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BRIEF REPORT

Risk Factors for Mortality Among Older Adults with Hospital-Acquired Bloodstream Infections in the Intensive Care Unit: A Multicenter Cohort Study

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ABSTRACT

Introduction: We aimed to investigate risk factors for mortality among older adults (≥ 75 years) with hospital-acquired bloodstream infections (HA-BSI) in the intensive care unit (ICU).

Methods: We included patients aged ≥ 75 years with HA-BSI in ICU from the EUROBACT-2 cohort (2019–2021). Univariable and multivariable analyses were conducted to identify predictors of 28-day mortality.

Results: The cohort included 563 patients (median age 80, 39% women). Mortality at 28 day was 50%. Factors associated with mortality in multivariate analysis were admission due to COVID-19, failure to achieve source control, and higher SOFA. Among older adults with Gram-negative BSI, corticosteroid administration for septic shock was an additional factor.

Tomer Hoffman and Ili Margalit contributed equally to the manuscript.

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Among functionally independent patients, age itself was not associated with mortality.
Conclusions: HA-BSI in older adults in ICU are associated with high mortality. Inadequate source control is a significant modifiable risk factor. The use of corticosteroids in ICU management of older adults should be further investigated.

Keywords: ICU; Mortality; BSI; Older adults; Risk factors

Key Points
Hospital-acquired bloodstream infections (HA-BSI) carry substantial mortality among older adults hospitalized in ICU.
Among 563 patients aged ≥ 75 years with HA-BSI in ICU, predictors of mortality were COVID-19, no source control, and higher SOFA.
Corticosteroids administration for septic shock was a risk factor for mortality in those with Gram-negative bacteremia.
For older adults with preserved functional capacity, age itself is not a risk factor for mortality.

INTRODUCTION

As the proportion of older adults is growing worldwide, their percentage among intensive care unit (ICU) admissions is also increasing [1, 2]. ICU admissions of older adults still carry a poor prognosis in general, and specifically following an infection [1]. Among critically ill older adults diagnosed with sepsis, recently reported in-hospital mortality was 47% and 54% in patients aged 65–74 and ≥ 80 years, respectively [2].

Hospital-acquired bloodstream infections (HA-BSI) are among the leading complications of ICU patients, carrying an overall mortality rate of approximately 40%, as well as prolonged ICU and hospital stays [3]. Blot et al. previously demonstrated 49% and 56% mortality rates from bacteremia among ICU patients aged 65–74 and ≥ 75 years, respectively [4].

Older ICU patients represent a unique population with specific characteristics that may influence their risk of mortality from sepsis. These include higher likelihood for baseline comorbidities, atypical presentations of infection, altered pharmacokinetic/pharmacodynamic (PK/PD) of antimicrobial drugs due to renal and/or hepatic impairment and drug interactions, higher risk for multidrug-resistant bacteria, and differences in management compared to younger patients [1, 2].

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We designed this study to investigate predictors of mortality among older ICU patients with HA-BSI in order to identify possible clinical correlates specific for this population that may contribute to prevention and management decisions.

METHODS

Study Design and Population

The current study is nested within the EUROBACT-2 study database, a multicenter multinational prospective cohort study of adults (≥18 years) who developed HA-BSI. Individuals were included if they acquired the bloodstream infection (BSI) while hospitalized in the ICU or were transferred to the ICU because of a HA-BSI in other departments. The EUROBACT-2 study recruited 2600 individuals from 333 ICUs in 52 countries, with a minimum of 10 consecutive patients per ICU, or for a 3-month period during June 2019 to January 2021 [5].

In the present study, we evaluated predictors for 28-day mortality in a subset of patients aged ≥75 years (defined hereafter as older adults) with HA-BSI included in the EUROBACT-2. For definitions and further details see the Supplementary material and the EUROBACT-2 study [5].

Statistical Analysis

Continuous variables were compared using the Mann–Whitney *U* test and categorical variables using chi-square test or Fisher's exact test, as appropriate. Multivariable analyses for predictors of 28-day mortality were performed using logistic regression models, while generalized estimating equations were implemented to control for center effect. Variables were selected for the multivariable analysis if clinically reasonable and statistically significant ($p<0.05$) based on the univariable analysis. Correlations between the independent variables were assessed using Spearman's rank correlation coefficient. Whenever collinearity (variables with a correlation coefficient >0.4) existed, we assessed each variable in a separate model. The optimal model was chosen on the basis of the smallest quasi-likelihood information criterion.

