Original Article

Relationship between age and intensive care unit-acquired bloodstream infections in infectious disease patients in Croatia

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Abstract

Introduction: Intensive care unit-acquired bloodstream infections (ICU-BSI) belong to the most important nosocomial infections. Since there is scarce data available on their relationship with older age, we performed this study to estimate the age-related incidence of ICU-BSI and the odds of acquiring ICU-BSI in elderly critically ill infectious disease patients.

Methodology: A retrospective observational analysis of prospectively collected demographic and clinical data of adult mechanically ventilated infectious disease patients, treated in a teaching hospital in Croatia between 1994 and 2008, using univariate, bivariate, and multivariate logistic regression analyses.

Results: Of the 1,093 included patients, 509 (46.6%) were $\geq$ 65 years old, among 256 (23.4%) of whom a total of 353 ICU-BSI episodes were recorded. No significant difference among ICU-BSI causative microorganisms between the observed age groups was found (P = 0.4940). The rate of patients with ICU-BSI was higher among elderly ones (26.1 *vs.* 21.1%, *P* = 0.048), and elderly patients used the ICU facilities (ICU stay, duration of mechanical ventilation and central venous catheter [CVC] use) significantly longer (P < 0.05). However, older age was not positively related with the development of ICU-BSI (OR 0.99, 95% CI: 0.71-1.38); as opposed to the duration of CVC use (OR 1.09, 95% CI: 1.07-1.10).

Conclusion: It seems that among adult mechanically ventilated infectious disease patients, borderline significantly higher rate of ICU-BSI among those aged $\geq$ 65 years was related to longer use of ICU facilities, rather than to their older age itself. The duration of CVC use was identified as the only factor positively related to the development of ICU-BSI.

Key words: elderly; intensive care unit; bloodstream infections.

Introduction

Population aging is a well-recognized phenomenon globally, and elderly people have become more frequent users of medical care services in general. According to previous reports from different countries, the proportion of ICU-treated elderly patients ranges between 26-52% [1,2] and a shift in primary ICU diagnoses from cardiovascular to infectious diseases in elderly patients has been observed in a recent study [3]. In comparison with the younger population, community-acquired infections are more common and associated with a poorer outcome in elderly patients [4]. The reasons for this increased susceptibility include epidemiological elements, immunosenescence, malnutrition as well as a large number of age-associated physiological and anatomical alterations [5].

The impact of ageing on the incidence of nosocomial infections seems to be a controversial issue. Keeping in mind the differences in study designs, used statistical methods, sample sizes and patients′ medical features, which could influence conclusions, when we observed studies that compared population aged $\geq$ 65 years with younger adults, some studies found higher incidence of nosocomial, particularly ICU-acquired infections among elderly patients, [6-8] while other failed to do so [9-12]. Despite of the assumed increased susceptibility for infection, few studies have shown that the incidence of ICU-BSI even decreased with age [13,14].

ICU-BSI cases are considered as the most common, most lethal and most expensive nosocomial infections, [15-17] reaching in elderly patients in developed countries mean attributable costs of $43,208 per episode [18]. It has been estimated that ICU-BSI complicate between 4.4 to 6.8% of admissions lasting longer than 48 to 72 hours [13,15,19].

Croatian population is regarded as one of the oldest in Europe. We performed an observational study in a large cohort of mechanically ventilated, critically ill

infectious disease patients, with the aim to estimate the age-related incidence and odds for acquiring ICU-BSI.

Methodology

Study of population and data sources

We performed a retrospective observational analysis of prospectively collected data of age-related ICU-BSI incidence among critically ill, mechanically ventilated infectious disease patients, treated at the 18-bedded adult ICU of the University Hospital for Infectious Diseases in Zagreb, Croatia, in the period from 1994 to 2008. Data were obtained from electronic database of ICU admissions, and hospital microbiology records of positive blood cultures. Standard protocols for the collection, analysis, and reporting of blood cultures were employed. For the analysis of routinely collected data the study was approved by the institutional review boards of the study hospital as well as the affiliated School of Medicine, waiving the requirement for specific patient consent.

Definitions

We used the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) definitions of ICU-BSI; and considered both primary and secondary BSIs in our analysis [20]. ICU-BSI was defined as the presence of clinical evidence of infection, accompanied by positive blood cultures for a bacterium or fungus obtained at the same time, but more than 48 hours after the admission to the ICU. In accordance with the US Centers for Disease Control and Prevention guidelines, we did not include cultures of coagulase-negative staphylococci or other common commensal skin organisms, unless two cultures separately isolated the same species of microorganism [21]. To allow the study of a population at risk, we excluded all ICU admissions lasting less than 48 hours. Elderly patients were defined as equal to or older than 65 years. The results were compared to patients aged 18-64 years.

