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ORIGINAL RESEARCH

PREDICTIVE FACTORS OF IN-HOSPITAL MORTALITY IN OLDER ADULTS WITH COMMUNITY-ACQUIRED BLOODSTREAM INFECTION

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Abstract: *Objectives:* To assess the prevalence of intra-hospital mortality and associated risk factors in older people aged 75+, admitted with blood stream infections (BSI). *Design:* Single center retrospective study performed in an 850-bed of the academic hospital of the Université Libre de Bruxelles. *Setting and Participants:* From January 2015 to December 2017, all inpatients over 75 years old admitted with BSI were included. *Measures:* Demographical, clinical and microbiological data were collected. *Results:* 212 patients were included: median age was 82 [79-85] years and 60 % were female. The in-hospital mortality rate was 19%. The majority of microorganisms were Gram-negative strains, of which Escherichia coli was the most common, and urinary tract infection was the most common origin of BSI. Compared to patients who survived, the non-survivor group had a higher SOFA score (6 versus 3, p<0.0001), a higher comorbidity score (5 versus 4, p<0.0001), more respiratory tract infections (28 vs 6 %, p < 0.0001) and fungal infections (5 vs 1 %, p = 0.033), bedridden status (60 vs 25 %, p < 0.0001), and healthcare related infections (60 vs 40 %, p = 0.019). Using Cox multivariable regression analysis, only SOFA score was independently associated with mortality (HR 1.75 [95%IC 1.52-2.03], p<0.0001). *Conclusions and Implications:* BSI in older people are severe infections associated with a significant in-hospital mortality. Severity of clinical presentation at onset remains the most important predictor of mortality for BSI in older people. BSI originating from respiratory source and bedridden patients are at greater risk of intra-hospital mortality. Further prospective studies are needed to confirm these results.

Key words: Blood stream infections, older adults, mortality, bacteremia, SOFA.

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Introduction

Bloodstream infection (BSI) is a common cause of hospitalization and mortality in older people (1). The incidence of BSI increases with age (2), due to multiple factors such as immune senescence, comorbidity, malnutrition, and environmental factors (3). The diagnosis of BSI in frail old people remains a challenge because of the high frequency of atypical clinical presentations (4). Geriatric symptoms such as delirium, drowsiness, loss of appetite, weight loss, falls, and incontinence may be in the foreground in the absence of specific symptoms of infection (5). Inflammatory biomarkers like C - reactive protein may be useful but lacks specificity and the use of procalcitonin as a specific biomarker of infection is still debated (6). Urinary tract infections are the most common source of bacteremia in the majority of studies, followed by respiratory infections. Gram-negative are more common than Gram-positive organisms. They are responsible for 40% to 60% of BSI in older people (1). Among them, Escherichia coli spp is the most common pathogen found, accounting for 40% of community-acquired BSI, and 10-20% of healthcare-associated BSI (7-11). In the last 20 years, the incidence of BSI has increased in the general population, and in-hospital case-fatality ratio has decreased (12). Four studies evaluated intra-hospital mortality rate in patients over 75 years of age, ranging from 15 to 56%. (11, 13-15). None of these studies assessed the mortality rate as a primary objective, and population and clinical characteristics varied considerably from one study to another.

The main objective of this study was to assess the prevalence of intra-hospital mortality in patients older than 75 years old admitted with BSI. The secondary objectives were to evaluate the characteristics of BSI and to identify risk factors for in-hospital mortality.

Materials and methods

Setting and design

We performed a single center retrospective study in the 850 beds of the academic hospital of the Université Libre de Bruxelles, Brussels, Belgium. From January 2015 to December 2017, we included all inpatients over 75 years admitted for BSI (bacteremia and fungemia), in whom positive blood cultures were obtained within the first 48 hours after admission. We identified the patients on the basis of laboratory reports generated by the microbiology department. We excluded patients whom blood cultures were positive for a germ considered as a contaminant, patients having signed an opt-out declaration (written declaration of refusal to participate in a clinical study) and patients for whom the medical files were incomplete. Source of infection was determined according to CDC definitions (16). The local Ethical Committee (Comité

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d'Ethique Hospitalo-Facultaire Erasme-ULB) approved the study (P2017/125) but waived the need for informed consent because of its retrospective nature.

Clinical data

We evaluated patient-related risk factors, BSI-related risk factors and environmental risk factors of BSI.