We conducted a sensitivity analysis by excluding all individuals discharged from the hospital prior to day 28, to control for potential uncertainties regarding mortality data after hospital discharge. Additional sensitivity analyses were performed by excluding individuals hospitalized for COVID-19; restriction of the cohort to BSI caused by Gram-negative bacteria; and excluding those whose death was preceded by a decision to withhold or withdraw life-sustaining treatment.

For all analyses, $p<0.05$ was considered statistically significant. Data analysis was performed using IBM SPSS Statistics, version 28.0 (IBM Corp., Armonk, NY, USA).

Ethical Considerations

The study was initially approved by the research ethics committee of the leading institution, and was further approved by the institutional ethics review boards at each participating site. The study was conducted in accordance with the ethical standards of the responsible committees on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975.

RESULTS

Of 333 participating ICUs, 219 (66%) reported ≥1 older adult, comprising a total of 563 older adults included in the study. (For the study flowchart, see Supplemental Fig. 1.) Median age was 80 (range 75–98) years, 219 (38.9%) were women, and 442 (78.5%) acquired the BSI in the ICU.

By 28 days, 281 (49.9%) participants had died. There were no differences in demographics and comorbidities between survivors and non-survivors. Adequacy of empirical antibiotic treatment within 24 h was not associated with mortality. Whereas source control was indicated at similar rates in both groups, patients who died were less

Table 1 Demographics and comorbidities of 563 older adults hospitalized in the ICU and diagnosed with HA-BSI

Variables	28-day mortality status		p^a
	Alive $N = 282$ (50%)	Dead $N = 281$ (50%)	
Age (years), median (IQR)	80 (7)	81 (8)	0.127
Female gender, *N* (%)	108 (38.3)	111 (39.5)	0.770
Body mass index (BMI), median (IQR)	26.05 (6.29)	26.30 (6.26)	0.381
Charlson score, median (IQR)	2 (3)	2 (3)	0.778
COPD (moderate or severe), *N* (%)	68 (24.1)	55 (19.6)	0.192
Heart failure (NYHA classes 3–4), *N* (%)	51 (18.1)	59 (21.0)	0.384
Myocardial infarction, *N* (%)	37 (13.1)	36 (12.8)	0.913
Peripheral vascular disease, *N* (%)	30 (10.6)	29 (10.3)	0.902
Cerebrovascular disease, *N* (%)	48 (17.0)	41 (14.6)	0.429
Dementia, *N* (%)	41 (14.5)	35 (12.5)	0.469
Hemiplegia, *N* (%)	15 (5.3)	8 (2.8)	0.138
Diabetes mellitus, *N* (%)	90 (31.9)	84 (29.9)	0.604
Moderate renal disease, *N* (%)	40 (14.2)	39 (13.9)	0.917
Hemodialysis, *N* (%)	14 (5.0)	8 (2.8)	0.195
Connective tissue disease, *N* (%)	4 (1.4)	6 (2.1)	0.545‡
Peptic ulcer disease, *N* (%)	15 (5.3)	12 (4.3)	0.560
Severe liver disease, *N* (%)	3 (1.1)	2 (0.7)	0.999‡
AIDS, *N* (%)	0	1 (0.4)	0.999‡
Malignancy, *N* (%)	40 (14.2)	36 (12.8)	0.634
Metastatic solid tumor, *N* (%)	13 (4.6)	24 (8.5)	0.060
Hematological malignancy, *N* (%)	9 (3.2)	14 (5.0)	0.283
Transplant recipients, *N* (%)	1 (0.4)	0	0.999‡
Corticosteroid therapy, *N* (%)	9 (3.2)	12 (4.3)	0.499
Functional status before hospitalization			0.392
No limitation, *N* (%)	78 (27.8)	78 (27.8)	
Mild to moderate limitation, *N* (%)	114 (40.6)	126 (44.8)	
Serious but not incapacitation restriction, *N* (%)	53 (18.9)	53 (18.9)	
Severe restriction including bedridden, *N* (%)	36 (12.8)	24 (8.5)	
Admission due to COVID-19, *N* (%)	22 (7.8)	59 (21.0)	< 0.001*

AIDS acquired immune deficiency syndrome, *BSI* bloodstream infection, *COPD* chronic obstructive pulmonary disease, *IQR* interquartile range, *NYHA* New York Heart Association

[a]Calculated using chi-square test or Fisher's exact test (‡) for categorical variables and the Mann–Whitney *U* test for continuous variables

*Statistically significant ($p < 0.05$)

Table 2 Infection characteristics and management of 563 older adults hospitalized in the ICU and diagnosed with HA-BSI