Data analysis

The following data were analyzed: patients` demographics, previous health status (according to Knaus classification), Glasgow Coma Score (GCS) on admission, Acute Physiology and Chronic Health Evaluation II (APACHE II) physiology score on admission, APACHE II score minus age points, type of primary infection on admission regarding central nervous system (CNS) involvement, usage of CVC, duration of CVC usage (in days), duration of mechanical ventilation (MV) (in days), incidence of

ICU-BSI, causative microorganism of ICU-BSI, incidence of other nosocomial infections (pneumonia, urinary tract infections), and duration of ICU stay. As an infection with CNS involvement we also considered sepsis with secondary CNS infection and tetanus.

Univariate analyses of continuous variables were reported as a mean value and standard deviation, and categorical variables as frequency and percentage. For comparison of the groups for continuous variables, the Mann-Whitney U test was used, and for categorical variables, the chi-squared test or Fisher`s exact test, when appropriate. We described an association of predictors with the dependent variable being the development of ICU-BSI with an "odds ratio" (OR). Logistic regression multivariate analysis was performed to test whether increased age is an independent factor for ICU-BSI development after adjustment for possible confounding factors. Besides age group, all variables which in univariate analysis showed significant association with BSI were included in the model. The Hosmer-Lemeshow test was used as a goodness-of-fit statistics. Statistical significance was defined as $P < 0.05$. Statistical analysis was performed using SAS 9.2 software, SAS Institute Inc., 2009, Cary, NC, USA.

Results

Of the 2,171 patients with severe infections treated in the ICU, 922 were excluded from the study due to lack of mechanical ventilation, and further 156 because of ICU-stay shorter than 48h. Among the remaining 1,093 included patients, 509 (46.6%) were ≥ 65 years (elderly group), while 584 (53.4%) were younger adults. In 256 (23.4%) observed patients a total of 353 ICU-BSI episodes were recorded. Among them, 195 episodes of ICU-BSI were recorded in 26.1% (133/509) elderly patients, and 158 episodes in 21.1% (123/584) younger adult patients.

The most common causative microorganisms were non-fermenting gram-negative bacteria causing 32.0% of a total of 353 ICU-BSI episodes, followed by *Enterobacteriaceae* (sensitive 9.9%, and 3rd generation cephalosporins resistant/ESBL 14.2%), *Staphylococcus aureus* (MRSA 9.3% and MSSA 2.0%), *Candida sp.* (7.1%), *Enterococcus sp.* (2.9% ampicillin sensitive and 1.1% ampicillin resistant), coagulase-negative staphylococcus (2.8%) and other bacteria (1.1%), respectively; however, 17.6% of ICU-BSIs were polymicrobial. No significant difference in the distribution of ICU-BSI causative microorganisms between the two observed age groups was found (p = 0.494).

Table 1. The comparison of basic demographic and clinical data and outcomes between two age groups of mechanically ventilated, critically ill infectious disease patients.

Variables	Patient age group (N = 1093)		P
	18-64 years (N = 584)	**≥ 65 years (N = 509)**	
Age mean (SD*)	47.6 (12.8)	74.9 (6.5)	
Female N (%)	211 (36.1)	259 (50.9)	< 0.001
Male N (%)	373 (63.9)	250 (49.1)	
Knaus classification N (%)			0.005
Healthy	213 (36.5)	141 (27.7)	
Mild chronic disease	215 (36.8)	224 (44.0)	
Severe chronic disease	126 (21.6)	105 (20.6)	
Terminal chronic disease	30 (5.1)	39 (7.7)	
Infection with CNS[§] involvement N (%)	321 (55.0)	217 (42.6)	< 0.001
Infection without CNS involvement N (%)	263 (45.0)	292 (57.4)	
Mean APACHE II[1] (SD)	19.1 (8.1)	22.3 (8.8)	< 0.001
Mean age-adduced APACHE II (SD)	17. (7.9)	16.9 (8.7)	0.106
Mean GCS[2] (SD)	10.1 (4.3)	10.9 (4.1)	0.001
CVC[3] use N (%)	549 (94.0)	484 (95.1)	0.437
Mean duration of CVC use in days (SD)	13.1 (12.2)	15.8 (14.6)	0.005
Mean duration of MV[4] in days (SD)	12.7 (14.1)	16.2 (20.4)	0.005
Mean duration of ICU stay in days (SD)	18.5 (18.1)	22.9 (26.4)	0.005
Episodes of nosocomial UTI[5] (% of patients)	94 (14.4)	141 (22.4)	0.005
Episodes of nosocomial pneumonia (% of patients)	90 (13.9)	72 (13.2)	0.917
Patients with ICU-BSI[6] N (%)	123 (21.1)	133 (26.1)	0.048
Incidence of ICU-BSI/1,000 CVC days	16.4	17.7	0.046
Incidence of ICU-BSI/1,000 ICU days	12.3	12.4	0.097
Overall mortality N (%)	250 (42.8)	268 (52.8)	< 0.001

