conflicts of interest to declare regarding this study. All authors have participated in the research and article preparation (LB-C made the article draft and interpreted the data, JP interpreted the data and made the statistical analysis, VP, JL-C, JAM, GS, JC, MMM, CH-L, MA, MG, MDQ, MV, SI, CG, RP, AC, AM, PB, MM, AL, MC, MFR-H, GG-P, MJM, ELC, EJM, AH, EL, ML, EC and MP made the acquisition of data and revised the article critically, OG made the conception and design of the study and revised the article critically. All authors have approved the final version.

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Table I. Univariate and multivariate analysis of risk factors for mortality of catheter-related bloodstream infections

	Alive	Dead	p-	HR	HR **
Age. Mean (ED)	63.8 (15.2)	69.2 (13.2)	<0.001	**1.03 (1.03-1.04)**	**1.03 (1.02-1.04)**
Female n(%)	2,655 (86.4)	415 (13.6)	0.94	0.98 (0.83-1.15)	0.98 (0.83-1.15)
Year			<0.001	**0.94 (0.92-0.97)**	**0.95 [0.92-0.98]**
Place of acquisition n(%)					
- Surgical ward	1,363 (92.8)	106 (7.2)			
- Medical ward	1,838 (86.6)	284 (13.4)	<0.01	**2.14 (1.67-2.74)**	**2.07 (1.62-2.65)**
- ICU	931 (78.2)	260 (21.8)	<0.01	**3.56 (2.79-4.54)**	**3.45 (2.7-4.41)**
Type of catheter n(%)					
- CVC	2,466 (85.4)	423 (14.6)			
- PVC	1,025 (88.4)	134 (11.6)	0.009	**0.69 (0.54-0.88)**	
- PICC	641 (87.3)	93 (12.7)	0.14	0.92 (0.72-1.16)	
Catheter location n(%)					
- Arm/forearm	1,623 (88)	222 (12)			
- Jugular	1,120 (86.8)	171 (13.2)	0.30		1.18 (0.94-1.49)
- Femoral	281 (74.7)	95 (25.3)	<0.001		**1.78 (1.33-2.38)**
- Subclavian	1,053 (87.1)	156 (12.9)	0.41		1.21 (0.96-1.53)
Use of catheter n(%)					
- Haemodyalisis	182 (78.1)	51 (21.9)	0.001		
- Parenteral nutrition	1096 (87.8)	153 (12.2)	<0.001	0.79 (0.56-1.12)	0.9 (0.63-1.29)
- Drugs or fluids	2854 (86.5)	446 (13.5)		0.78 (0.58-1.07)	0.85 (0.62-1.17)
Days from catheter insertion Md (IQR)	10 (IQR 6 - 18)	10 (IQR 6 -17)	0.38		

Days from admission Md (IQR)	15 (IQR 8 - 28)	17.5 (IQR 10 - 34)	0.29		
Aetiology n(%)					
- Coagulase-negative *Staphylococci*	1,587 (89)	197 (11)			
- *Staphylococcus aureus*	972 (84.7)	176 (15.3)	<0.001	**1.63 (1.3-2.05)**	**1.59 (1.27-1.99)**
- Gram-negative bacilli	1104 (88)	151 (12)	0.35	0.97 (0.77-1.21)	0.95 (0.76-1.18)
- *Candida sp*	200 (77.2)	59 (22.8)	<0.001	**2.15 (1.6-2.89)**	**2.19 [1.64- 2.94]**
- Other	259 (79.4)	67 (20.6)		**1.64 (1.23-2.17)**	**1.6 (1.20-2.12)**

(*) Cox regression model adjusted with the variable 'Type of catheter' and other significative variables in the univariate analysis (**) Cox regression model adjusted with the variable 'Catheter location' and other significative variables in the univariate analysis. ICU: intensive care unit; CVC: central venous catheter; PVC: peripheral venous catheter; PICC: peripherally-inserted central catheter