Variables	Alive at 28 days $N = 282$ (50%)	Dead by 28 days $N = 281$ (50%)	p[a]
ICU-acquired BSI, *N* (%)	215 (76.2)	227 (80.8)	0.190
Duration of hospital stay prior to BSI detection, median (IQR)	13 (19)	14 (15)	0.712
Length of ICU stay prior to BSI detection, median (IQR)	6 (15)	7 (11)	0.617
Most likely source of BSI			0.914
Respiratory, *N* (%)	80 (28.4)	77 (27.4)	
Primary, *N* (%)	52 (18.4)	60 (21.4)	
Vascular catheter-related, *N* (%)	61 (21.6)	61 (21.7)	
Intra-abdominal, *N* (%)	40 (14.2)	38 (13.5)	
Urinary, *N* (%)	28 (9.9)	22 (7.8)	
Other, *N* (%)	21 (7.4)	23 (8.2)	
SOFA at BSI onset, median (IQR)	7 (5)	10 (7)	< 0.001*
Maximal C-related protein (mg/L) at BSI onset, median (IQR)	121 (163)	124 (179)	0.183
Maximal procalcitonin (ng/mL) at BSI onset, median (IQR)	2.6 (13.3)	1.5 (8.1)	0.135
Maximal creatinine (mg/dL) at BSI onset, median (IQR)	1.8 (3.4)	1.9 (2.7)	0.823
Ventilatory requirements during BSI			< 0.001*
Invasive mechanical ventilation, *N* (%)	165 (58.5)	219 (77.9)	
Non-invasive ventilation, *N* (%)	20 (7.1)	17 (6.0)	
High flow oxygen, *N* (%)	21 (7.4)	15 (5.3)	
Low flow or no need for oxygen supplementation, *N* (%)	76 (27.0)	30 (10.7)	
Septic shock at presentation, *N* (%)	84 (29.8)	119 (42.3)	0.002*
Glasgow Coma Scale at BSI onset, median (IQR)	13 (7)	10 (9)	< 0.001*
Antimicrobial therapy during the 7 days prior to BSI, *N* (%)	189 (67.0)	219 (78.2)	0.003*
Causative pathogen[b]			0.047*
Gram-negative bacteria, *N* (%)	150 (53.2)	142 (50.5)	0.528
Gram-positive bacteria, *N* (%)	71 (25.2)	74 (26.3)	0.754
Resistance pattern of the isolate[c]			0.194[‡]
Difficult to treat Gram-negative bacteria, *N* (%)	28 (9.9)	45 (16.0)	
Methicillin-resistant *Staphylococcus aureus*, *N* (%)	8 (2.8)	13 (4.6)	
Methicillin-resistant *Staphylococcus epidermidis*, *N* (%)	14 (5.0)	16 (5.7)	
Vancomycin-resistant *Enterococcus*, *N* (%)	5 (1.8)	5 (1.8)	
Adequate therapy within 24 h, *N* (%)	136 (48.2)	137 (48.8)	0.900

Table 2 continued

Variables	Alive at 28 days $N = 282$ (50%)	Dead by 28 days $N = 281$ (50%)	p[a]
Source control indicated, *N* (%)	127 (45.0)	121 (43.1)	0.637
Source control accomplished[d], *N* (%)	111 (87.4)[d]	79 (65.3)[d]	< 0.001*
Failure to achieve source control[e], *N* (%)	16 (5.7)	42 (14.9)	< 0.001*
Corticosteroid therapy for sepsis or septic shock, *N* (%)	54 (19.3)	83 (30.1)	0.003*
Renal replacement therapy at onset of BSI, *N* (%)	41 (14.5)	63 (22.4)	0.016*
Renal replacement therapy on day 7, *N* (%)	33 (11.7)	36 (12.8)	0.688
Clinical failure on day 7, *N* (%)	24 (10.5)	57 (33.9)	< 0.001*
Persistent bacteremia ≥ 3 days, *N* (%)	27 (9.6)	25 (8.9)	0.781

BSI bloodstream infection, *ICU* intensive care unit, *IQR* interquartile range, *SAPS* Simplified Acute Physiology Score

[a]Calculated using chi-square test or Fisher's exact test (†) for categorical variables and the Mann–Whitney *U* test for continuous variables

[b]For further details on the causative pathogens, see Supplementary Table S1

[c]Four individuals were diagnosed with polymicrobial bacteremia, two of these with resistant pathogens: 2 individuals with both carbapenem-resistant *Acinetobacter baumannii* and difficult to treat *Klebsiella* sp., 1 individual with carbapenem-resistant *A. baumannii* and methicillin-resistant *S. epidermidis*, and 1 individual with difficult to treat *K. pneumonia* and difficult to treat *Providencia* sp.