Patient's factors were age (years), gender (Male = 1, Female = 0), Sequential Organ Failure Assessment (SOFA) score (from 0 to 24 points) (17), Charlson Comorbidity Index (from 0 to 37 points) (18), and immunosuppression (Yes = 1; No = 0). Immunosuppression was defined as HIV patients with lymphocytes CD4+<200/mm^3, patients taking immunosuppressive drugs in a context of organ transplant or autoimmune pathology, patients taking at least 7.5 mg of prednisolone for more than 3 months, and/or neutropenia with <500 neutrophils/mm3. Others factors were: active solid or hematological tumor (Yes = 1; No = 0), chronic renal insufficiency (Yes = 1; No = 0), defined in patients with a glomerular filtration rate (GFR) < 60 mL/min according to CKD- EPI and/or under dialysis, severe dementia (Yes = 1; No = 0), defined according to medical data recorded, and bedridden patients (Yes = 1; No = 0), defined as patients unable to get out of bed for more than 3 days during hospitalization.

Factors related to BSI were: adequate antibiotic therapy initiated in the first 48h of BSI onset (according to the antibiogram) (Yes = 1; No = 0); Health care-associated bloodstream infection (HCA-BSI) (Yes = 1; No = 0) defined as those having at least one of the following characteristics (19): having been discharged from an acute care hospital within the last 30 days, receiving hemodialysis or any kind of intravenous therapy provided by a hospital-dependent facility within 30 days prior to the BSI, residence in a long-term care facility. Other factors were: BSI with multi-resistant bacteria (BMR-BSI) (Yes = 1; No = 0), defined as a bacterium resistant to at least 3 classes of antibiotics including a third-generation cephalosporin (20), the microorganisms responsible for the BSI divided in four categories (GRAM-positive strains, GRAM-negative strains, fungal and polymicrobial infections) (Yes = 1; No = 0), the source of BSI divided in five categories (urinary, respiratory, intra-abdominal, other sources and unknown sources) (Yes = 1; No = 0) and the need for a surgical or endoscopic treatment for source control (Yes = 1; No =0).

Environmental factors were: residence in a nursing home before hospitalization (Yes = 1; No = 0), recent hospitalization in the last 30 days (Yes = 1; No = 0) and treatment with any antibiotic in the previous 30 days (Yes = 1; No = 0). The survivor group was defined as patients who were discharged from the hospital alive. The non-survivor group was defined as patients who died during hospitalization, regardless of the cause and the length of hospitalization.

Statistical analysis

Analyses were conducted using Stata-12 software (Stata Corp LLC, College Station, TX, USA). Descriptive results were reported as number and percentage (categorical variables). Continuous variables were expressed as mean ± SD or median (interquartile range, IQR). Comparison of the clinical characteristics differences in both groups (Survivors and Non-survivors patients) were performed using Chi2 test or Fischer's test for categorical variables, non-paired Student's t test or Mann Whitney test respectively for parametric and non-parametric continuous variables.

Patient survival was calculated by the Kaplan Meier method. The association between patient mortality and independent variables was estimated by univariate Cox proportional hazards model.

Thereafter, factors significantly associated with mortality were identified using univariable Cox's regression. Multivariable models were built using all significant variables detected in the univariable Cox's regression. Because of the number of variables allowed in the final model (cases=40), a first model was selected by using a forward stepwise procedure. Only one variable was selected and the final model was presented with the significant variable (SOFA) and isolates.

We have presented the HRs with 95% confidence interval derived from the Cox model and p-value corresponding to the Wald's test. The proportional hazards assumption for variables in the final Cox model was tested graphically for categorical variables and by using interaction with time for quantitative variable.

Two-sided p-values < 0.05 were considered as statistically significant.

Results

Two hundred and twelve (60 %) patients with BSI were included, and 143 patients (40 %) were excluded because of positive blood cultures considered as contaminants. The most common pathogen considered as a contaminant was Staphylococcus epidermidis spp (48%) found in single bottle. The median age of the study group was 82 [79-85] years and two thirds were female. Forty patients died (19%) after an average of 11 [5-10] days after admission. Figure 1 shows the survival curve: sixty (40 %) died within the first week of hospitalization, twenty-five (62%) within the first 15 days, and thirty- five (87%) within the first 30 days of hospitalization. Table 1 shows the characteristics of survivor et non-survivor groups. SOFA score and comorbidity according to the Charlson Comorbidity Index was higher in the non-survivor group. Fourteen (35%) of them were admitted at least once to Intensive Care Unit. Twenty-five (62%) died while receiving antibiotic therapy. The survival rate was equal with or without source control of bacteremia, either by endoscopy (p=0.628), or by surgical treatment (p=0.103). No difference was seen between groups for the number of adequate empirical antibiotherapy (p=0.194).

