Original

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Morbidity and mortality associated with primary and catheter-related bloodstream infections in critically ill patients

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ABSTRACT

Purpose. To analyze the impact of primary and catheter-related bloodstream infections (PBSI/CRBSI) on morbidity and mortality.

Methods. A matched case-control study (1:4) was carried out on a Spanish epidemiological database of critically ill patients (ENVIN-HELICS). To determine the risk of death in patients with PBSI/CRBSI a matched Cox proportional hazard regression analysis was performed.

Results. Out of the 74,585 registered patients, those with at least one episode of monomicrobial PBSI/CRBSI were selected and paired with patients without PBSI/CRBSI for demographic and diagnostic criteria and seriousness of their condition on admission to the Intensive Care Unit (ICU). For mortality analysis, 1,879 patients with PBSI/CRBSI were paired with 7,516 controls. The crude death rate in the ICU was 28.1% among the cases and 18.7% among the controls. Attributable mortality 9.4% (HR:1.20; 95% confidence interval: 1.07–1.34; p<0.001). Risk of death varied according to the source of infection, aetiology, moment of onset of bloodstream infection and severity on admission to the ICU. The median stay in the ICU of patients who survived PBSI/CRBSI was 13 days longer than the controls, also varying according to aetiology, moment of onset of bloodstream infection and severity on admission.

Conclusions. Acquisition of PBSI/CRBSI in critically ill patients significantly increases mortality and length of ICU stay, which justifies prevention efforts.

Key words: Primary bloodstream infection; Catheter-related bloodstream infection; Mortality; Morbidity; Critical Care Unit.

Morbi-mortalidad asociada a la bacteriemia primaria y relacionada con catéter en pacientes críticos

RESUMEN

Objetivos. El propósito de este estudio es analizar el impacto de la bacteriemia primaria y relacionada con catéter (BP/BRC) en la morbilidad y mortalidad.

Métodos. Con datos pertenecientes a la base de datos epidemiológica de pacientes críticos en España ENVIN-HELICS, se realiza un estudio casos controles (1:4). Para analizar el riesgo de muerte en pacientes con BP/BRC se realiza un estudio emparejado de riesgos proporcionales de Cox.

Resultados. De 74.585 pacientes registrados, se buscó pacientes con al menos un episodio de BP/BRC monomicrobiana y fueron emparejados con pacientes sin BP/BRC por criterios demográficos, diagnósticos y de gravedad al ingreso en la Unidad de Cuidados Intensivos (UCI). Para el análisis de mortalidad 1.879 pacientes con BP/BRC fueron emparejados con 7.516 controles. La mortalidad cruda en UCI fue del 28,1 % en los casos y 18,7 % en los controles. Mortalidad atribuida 9,4 %. (HR:1,20; intervalo confianza 95 %: 1,07 – 1,34; p<0,001). El riesgo de muerte varía de acuerdo a la fuente de la infección, la etiología, el momento de aparición de la bacteriemia y la gravedad al ingreso en UCI. Los pacientes que sobreviven y sufren una BP/BRC tienen una estancia en UCI 13 días de mediana más prolongada que los controles, variando también según la etiología, el momento de aparición de la bacteriemia y la gravedad al ingreso en UCI.

Conclusiones. En pacientes críticos, la adquisición de una BP/BRC produce un significativo incremento de la mortalidad y la estancia, lo que justifica los esfuerzos de prevención.

Palabras clave: Bacteriemia primaria, bacteriemia relacionada con catéter, mortalidad, morbilidad. Unidad de Cuidados Intensivos.

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INTRODUCTION

Primary bloodstream infection (PBSI) and catheter-related bloodstream infection (CRBSI) account for almost 30% of all nosocomial infections in the intensive care environment, taking second place only to ventilator-associated pneumonia[1]. While the CRBSI rate has fallen in recent years[1-3], its consequences on the morbidity of critically ill patients is still considerable. The risk factors for CRBSI acquisition are related to the severity of the patient's condition and the therapeutic procedures undertaken[4].