*SD: Standard deviation; [§]CNS: Central Nervous System; [1]APACHE II: Acute Physiology and Chronic Health Evaluation score II; [2]GCS: Glasgow Coma Score; [3]CVC: Central Venous Catheter; [4]MV: Mechanical Ventilation; [5]UTI: Urinary Tract Infection; [6]ICU-BSI: Intensive- Care-Unit-acquired Bloodstream Infection.

Table 2. The comparison of basic demographic and clinical data between groups with and without intensive care unit-acquired bloodstream infection among mechanically ventilated, critically ill infectious disease patients.

Variables	ICU-BSI* (N = 1093)		P
	No (N = 837)	**Yes (N = 256)**	
Age mean (SD) [§]	59.5 (17.6)	62.9 (15.1)	0.017
Age group N (%)			0.048
18-64 years	461 (55.1)	123 (48.0)	
≥ 65 years	376 (44.9)	133 (52.0)	
Sex N (%)			< 0.001
Female	334 (39.9)	136 (53.1)	
Male	503 (60.1)	120 (46.9)	
Knaus classification N (%)			0.083
Healthy	276 (33.0)	78 (30.5)	
Mild chronic disease	320 (38.2)	119 (46.5)	
Severe chronic disease	188 (22.5)	43 (16.8)	
Terminal chronic disease	53 (3)	16 (6.3)	
Infection with CNS[1] involvement N (%)			< 0.001
Yes	386 (46.1)	152 (59.4)	
No	451 (53.9)	104 (40.6)	
APACHE II[2] mean (SD)	21.1 (8.6)	19.0 (8.1)	< 0.001
Age-adduced APACHE II mean (SD)	17.7 (8.3)	15.3 (8.1)	< 0.001
GCS[3] mean (SD)	10.2 (4.2)	11.2 (4.2)	< 0.001
Duration of CVC[4] use in days mean (SD)	10.9 (9.6)	25.6 (17.4)	< 0.001
Duration of MV[5] in days mean (SD)	10.1 (10.3)	28.3 (26.4)	< 0.001
Duration of ICU[6] stay in days mean (SD)	15.1 (14.3)	38.4 (32.8)	< 0.001
Overall mortality N (%)	416 (49.7)	103 (40.2)	0.008

*ICU-BSI: Intensive Care Unit-acquired Bloodstream Infection; [§]SD: Standard deviation; [1]CNS: Central Nervous System; [2]APACHE II: Acute Physiology and Chronic Health Evaluation score II; [3]GCS: Glasgow Coma Score; [4]CVC: Central Venous Catheter; [5]MV: Mechanical Ventilation; [6]ICU: Intensive Care Unit.

Among the two observed age groups, a significantly higher mean duration of CVC use, duration of MV and ICU stay, as well as higher mortality rate was found in the elderly, while the rate of patients with ICU-BSI, and the incidence of ICU-BSI per 1,000 CVC days were borderline significantly higher in elderly patients; detailed comparison of baseline demographic and clinical data and outcomes is shown in Table 1.

Bivariate analyses of groups with and without ICU-BSI, according to demographic and clinical data, and ICU facility use, shown in Table 2, identified the following variables (P < 0.05) as variables that could influence the development of ICU-BSI: sex, age group, type of primary infection regarding involvement of CNS, APACHE II score minus age points, duration of MV as well as the duration of CVC use. These variables (except the duration of MV, because of its interaction with duration of CVC use) were included in logistic regression analyses as independent variables. The results of multivariate analysis are shown in Table 3. The model fitted well showing a high explanatory value (c = 0.802). The incidence of ICU-BSI was equally distributed between two age groups (OR: 0.99, 95% CI: 0.71-1.38). APACHE II score corrected for age (OR 0.97, 95% CI: 0.95-0.99) and the overall duration of CVC use (OR 1.09, 95% CI: 1.07-1.10) were two parameters independently associated with ICU-BSI.