Table 1
Descriptive results in total, Non Survivor and Survivor groups

	Total n = 212	Non Survivor Groupn = 40(19%)	Survivor Group n = 172(81%)	p
Patient-related factors				
Age (years)	82[79-85]	83[79-87]	82[78-85]	0.214
Gender (males)	85(40)	16(40)	69(40)	0.989
Length of stay (days)	12[7-24]	11[5-10]	12[8-24]	0.247
SOFA score	3[2-4]	6[2-4]	3[2-4]	<0.0001
Charlson Comorbidity Index	4±2	5±2	4±2	<0.0001
Immunosuppression	33(16)	5(13)	28(16)	0.553
Cancer	78(37)	14(35)	64(37)	0.794
Chronic Renal Insufficiency	100(47)	24(60)	76(44)	0.071
Dementia	48(23)	11(28)	37(22)	0.415
Bedridden status	67(32)	24(60)	43(25)	<0.0001
BSI-related factors				
Healthcare acquired	92(43)	24(60)	68(40)	0.019
Multi drug resistant bacteria	34(16)	7(18)	27(16)	0.780
Source control	48(22)	11(28)	37(22)	0.415
Adequate empirical antibiotics	144(68)	26(65)	118(69)	0.660
Bacteria				
Gram positive strains	57(27)	15(38)	42(24)	0.093
Gram negative strains	132(62)	20(50)	112(65)	0.076
Polymicrobial	19(9)	3(8)	16(9)	0.719
Fungal	3(1)	2(5)	1(1)	0.033
Source				
Urinary	88(42)	9(23)	79(46)	0.007
Intra-abdominal	50(24)	7(18)	43(25)	0.314
Respiratory	21(10)	11(28)	10(6)	<0.0001
Unknown source	27(12)	6(15)	21(12)	0.633
Other source	26(12)	7(18)	19(11)	0.262
- Skin	4(2)	0(0)	4(2)	0.330
- Foreign material	8(4)	2(5)	6(3)	0.651
- Osteoarticular	6(3)	1(2.5)	5(3)	0.889
- Endocarditis	4(2)	2(5)	2(1)	0.108
- Meningitis	3(1)	2(5)	1(1)	0.033
- Vascular	1(1)	0(0)	1(1)	0.629
Environmental factors				
Living in nursing-home	39(18)	10(25)	29(17)	0.068
Hospitalization < 1 month	50(23)	10(25)	40(23)	0.815
Antibiotic use < 1 month	39(18)	6(15)	33(19)	0.538

SOFA : Sequential Organ Failure Assessment. Continuous data are expressed in medians ([IQR] or means ± SD. Categorical data are expressed in total numbers (percentages)

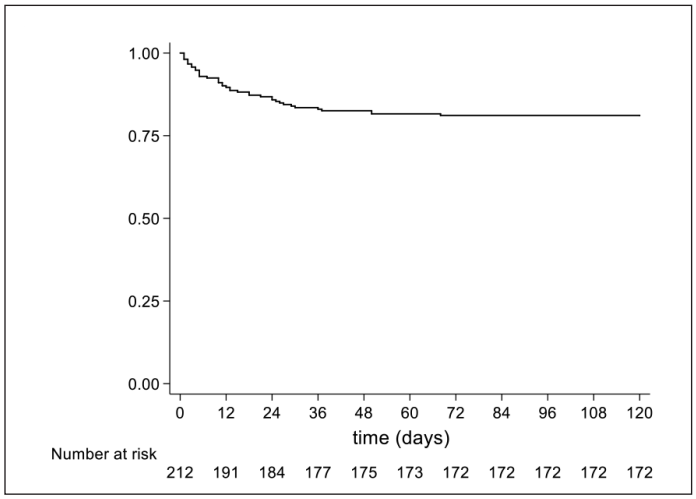
Table 2
List of microbiological isolates found in blood cultures