The literature has produced contradictory data on the effects of nosocomial bloodstream infection (BSI) on the morbidity and mortality of critically ill patients. Attributable mortality as high as 35% has been reported[5-7]. Other investigations report lower attributable mortality rates (20 to 29%)[8-9], whilst in some studies, CRBI has been shown to have no effect on mortality[10-12], a result that has been repeated in a number of cause-specific studies[13-15], with the exception of infection caused by fungi[16-18]. The reasons for these discrepancies lie in the study population, type of BSI, statistical power of the study and the methodology used to make the comparison and handle the confounders[19]. The majority of these papers are case-control studies, which are handicapped by the difficulty of finding adequately paired controls.

There is greater consensus in the literature with regard to the effects of BSI on morbidity, measured by length of stay, since all investigations report an increase in ICU stay, with the median ranging between 6 and 12.5 days[5,6,12]. Knowledge of the impact of and costs related to nosocomial infections is crucial in order to be able to demonstrate the cost-effectiveness of preventive measures[20].

The main objective of the present study is to identify the effects of PBSI and/or CRBSI on mortality and morbidity (expressed as an increase in length of stay in the ICU) in critically ill patients. The secondary objective is to analyze the factors related to increased morbidity and mortality in critically ill patients who acquire PBSI or CRBSI.

METHODS

A double case-control study was carried out on patients with records in the Spanish National Register for Surveillance of Nosocomial Infection in the ICU (ENVIN-HELICS)[1,21], analyzing data gathered during a three-month period every year between 1997 and 2007 inclusive, on patients admitted to ICUs for more than 24 hours.

These patients were subjected to continuous surveillance, being monitored until discharged from the ICU or for a maximum of 60 days. Demographic variables were gathered for all selected patients, as well as underlying pathology, any instrumentation received, length of hospital stay prior to admission to the ICU, length of stay in the ICU and clinical status on discharge.

Definitions. Definitions were taken from the registry manual (available at: http://hws.vhebron.net/envin-helics/) and a suitable computer program was used for data capture. Patients were classified in accordance with their underlying pathology, as coronary, medical, surgical or trauma. Coronary patients were defined as those whose reason for admission was an acute ischaemic episode. Trauma patients included those whose reason for admission was acute injuries produced by trauma. Surgical patients were those whose reason for admission was postoperative monitoring of a operation. Medical patients were considered as those whose reason for admission was none of the above, Patient severity was evaluated using the APACHE II scoring system on admission[22] or failing this, the SAPS II system[23]. Attributable mortality was defined as the difference in crude death rate between cases and controls during their ICU stay. Stay attributable to infection, or 'excess length of stay,' was defined as the difference between the median ICU stay for cases and their controls.

PBSI and CRBSI episodes occurring more than 48 hours after admission to the ICU were analyzed separately and together, given the general controversy as to whether a large number of cases typically labelled as PBSI are in fact undiagnosed CRBSI[6,10]. In accordance with the (CDC) definitions[24], PBSI was defined as the presence of a clinical context compatible with infection and the obtainment of positive cultures in the blood, with no known source of infection. CRBSI was defined as the isolation of the same microorganism in the blood and on the tip or connections of a central venous catheter, in association with a compatible clinical context. When the isolated pathogen was a skin-colonizing microorganism, two blood cultures positive for the same pathogen were required. The causal pathogen was identified in the microbiology laboratory of each participating hospital. BSI rates were calculated by dividing the number of episodes by the number of days of patient exposure to central venous catheters and expressed as the incidence density for the number of PBSI/CRBSI episodes per 1,000 patient-days.

Patient selection. A total of 162 ICUs participated, starting with 51 in the first year and totalling 112 in the final year, with 2,393 patients being recruited in 1997 and 12,453 in 2007. Overall, 74,585 patients were included in the analysis. From among these, 2,499 PBSI/CRBSI episodes were recorded in a total of 2,193 patients; in a number of cases more than one microorganism was identified, with the total number of positive isolations of a pathogen at 2,719. In those patients who had suffered more than one episode, only the first episode was selected, assuming that subsequent episodes or other infections occur as a result of a more prolonged stay due to the PBSI/CRBSI. In order to study the influence of the aetiology those episodes of BSI with more than one causal microorganism were excluded; whilst for those in which, in addition to the pathogen, another microorganism was isolated from the skin, the aetiology of the BSI infection was assigned to the non-skin-colonizing pathogen. Using these criteria, the initial case database totalled 2,116 patients, with the controls being the remainder of patients who had not developed PBSI/CRBSI, although they may have suffered from other nosocomial infections.