Table 2: Risk factors for mortality of catheter-related bloodstream infections adjusting by catheter type

CVC Risk factor, (HR; 95%CI)	PICC Risk factor, (HR; 95%CI)	PVC Risk factor, (HR; 95%CI)
Age 1.03 [1.02;1.04]	Age 1.03 [1.01;1.05]	Age 1.04 [1.03;1.06]
Medical ward 2.11 [1.54;2.88]	Medical ward 2.12 [1.2;3.75]	
ICU 3.55 [2.65;4.75]	ICU 3.41 [1.82;6.4]	
S aureus 1.85 [1.36;2.51] (*)	*Candida sp.* 2.36 [1.27;4.39]	
*Candida sp.*2.08 [1.46;2.96] (*)		
Other microorganisms 1.71 [1.25;2.36] (*)		

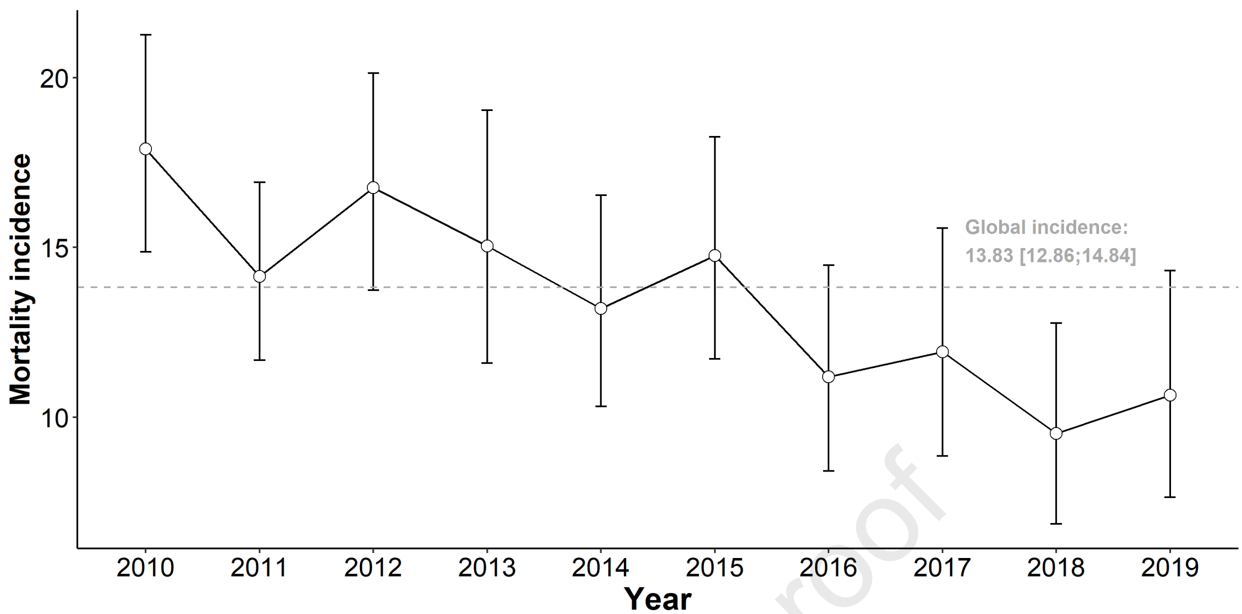
CVC: central venous catheter; PVC: peripheral venous catheter; PICC: peripherally-inserted central catheter (*) Coagulase-negative staphylococci is the reference cathegory. ICU: intensive care unit;