Name	N(%)
Gram negative strains n = 132 (62)	
Escherichia species	84 (39)
- Escherichia Coli non-ESBL	68(32)
- Escherichia Coli ESBL	16(7)
Klebsiella species	23(10)
Klebsiella non-ESBL	15(7)
- Klebsiella pneumoniae	12(5)
- Klebsiella oxytoca	3(2)
Klebsiella Pneumoniae ESBL	8(3)
Proteus Mirabilis	7(3)
Bacteroides species	6(2)
Pseudomonas Aeuruginosa	2(1)
Other gram negative strains	10(4)
Gram positive strains n = 57 (26)	
Streptococcus species	22(10)
Group A Streptococci	2(0)
Group D Streptococci	6(2)
Oral Streptococci	4(1)
Streptococcus Pneumoniae	10(4)
Staphylococcus species	17(8)
Staphylococcus aureus	16(8)
- Methicillin-sensitive	12(5)
- Methicillin-resistant	4(2)
Coagulase-negative Staphylococci	1(0)
Enterococcus species	15(7)
-Ampicillin sensitive	8(4)
-Ampicillin resistant	7(3)
Clostridium species	3(1)
Polymicrobial n = 19 (8)	
Fungal n = 3 (1)	
Candida species	3(1)
- Candida Albicans	3(1)
Other bacteria n = 1(0)	
Mycobacterium species	1(0)

ESBL = Extended-Spectrum ß-Lactamase

The majority of causative microorganisms were Gram-negative strains with E. coli as the most frequently isolated bacteria; urinary tract infection was the most common origin of BSI (Tables 1, 2). Cox univariate regression analysis identified the following risk factors for in- hospital mortality: the SOFA score, the Charlson Comorbidity Index, the status of being bedridden, the healthcare related infections, and the respiratory source (Table 3). On the other hand, infections caused by Escherichia coli (HR 0.36 [CI 95% 0.16-0.77], p=0.009) were found to be protective factor in terms of mortality. Using Cox multiple regression analysis, only the SOFA score was independently significantly associated with mortality.

Figure 1
Kaplan-Meier curve



Discussion

We described the factors associated with mortality inpatients older than 75 years old with community-acquired bloodstream infections, hospitalized in medical and surgical units in an academic center. The patient population included in our study has similar characteristics to patients older than 75 years old hospitalized in acute care units in Belgium, in terms of age, sex and length of stay (30). The most common source of BSI was urinary tract infection, as has been shown in many studies (7-10, 13-15). Urinary tract infection (UTI) is the most frequent bacterial infection in old people (21). Although bacteremia is classically considered as a marker of severe disease (22), two studies demonstrated that the prognosis of UTI associated with bacteremia is not worse than UTI without bacteremia in old patients (23, 24). We found multi-drug resistant gram-negative strains in 16% of cases, mainly E. Coli and K. Pneumoniae producing extended-spectrum ß-lactamase (ESBL). Only 2% were associated with Methicillin-resistant Staphylococcus Aureus and no patients presented BSI related to Vancomycin-resistant Enterococci (VRE) or Carbapenemase-producing Klebsiella species (KPC). The presence of multi drug resistant and classically healthcare associated bacteria in this population is due to the the fact that Gram negative strains producing ESBL are an emerging cause of community infections (25) and to the fact that many patients included in our study presented one or more risk factors like living in a nursing home (18%), a history of recent hospitalization (23%) or recent antibiotherapy (18%). The source of anaerobic BSI, essentially Clostridium species (1%) and Bacteroides species (2%), and polymycrobial BSI (8%) originated from intra-abdominal in almost all cases.

Table 3
Univariate Cox regression model

	HR	95%CI	p
Age (years)	1.06	0.99-1.12	0.059
Gender (males)	1.01	0.54-1.90	0.972
Length of stay (days)	0.99	0.97-1.01	0.287
SOFA score	1.81	1.62-2.03	<0.0001
Charlson Comorbidity Index	1.54	1.30-1.84	<0.0001
Immunosuppression	0.77	0.30-1.97	0.589
Cancer	0.93	0.49-1.78	0.825
Chronic Renal Insufficiency	1.80	0.96-3.39	0.068
Dementia	1.36	0.68-2.73	0.383
Bedridden status	3.82	2.03-7.20	<0.0001
Healthcare acquired	2.11	1.12-3.97	0.021
Living in nursing-home	1.60	0.78-3.27	0.199
Hospitalization < 1 month	1.07	0.52-2.19	0.857
Antibiotic use < 30 days	0.75	0.32-1.79	0.517
Adequate empirical antibiotics	0.89	0.46-1.70	0.719
Source control	1.26	0.63-2.53	0.507
Isolates :			
Gram positive	1		
Gram negative	0.53	0.27-1.04	0.07
Polymicrobial	0.54	0.16-1.86	
Fungal	2.64	0.60-11.59	
Source :			
Urinary	1		
Respiratory	7.11	2.94-17.20	0.0002
Intra-abdominal	1.34	0.50-3.61	
Other	2.83	1.05-7.59	
Unknown	2.29	0.82-6.45	

HR = Hasard Ratio. 95%CI = 95% Confidence Interval; SOFA : Sequential Organ Failure Assessment.