Table 1 **Aetiology of episodes of monomicrobial primary bloodstream infection (PBSI) and catheter-related bloodstream infection (CRBSI) and the sum of both (n (%)). Difference in percentage between PBSI and CRBSI.**

	All types of BSI (n=2,116)	PBSI (n=971)	CRBSI (n=1,145)	p^a
Gram-negative	579 (27.4)			
Gramnegative bacilli	337 (15.9)	188 (19.3)	149 (13.0)	<0.001
Acinetobacter spp.	111 (5.3)	41 (4.2)	70 (6.1)	0.062
Pseudomonas spp.	131(6.2)	63 (6.5)	68 (5.9)	0.623
Gram-positive	1,428 (67.5)			
Enterococcus spp.	217 (10.3)	139 (14.3)	78 (6.8)	<0.001
Coagulase-negative Staphylococci	972 (45.9)	372 (38.3)	602 (52.6)	<0.001
MRSA	56 (2.6)	19 (1.9)	37(3.2)	0.076
MSSA	131 (6.2)	50 (5.1)	81 (7.1)	0.085
Other grampositive cocci	52 (2.5)	41(4.2)	11 (0.9)	<0.001
Fungi	92 (4.4)			
Candida albicans	49 (2.3)	26 (2.7)	23 (2.0)	0.319
Candida spp.	43(2.0)	21 (2.2)	22 (1.9)	0.700
Other pathogens	17 (0.8)	12 (1.2)	5 (0.4)	0.041

NOTE. MRSA: Methicillin-resistant *Staphylococcus aureus*.
MSSA: Methicillin-sensitive *Staphylococcus aureus*.
[a]Chi-square test

The microorganisms responsible for BSI were grouped by Gram staining and by their potential effect on mortality, classifying as high-risk the BSI episodes caused by *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus*, *Acinetobacter baumannii*, enterobacteriaceae producing extended-spectrum beta-lactamase and fungi, whilst including all other pathogens in the low-risk group[8].

Pairings. Two types of pairing were carried out, one to calculate mortality and the other to calculate the excess length of stay in the ICU as a consequence of PBSI/CRBSI. For the former, cases and controls were paired using the following pairing criteria: sex, age (±10 years), year of admission (between 1997 and 2007), underlying pathology (coronary, medical, surgical or trauma) and APACHE II on admission to the ICU (±5 points) or when this data was lacking, SAPS II (±10 points). Four controls were found for each case. The year on admission has been selected as paring criteria in order to control the time effect.

For calculating excess length of stay, controls were selected according to the same criteria as above with the additional factor that the control's ICU stay had to be equal to or greater than the time until onset of BSI in the corresponding case, assuming that the excess stay in the cases from this moment on was due to BSI and not to other factors.

Statistical analysis. A descriptive analysis was performed, with continuous variables described as the mean, 95% confidence interval (95% CI), median and interquartile range (IQR). Qualitative variables were described in terms of frequency and percentage. The chi-square test was used to compare percentages and the Mann-Whitney *U* test to compare continuous variables. A matched (1:4) Cox proportional hazard regression analysis was carried out to determine the risk of death in the set of patients with BSI. Statistical analysis was carried out using Statistical Analysis Software (SAS Institute, Cary, NC, USA).

RESULTS

The mean incidence density of PBSI/CRBSI in all participating ICUs was 6.61 episodes of PBSI/CRBSI per 1,000 patient-days of central venous catheter, ranging between 7.93 (in 2004) and 4.65 (in 2007). The aetiology of the monomicrobial PBSI/CRBSI episodes is described in table 1, differentiating the causal agent according to type of bloodstream infection: PBSI or CRBSI. Coagulase-negative *Staphylococcus* form the majority (45.9%) followed by fermenting gram-negative bacilli (15.9%) and *Enterococcus* spp. (10.3%). The proportion of gram-negative bacilli, *Enterococcus* spp, other gram-positive cocci and other pathogens is greater in PBSI, whilst the proportion of coagulase-negative *Staphylococcus* is greater in

Table 2 **Characteristics of the patients included in the pairing database for mortality.**