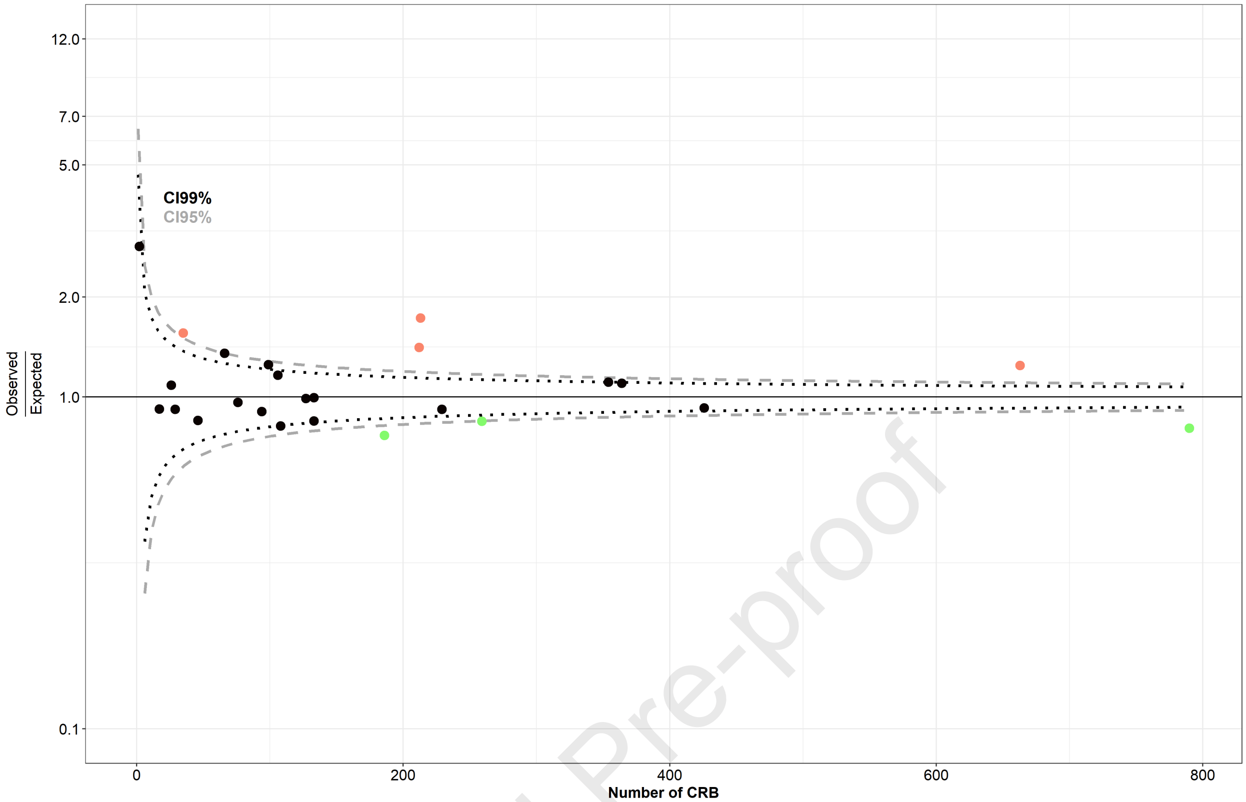
Figures legends

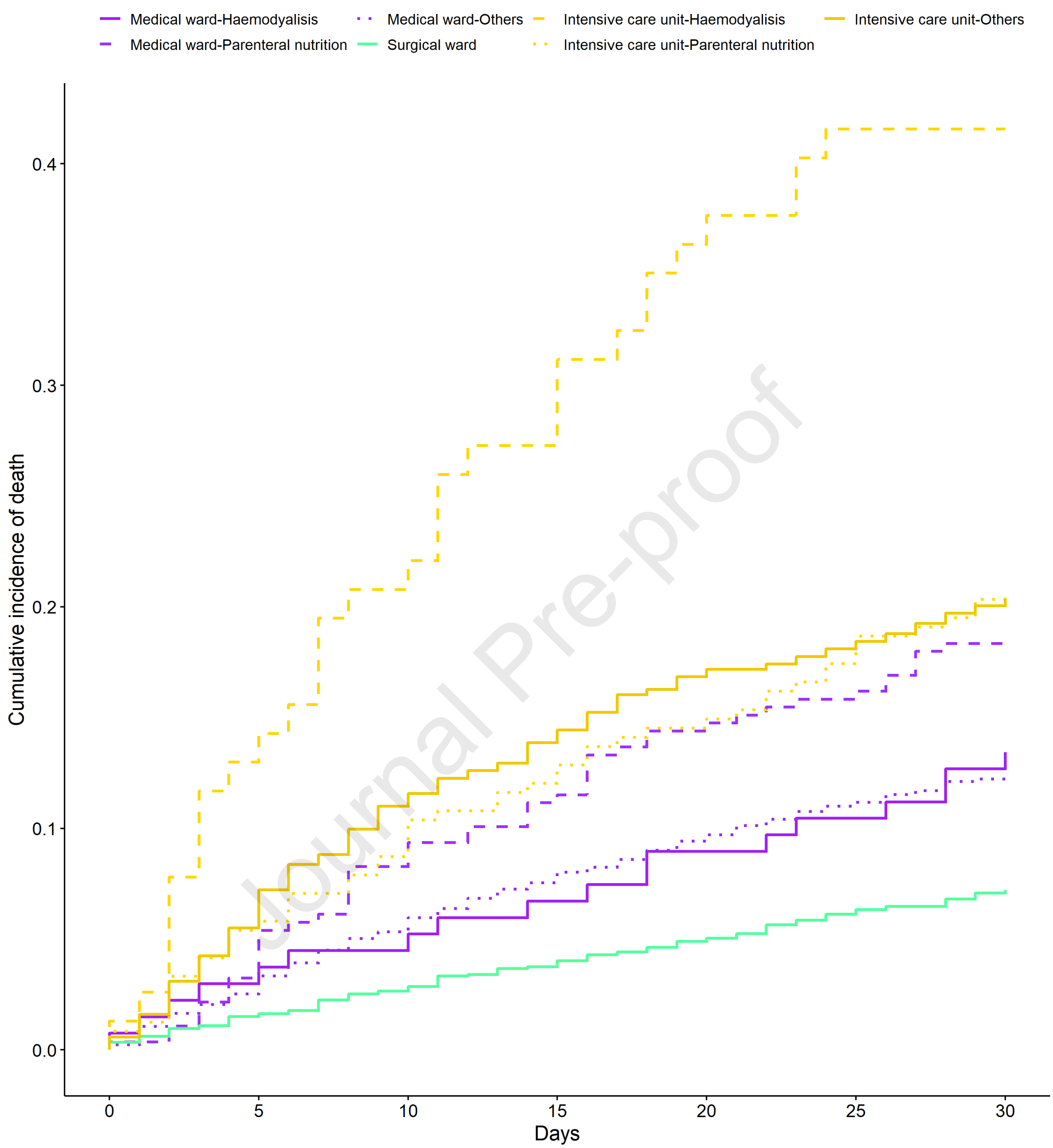
Figure 1. **Incidence of mortality of catheter-related bloodstream infections per year in VINCat hospitals**

Figure 2. Cumulative incidence of death according to place of acquisition and catheter use in catheter-related bloodstream infections

Figure 3. Funnel plot with the ratio of the observed versus expected deaths regarding the hospital of acquisition of the catheter-related bloodstream infection


Mortality incidence
20
15
10
Global incidence:
13.83 [12.86;14.84]
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
Year


12.0
7.0
5.0
2.0
1.0
0.1
CI99%
CI95%
Observed / Expected
0
200
400
600
800
Number of CRB



Medical ward-Haemodyalisis
Medical ward-Others
Intensive care unit-Haemodyalisis
Intensive care unit-Others
Medical ward-Parenteral nutrition
Surgical ward
Intensive care unit-Parenteral nutrition
Cumulative incidence of death
0.0
0.1
0.2
0.3
0.4
0
5
10
15
20
25
30
Days