[d]Of 127 and 121 patients who required source control, respectively

[e]Those without appropriate source control vs those with either no indication for source control or appropriate source control

*Statistically significant ($p < 0.05$)

likely to achieve source control; more likely to receive corticosteroids for sepsis/septic shock; and renal replacement therapy (Tables 1 and 2).

Multivariable analysis revealed three independent risk factors for mortality (Table 3): COVID-19 as admission diagnosis (odds ratio [OR] 4.26, 95% confidence interval [CI] 1.64–11.05); failure to achieve source control (OR 3.21, 95% CI 1.61–6.42); and higher SOFA score at time of BSI presentation (OR 1.18 per SOFA point, 95% CI 1.10–1.26).

Age by itself was not associated with mortality. Age over 85 was associated with increased mortality in patients with baseline functional limitations, but not in independent patients (Table 4).

Results remained unchanged across several sensitivity analyses: excluding 67/563 (12%) individuals who were discharged before day 28 (Tables S1–S2); excluding 81/563 (14%) participants admitted with COVID-19 (Tables S3–S4); and excluding 77/281 (27%) older adults whose death was preceded by a decision to withhold/withdraw life-sustaining treatments (Tables S5–S6).

By including only BSI caused by Gram-negative bacteria (292/563, 52%) (Tables S7–S8a), corticosteroid therapy for critical illness management appeared to independently predict 28-day mortality. Introducing an interaction variable of corticosteroids and septic shock improved the model, demonstrating COVID-19 on admission and corticosteroids by septic shock interaction (i.e., patients who received corticosteroids and had shock) as independent risk factors for mortality, while source control was protective (Table S8b).

To explore subgroups, an additional regression was conducted, introducing into the model the following variables: gender, source of infection (pneumonia vs other), and appropriate antibiotics (i.e., whether in vitro covering antibiotics were administered within 24 h or not). In this analysis,

Table 3 Independent risk factors for 28-day mortality among older adults diagnosed with bacteremia, multivariable analysis

Variable	aOR (95% CI)[a]	p[a]
Admission due to COVID-19	4.26 (1.64–11.05)	0.003*
Failure to achieve source control	3.21 (1.61–6.42)	< 0.001*
SOFA at time of BSI (per point)	1.18 (1.10–1.26)	< 0.001*

The following variables were not included in the final model because of either collinearity or lack of contribution to the model: causative pathogen, ventilatory requirements during BSI, septic shock at presentation and Glasgow Coma Scale, corticosteroid therapy for sepsis or septic shock, and renal replacement therapy

CI confidence interval, *aOR* adjusted odds ratio

[a]Calculated using logistic regression model implemented through generalized estimating equations controlling for center effect. Optimal model was chosen on the basis of the smallest quasi-likelihood information criterion (QIC). Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were obtained from the logistic regression models. QIC for the model = 301.452

*Statistically significant ($p < 0.05$)

Table 4 Mortality risk by functional capacity and age subcategories

	28-day mortality status		p[a]
	Alive $N = 282$	Dead $N = 281$	
Any functional limitation ($N = 406$)			
Age 75–85	167 (53.2)	147 (46.8)	0.018
Age > 85	36 (39.1)	56 (60.9)	
Functionally independent ($N = 156$)			
Age 75–85	70 (50.7)	68 (49.3)	0.616
Age > 85	8 (44.4)	10 (55.6)	

[a]Calculated using chi-square test

the same independent variables as in the main model remained significant (Table S9).

DISCUSSION

Among 563 older adults hospitalized in the ICU with HA-BSI during 2019–2021, we found a 28-day mortality rate of 50%. Risk factors for mortality included COVID-19 as admitting diagnosis (OR 4.26, 95% CI 1.64–11.05), higher SOFA scores (OR 1.18, 95% CI 1.10–1.26), and failure to achieve source control (OR 3.21, 95% CI 1.61–6.42). Source of BSI, causative pathogen, antimicrobial resistance, and appropriate empirical therapy were not associated with mortality. Among patients whose BSI was caused by Gram-negative bacteria, corticosteroid therapy for sepsis/septic shock was an additional predictor of mortality, whereas higher SOFA score was not. Mortality rates above 50%, similar to those reported in our study, have been previously described among similar patients aged ≥ 75 years [2, 4]. The association of lower mortality with source control has been previously reported for general ICU patients with sepsis or septic shock, but not specifically for older adults with HA-BSI [6]. It is recognized that older adults are less likely to accomplish source control because of their age and presumed frailty. Moreover, it has been previously reported that older adults are less likely to be admitted to ICU [7], receive infectious diseases consultation, undergo imaging studies, and have transesophageal echocardiography performed in case of suspected endocarditis, compared with their younger counterparts [8–10]. In our study, among patients with baseline functional limitation, age > 85 was associated with increased mortality, while among independent patients, age by itself was not. This may have implications on decisions regarding ICU admission.