	Cases n=1,879	Controls n=7,516
Gender (male): n (%)	1,313 (69.9)	5,253 (69.9)
Age: m (95% CI)	57.39 (56.6–58.2)	57.51 (57.1–57.9)
Underlying pathology: n (%)		
Coronary	139 (7.4)	556 (7.4)
Medical	1,049 (55.8)	4,197 (55.8)
Surgical	396 (21.1)	1,583 (21.1)
Trauma	295 (15.7)	1,180 (15.7)
APACHE II[a]: m (95% CI)	18.36 (18.02–18.69)	18.19 (18.02–18.36)
SAPS II[b]: m (95% CI)	36.71 (34.13–36.70)	36.24 (34.99–37.49)
Year of admission: n (%)		
1997	44 (2.3)	176 (2.3)
1998	85 (4.5)	339 (4.5)
1999	123(6.5)	491 (6.5)
2000	134 (7.1)	534 (7.1)
2001	114 (6.1)	482 (6.4)
2002	182 (9.7)	711 (9.5)
2003	168 (8.9)	680 (9.0)
2004	196 (10.4)	768 (10.2)
2005	272 (14.5)	1,052 (14.0)
2006	284 (15.1)	1,159 (15.4)
2007	277 (14.7)	1,124 (15.0)
Days of ICU stay[c]: m (mdn) [IQR]	26.96 (24) [15–35]	7.19 (5) [3–8]
Mortality in ICU[c]: n (%)	529 (28.1)	1407 (18.7)

m: mean; mdn: median; IQR: interquartile range (25–75%)

[a]APACHE II in 1726 cases and 6904 controls

[b]SAPS II in 153 cases and 622 controls

[c]Differences between cases and control: p <0.001.

CRBSI.

Case-control study for mortality. Of the 2,116 cases, 237 (11.2%) were excluded for not having had APACHE II or SAPS II recorded on admission and a further two cases were excluded due to an inability to find controls for the remaining variables. The final total for inclusion was 1,879 cases and 7,516 controls. The aetiology among the excluded cases was similar to that for the total group (data not displayed). The median stay in the ICU of the excluded patients was 27 days (IQR: 16–38 days) and mortality, 28.4%.

Table 2 displays the data of the variables that were used for the pairing. There are no differences in any of the data, between the patients who developed BSI and those who did not. Table 3 reflects the differences between those patients that died and those that survived. The patients who died were older (61.19 years; 95% CI: 60.50–61.88 vs. 56.53 years; 95% CI: 56.13–56.93; p<0.001), with BSI, predominantly 'medical' pathologies and higher APACHE II and SAPS II scores. A greater proportion of PBSI patients died (30.3%) than CRBSI patients (25.9%) (p= 0.081; 95% CI 0.98-1.32). Overall, there are differences in mortality according to aetiology (p=0.001), notably with a 57.4% death rate in patients who suffered from BSI due to *Candida albicans*.

The impact on mortality varies depending on the type of BSI, the time elapsed in the ICU before onset, the causal microorganism and the severity of the patient's condition on admission to the ICU (table 4). Mortality attributable to PBSI/CRBSI is 9.4% (hazard ratio (HR) 1.20; 95% CI: 1.07–1.34; p<0.001), with an even higher percentage for PBSI alone (12.4%; HR: 1.29; 95% CI: 1.10–1.51; p=0.001), whilst mortality directly attributable to CRBSI is not significant (6.8%; HR: 1.12; 95% CI: 0.96–1.30; p=0.13). Attributable mortality is greater when the BSI occurs after the seventh day after admission to the ICU (14.4%; HR: 1.20; 95% CI: 1.05–1.38; p=0.009), in patients who suffer from PBSI/CRBSI caused by fungi (27.5%; HR: 3.97 95% CI: 1.93–8.17; p<0.001) or microorganisms considered as high-risk (13.9%: HR: 1.27 95% CI 1.05–1.54; p=0.025) and in those whose APACHE II score on admission to the ICU is less than 20 points (13.8%; HR 1.21: 95% CI: 1.02–1.43; p<0.001) (table 4).