We also found a high prevalence of BSI due to abdominal infections, partially due to a large and active medico-surgical digestive department in our hospital. The prevalence of BSI from unknown source varies from one study to another, depending on the definitions used to describe the presence of an infection (1). In our study, the source was identified in 87% of cases, which is equivalent to other studies (7, 9, 13-15). The unknown source might also reflect the fact that clinicians limit investigations and privilege an empirical strategy, because of old age itself or because of pre-defined therapeutic limitations. Gram-negative strains were responsible of two thirds of BSI. In the literature, Gram-negative strains are more common than Gram-positive pathogens in BSI of older patients (15). The risk of colonization with Gram-negative microorganisms increases with age, functional status, nursing home residency, hospitalization and respiratory disease.

Table 4
Multiple cox regression model (cases=40/ n=212)

	aHR	95%CI	p
Source			
Urinary source	1		
Respiratory source	1.37	0.49-3.80	0.15
Intra-abdominal source	0.82	0.30-2.25	
Other source	3.02	1.11-8.20	
Unknown source	1.43	0.49-4.15	
SOFA Score	1.84	1.61-2.09	<0.0001

aHR = adjusted Hasard Ratio. 95%CI = 95% Confidence Interval; SOFA : Sequential Organ Failure Assessment.

The mortality associated with BSI was significant (19%) but lower than what is reported in other studies (11, 13-15). Mortality varies according to the characteristics of the population studied. For example, Blots et al. described a mortality rate of 56% but they considered only nosocomial BSI in patients hospitalized in intensive care units (11). The low mortality rate might also be due to the systematic co-management of patients with BSI in our hospital: the infectious diseases physician is immediately informed by the microbiology laboratory if a patient has positive blood cultures. Patients are then examined and antibacterial treatment is immediately reviewed: treatment is started, maintained if considered appropriate, or adapted to the pathogen identified in blood cultures (26).

More than one third of the non-survivor group died after the end of the antibiotic treatment, suggesting that the risk of mortality from BSI is not only a direct consequence of infection but also the consequence of the complications from the infection during hospitalization (anorexia, weakness, bedbound status, cardiac failure, altered neurological status, etc.). Although we found different patient-related, BSI-related and environmental-related risk factors associated with hospital mortality in Cox univariate analysis like bedridden status, respiratory infection, only SOFA score was found to be an independent risk factor of mortality. The SOFA score is an organ dysfunction/failure and morbidity estimation tool predicting the clinical outcomes in critically ill patients (17). In our study, a median score of 6 in the non-survivor group means a significant dysfunction of at least 2 systems. We hypothesize that the severity of the clinical presentation at the onset remains the most important predictor of mortality for BSI in older people, as already described in other studies (1, 7, 11, 13). Since this score has been validated for critically ill ICU patients, future studies are needed to assess the prognosis of patients with BSI.

The association between poor functional status and mortality in BSI has already been described; it may reflect both the poor condition of the patient prior to the infection and the severity

of the infection itself (10, 27, 28). Gavazzi et al. demonstrated that an ADL score <2 was associated with 30-day mortality in nosocomial BSI (27). In Belgium, Reunes et al. found that increased age and bedridden status were independent risk factors for death in nosocomial BSI (10). Based on this, we suggest that early mobilization in case of bacteremia could influence the rate of mortality of these patients.

The respiratory source has also been described in other studies as an independent risk of mortality in BSI (7, 11). In case of pneumonia, the yield of blood cultures increases significantly with the severity of pneumonia (29).

There are several study limitations that should be acknowledged. First, this is a retrospective study; geriatric syndromes like depression, malnutrition or functional status were therefore not systematically assessed. For the same reason, information on therapeutic limitations and vaccination status were lacking in the medical files. Second, it is a single center study, limiting its external validity.

Conclusion and implications

Our study confirms that BSI in older people are severe infections associated with a significant in-hospital mortality. The severity of clinical presentation assessed by the SOFA score at admission remains the most important predictor of mortality for BSI in older people. We highlight that BSI originating from pneumonia are the most lethal and that bedridden patients are at greater risk of in-hospital mortality. On the other hand, urinary BSI are the most common but are less dangerous. Further multi-centric, long-term prospective studies are needed to better identify the patients older than 75 years old with a BSI at risk of dying during their hospitalization.

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Conflicts of Interest: The author(s) declare(s) that there is no conflict of interest regarding the publication of this article.

Ethical standards: All procedures followed were in accordance with the ethical standards.

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