Recent meta-analyses evaluating corticosteroid therapy in septic shock failed to demonstrate a survival benefit. In a recent patient-level meta-analysis, subgroup analysis of adults aged > 74 years showed no significant difference in mortality, along with a higher risk for

adverse events with corticosteroid use for septic shock [11]. In our cohort, use of corticosteroids for septic shock among individuals with Gram-negative BSI was associated with mortality. This finding reinforces the aforementioned concerns for adverse events of corticosteroids in the older population. Nevertheless, considering the study design, we cannot rule out confounding by indication, with sicker patients selected for corticosteroids administration.

Considering the enormous mortality among critically ill older adults with HA-BSI, efforts should be focused on prevention of infection in these patients. Previously demonstrated risk factors for HA-BSI in older adults include obesity, presence of a central line, urinary incontinence, and gastrostomy. These should be avoided as much as possible [12]. Other interventions to prevent HA-BSI should also be considered among older adults. Universal decolonization could be considered for older adults in acute-care hospitals as in long-term care facilities [13].

Our study has several limitations. Firstly, data were collected during the COVID-19 pandemic. However, this was mitigated through a sensitivity analysis excluding patients admitted for COVID-19, which demonstrated similar results. In addition, as in the main EUROBACT-2 cohort, underrepresentation of ICUs from low-income countries limited the generalizability of results to older adults living in these countries. Another limitation is the short-term follow-up. Increased long-term mortality, cognitive impairment, and functional disability have been demonstrated in older adults following ICU hospitalization with BSI [1]. As a result of the retrospective design, frailty score was not available, and we could only present functional capacity data.

CONCLUSION

Mortality rates among older adults hospitalized in the ICU with HA-BSI are high. Factors associated with mortality include COVID-19 as admitting diagnosis, failure to achieve source control, and higher infection severity. Among functionally independent patients, age itself is not associated with mortality; however, patients>85 years with baseline functional limitation are at increased risk for mortality. Among Gram-negative BSI, corticosteroid therapy for septic shock was an additional risk factor for mortality. The adequacy of empirical antibiotic treatment during the first 24 h was not associated with mortality. Outcomes of older adults may be improved by achieving control of infection's source, despite the older age and increased frailty. The effectiveness and safety of corticosteroid therapy in ICU management of older adults should be evaluated in future studies.

Author Contributions. Tomer Hoffman, Ili Margalit, Dafna Yahav, Virginie Prendki, and Niccolò Buetti initiated this study and wrote the protocol; Alexis Tabah, Stéphane Ruckly, François Barbier, Pierre Singer, Jean-François Timsit, Virginie Prendki, Nasreen Hassoun-Kheir, and Niccolò Buetti obtained the data; Tomer Hoffman, Ili Margalit, Dafna Yahav, Niccolò Buetti, Virginie Prendki, Stéphane Ruckly and Alexis Tabah analyzed the data; Tomer Hoffman, Ili Margalit, and Dafna Yahav drafted for the manuscript; all authors have read, revised, and approved the manuscript.

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Data Availability. The datasets used and/or analysed during the EUROBACT-2 study are available from the OUTCOMEREA organisation on reasonable request.

Declarations

Conflict of Interest. François Barbier have received over the past three years lecture and consulting fees from MSD, lecture fees for BioMérieux,

and conference invitation from Pfizer, not related to the submitted work; Jean-François Timsit reported advisory boards participation for Merck, Gilead, Beckton-Dickinson, Pfizer, Shinogi, Medimune, Paratek, research grants from Merck, Pfizer, Thermofischer; Niccolò Buetti received a post.doc Mobility grant (2021) from the Swiss National Science Foundation (Grant Number: P4P4PM_194449); Dafna Yahav is an Editorial Board member of *Infectious Diseases and Therapy*. Dafna Yahav was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions; Tomer Hoffman, Ili Margalit, Alexis Tabah, Stephane Ruckly, Pierre Singer, Virginie Prendki, and Nasreen Hassoun-Kheir declare no conflict of interest.

Ethical Approval. The EUROBACT-2 trial was initially approved by the Research Ethics Committee of Royal Brisbane & Women's Hospital, Queensland, Australia (LNR/2019/QRBW/48376). The study was further approved by the institutional ethics review boards at each participating site (for further details on the national coordinators, scientific committees, and participating ICUs, see the Supplementary Information of Tabah et al. [5]). The study was conducted in accordance with the ethical standards of the committees responsible on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975.

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