Case-control study for excess length of ICU stay. On 392 occasions (18.5%), no controls were found for whom length of stay was at minimum the length of time before BSI occurred in the corresponding case, for which reason these cases were excluded. These cases had a median length of stay before BSI of 26 days, which explains the difficulty in finding controls that fulfil the time condition. In these cases, median ICU stay was 40 days and mortality was 23.1%. A further 221 cases (10.4%) were excluded due to their having no APACHE II or SAPS II score. For 65 cases, only one control was found, for 30 cases, only two and for 36 cases, only three controls. In total, 1,503 cases (71.0%) and 5,721 controls were included (3.8 controls per case), out of which 1,074 cases and 4,710 controls survived.

Excess length of stay in PBSI/CRBSI survivors was 13 days, given that the median length of stay was 22 days for patients with PBSI/CRBSI (IQR: 14–32) and 9 days for their controls (IQR: 6–14) (table 5). Length of ICU stay attributable to infection in PBSI patients who survived was 13 days, compared to 12 days in CRBSI patients. The excess length of stay attributable to PBSI/CRBSI was longer in patients with late-onset infections (14 days), infection due to fungus (18 days) and in those

Table 3 Analysis of factors related to mortality.

	Died n=1,936	Survived n=7,459	p
Gender (male): n (%)	1,302 (67.2)	5,263 (60.2)	0.005[b]
Age: m (95% CI)	61.19 (60.50–61.88)	56.53 (56.13–56.93)	<0.001[c]
Underlying pathology: n (%)			<0.001[b]
Coronary	92 (4.8)	603 (8.1)	
Medical	1,325 (68.4)	3,921 (52.6)	
Surgical	268 (13.8)	1,711 (22.9)	
Trauma	251 (13.0)	1,224 (16.4)	
APACHE II: m (95% CI)	22.73 (22.41–23.05)	17.05 (16.89–17.20)	<0.001[c]
SAPS II: m (95% CI)	43.81 (41.03–46.59)	34.58 (33.40–35.76)	<0.001[c]
Days of ICU stay: m (mdn) [IQR]	7 (12.13) [4–16]	6 (10.89) [4–13]	0.017[c]
Bloodstream infection n (%)			<0.001[b]
Primary (868)	267 (13.8)	601 (8.1)	
Catheter-related (1,011)	262 (13.5)	749 (10.0)	
No bloodstream infection (7,516)	1,407 (72.6)	6,109 (81.9)	
Microorganism[a]			
Gram-positive			<0.001[b]
Enterococcus spp. (190)	50 (26.3)	140 (73.7)	
Coagulase-negative staphylococci (872)	217 (24.9)	655 (75.1	
MRSA (51)	16 (31.4)	35 (68.6)	
MSSA (117)	33 (28.2)	84 (71.8)	
Other gram-positive cocci (50)	19 (38.0)	31 (62.0)	
Gram-negative			
Acinetobacter (99)	68 (38.4)	61(61.6)	
Gram-negative bacilli (282)	76 (27.0)	206 (73.0)	
Pseudomonas spp. (118)	36 (30.5)	82 (69.5)	
Fungi			
Candida albicans (47)	27 (57.4)	20 (42.6)	
Candida spp. (41)	14 (34.1)	27 (65.9)	
Other pathogens (12)	3 (25.0)	9 (75.0)	

m: mean; mdn: median; IQR: interquartile range (25–75%)

MRSA: Methicillin-resistant *Staphylococcus aureus*. MSSA: Methicillin-sensitive *Staphylococcus aureus*.

[a] Expressed as n and percentage of patients who died or survived for each variable.

[b] Chi-square test. [c] Mann-Whitney U test

patients who had higher APACHE II on admission and survived (16 days) (table 5).

DISCUSSION

In the present study, patients with PBSI/CRBSI had attributable mortality of 9.4% and a median extended ICU stay of 13 days. PBSI has a substantial effect on patient mortality (HR 1.20; 95% CI: 1.07–1.34; p=<0.001), but CRBSI does not (HR 1.12; 95% CI: 0.96–1.30; *p*=0.13). A greater effect on mortality is observed with BSI caused by pathogens considered to have a high risk of mortality, fungi as compared to bacteria, and

Table 4 **Factors related to attributable mortality, by type of bloodstream infection (BSI), causal pathogen and severity of patient's condition.**

Factor (cases / controls)	Mortality: cases (%)	Mortality: controls (%)	Attributable mortality (%)	HR[b]	95% CI	p
Type of BSI						
PBSI and CRBSI (1,879 / 7,516)	28.1	18.7	9.4	1.20	1.07–1.34	<0.001
PBSI (868 / 3,472)	30.7	18.3	12.4	1.29	1.10–1.51	0.001
CRBSI (1,011 / 4,044)	25.9	19.1	6.8	1.12	0.96–1.30	0.13
Early-onset PBSI/CRBSI (< 7 days in ICU) (1,357 / 5,500)	27.1	19.3	7.8	1.21	1.01–1.45	0.03
Late-onset PBSI/CRBSI (≥ 7 days in ICU) (504 / 2,016)	31.5	17.1	14.4	1.20	1.05–1.38	0.009
Causal microorganism						
Gram-negative (499 / 1,996)	30.1	18.0	12.1	1.25	1.02–1.55	0.039
Gram-positive (1,280 / 5,120)	26.2	18.8	7.4	1.16	1.02–1.33	0.021
Fungus (88 / 352)	46.6	19.1	27.5	3.97	1.93–8.17	<0.001
High-risk[a] (638 / 2,552)	32.5	18.6	13.9	1.27	1.05–1.54	0.012
Low-risk[a] (1,229 / 4,916)	25.9	18.8	7.1	1.16	1.01–1.33	0.025
Severity of patient's condition						
APACHE II <20 on admission (1,006 / 4,308)	22.5	8.7	13.8	1.21	1.02–1.43	0.023
APACHE II ≥20 on admission (720 / 2,093)	35.4	34.4	1.0	1.23	1.03–1.47	0.019

PBSI: Primary bloodstream infection; CRBSI: Catheter-related bloodstream infection

[a] High-risk: BSI caused by Methicillin-resistant *Staphylococcus aureus, Pseudomonas aeruginosa, Acinetobacter baumannii* and *Enterobacteriaceae* producing extended-spectrum beta-lactamase. Low- risk: BSI caused by any other microorganism.

[b] Matched Cox proportional hazard regression analysis.

patients with APACHE II lower than 20 on admission. There are also differences with regard to excess length of stay in survivors, between early-onset BSI (9 days) and late-onset BSI (14 days), between BSI produced by fungi (18 days) and produced by bacteria (13 days for Gram-negative bacteria and 12 for Gram-positive bacteria) and between patients with APACHE II greater than 20 on admission (16 days) and less than 20 (11 days). The 'case-control' study format was selected due to the fact that relatively few variables were available for each patient (thus limiting the usefulness of a matched cohort study) and the cohort was extremely large (the largest to be published in this domain), making it possible to obtain a high percentage of pairings, which tends to be one of the problems of case-control studies, although it is recognized that this type of studies can overestimate the impact of nosocomial infection[19]. On the other hand, carrying out the matched Cox regression analysis allows to determine the risk of death in each set of patients with BSI (cases and its respective controls) controlling the effect ICU length of the stay on mortality.

The literature contains both higher[6-9,25-27] and lower[10-12] figures for mortality attributable to BSI. One multicentre study on patients admitted to ICUs, containing 123 PBSI/CRBSI cases, reports an attributable mortality rate of 16.7%[8], which can be explained by the fact that mortality in the study in question is 57.8% for the cases and 41.1% for the controls, figures which are much higher than those of the present work (28.1 % and

Table 5 Excess length of stay attributable (days) to bloodstream infection (BSI), by type of BSI, causal microorganism and patient severity

	Stay (all patients) mdn.		Stay (survivors) mdn. [IQR]		
Factor (cases / controls)	Cases n=1,503	Controls n=5,721	Cases n=1,074	Controls n=4,710	Difference, survivors only (days)[b]
Type of BSI					
PBSI and CRBSI (1,503 / 5,721)	21	9	22 [14–32]	9 [6–14]	13
PBSI (726 / 2,767)	21	9	22 [14–32]	9 [6 –13]	13
CRBSI (777 / 2,954)	21	10	22 [14–33]	10 [7–15]	12
Early-onset PBSI/CRBSI (< 7 days in ICU) (1,000 / 3,709)	14	5	14 [8–23]	5 [4–6]	9
Late-onset PBSI/CRBSI (≥ 7 days in ICU) (503 / 2,012)	25	13	26 [18–36]	12 [9–16]	14
Causal microorganism					
Gram-negative (392 / 1,465)	21	10	23 [14–33]	10 [6–14]	13
Gram-positive (1,036 / 3,984)	21	9	21 [14–32]	9 [6–14]	12
Fungus (64 / 228)	26	10	28 [23–56]	10 [7–16]	18
High-risk[a] (497 / 1,843)	21	10	23 [14–33]	10 [7–15]	13
Low-risk[a] (995 / 3,834)	21	9	21 [14–32]	9 [6–13]	12
Severity of patient's condition					
APACHE II < 20 on admission (832 / 3,270)	20	9	20 [13–31]	9 [6–14]	11
APACHE II ≥ 20 on admission (554 / 2,017)	24	10	26 [18–35]	10 [7–15]	16

PBSI: Primary bloodstream infection; CRBSI: Catheter-related bloodstream infection; mdn: median. IQR: interquartile range

[a] High-risk: BSI caused by Methicillin-resistant *Staphylococcus aureus, Pseudomonas aeruginosa, Acinetobacter baumannii* and *Enterobacteriaceae* producing extended-spectrum beta-lactamase. Low-risk: Bacteraemia caused by any other microorganism

[b] All differences in stay between cases and controls p <0.001 (Mann-Whitney U test).

18.7% respectively). This difference might in part be explained by the greater proportion, in the present study, of BSI caused by coagulase-negative *Staphylococcus* (45.9%), which is associated to lower morbidity and mortality[8,10,15]. Other studies have reported the absence of a link between CRBSI and mortality[8,28]. However a recent meta-analysis found higher mortality (OR 1.96; 95% CI: 1.25–3.09) among patients with CRBSI compared to those did not suffer from CRBSI[28]. Grouping the microorganisms responsible for BSI by Gram staining, presence of yeast, or their association with high or low risk of mortality, as well as length of time in the ICU prior to onset of infection, has made it possible to quantify the impact of BSI on risk of death in various groups of patients exposed to PBSI/CRBSI. Our findings are in line with those of studies using similar methodologies[8], although the present study has lower attributable mortality percentages. The direct relationship between *Candida* infection and mortality should be highlighted, especially since this is a subject that elicits considerable controversy[18,29].

Predicted mortality[23] for an APACHE II score of 18 points (which was the mean for both cases and controls) is 29%, similar to the figure for the cases alone, but 10.5 percentage points above that of the controls. The present study finds that the

effect of BSI on mortality can be discerned among the less severe patients although also it can be found less effect among patients with a high death rate due to underlying illness.

All previously published studies refer to an excess length of stay in the ICU and in hospital[5,6,10-12] as a consequence of BSI. In the present study, excess length of stay has been quantified in relation to several factors, with greater increases caused by presence of fungus, late-onset PBSI/CRBSI or APACHE II >20 in survivors. To the authors' knowledge, this information has not been published previously and helps better to understand the effect of BSI on excess length of stay (and thus on the associated costs)[10,12].

The present study has several limitations. Firstly, the fact that it is multicentre in nature, meaning that there may be differences in policies regarding discharge from the ICU or withdrawal of active treatment, which may have an impact on length of stay and/or mortality. Secondly, the fact that some cases were excluded due to a lack of data relating to the severity of patient condition, even though the excluded cases had similar aetiology and progressed in a similar manner as those that were included. Thirdly, patient severity at onset of BSI (a factor that is considered important by some authors[8,10]) was not evaluated but rather severity of illness on admission to the ICU, given that the ENVIN-HELICS is an epidemiological study on nosocomial infection. Although it would appear logical to consider this as a limitation, our results are consistent with the literature and in some extent, similar to the investigations that measured clinical status in the days leading up to onset of BSI[8]. Finally, the appropriateness of the administered antibiotic treatment was not evaluated, neither was the way in which the supposedly infected catheters were handled. However, it should be taken into account that the patients included in the study were treated by Intensive Care specialists and that in general, standard recommendations and protocols would have been followed.

In conclusion, the present multicentre study, which includes the largest number of cases of BSI to date, contributes information about the impact of PBSI or BSI secondary to infection from a central venous catheter, on the morbidity and mortality of critically ill patients. This information may be useful for calculating the cost-effectiveness of programs aimed at reducing BSI related to central venous lines[21, 30].

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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