Discussion

With the average age of 41,7 years and with 17,7% of the ~4,285 million population being ≥ 65 years old in 2011, most likely due to the low natality and high emigration rate among young people, Croatian population is one of the five oldest in Europe [22]. Almost half of our ICU patients satisfy the criterion of being elderly, and we expected the greater risk of ICU-BSI in this group of patients. Contrary to our expectations, the results of this study show equal odds for the development of ICU-BSI among adult, critically ill infectious disease patients < 65 and those ≥ 65 years.

A negative relation between increasing age and the risk of ICU-BSI development, and incidence of ICU-BSI, respectively, has been found in two large retrospective studies (Prowle et al, 2011, Blot et al, 2009.) [13,14]. These unexpected results were explained with assumed under-diagnosing of ICU-BSI among the elderly, because of the association of older age with a weaker inflammatory response that could decrease the likelihood of blood culture sampling and reduce the observed incidence of BSI in older patients [5].

Microbiological characteristics of the ICU environment, ICU procedures, or even the impact of severe primary disease on defense mechanisms of ICU patients have been suggested as factors that affect the development of ICU-acquired infections.

A positive relationship between the duration of CVC use and the risk of developing a CVC-related and primary ICU-BSI has been well documented [23,24], but it seems that the incidence of CVC-related ICU-BSI is 3-5 times higher in developing countries in comparison to developed countries [25]. According to Maki's observations, 2/3 of primary nosocomial BSIs also originate from contaminated CVC [26]. The high rate of 81% of CVC-related BSI has been observed, and the presence of CVC was identified as an independent risk factor for nosocomial BSI development among elderly patients (OR 7.5, 95% CI: 2.5-22.9) [18,27]. The unusually high incidence of ICU-BSI expressed per 1,000 CVC days in our patients (16.4 in younger adults and 17.7 in elderly) is due to the jointly calculated incidence of CVC-related, primary and secondary ICU-BSIs in our study, and those incidences are approximately three times higher in comparison to

Table 3. Analysis of the correlation between significant factors and the development of intensive care unit-acquired bloodstream infection using logistic regression.

Variables	Probability of ICU-BSI* development		
	Odds Ratio	95% Confidence intervals (Wald interval)	
Age (years): 18-64 / ≥ 65	0.99	0.71	1.38
Sex: female / male	1.29	0.93	1.79
CNS[§] infections / other infections	1.17	0.83	1.63
APACHE II[1] minus age points	0.97	0.95	0.99
Duration of CVC[2] use (days)	1.09	1.07	1.10

*ICU-BSI: Intensive-Care-Unit-acquired Bloodstream Infection; [§]CNS: Central Nervous System; [1]APACHE II: Acute Physiology and Chronic Health Evaluation score II; [2]CVC: Central Venous Catheter.

those reported solely for CVC-related ICU-BSIs [23,28,29]. The multivariate analysis results have shown that the duration of CVC use was the only analyzed factor positively related to the development of ICU-BSI among our patients, which highlights the importance of CVC use in the epidemiology and pathogenesis of ICU-BSI. However, a significant decrease in the incidence of CVC-related ICU-BSIs from 5.7 to 1.5 per 1,000 CVC days, after the implementation of preventive measures, has been reported from Brasil [30], and a sustained very low incidence of CVC-related ICU-BSIs of 0.6/1,000 CVC days from a highly developed country in a large Swedish prospective study [31].

As expected, our two observed age groups differed significantly according to previous health status assessed by the Knaus classification, with higher rate of elderly patients belonging to the group with mild chronic disease (44.0 *vs.* 36.8%) and with terminal chronic disease (7.7 *vs.* 5.1%), in comparison to younger adults; however, the difference of mean age-adduced APACHE II scores at admission between the observed age groups was not found.

Conversely to our results, many previous studies have shown that greater illness severity on ICU-admission, expressed with APACHE II or APACHE III score, is related to the higher risk of developing ICU-BSI [13,32-34]. The finding of a negative relationship between APACHE II minus age points at ICU-admission, and the development of ICU-BSI in our study, suggests a high rate of early mortality among critically ill patients with domicile infections, which has lowered their chance for development of ICU-BSI.

Due to longer use of ICU facilities (CVC, MV and ICU stay) in our patients, the observed overall ICU-BSI rate of 26.1% in elderly and 21.1% in younger adults were much higher in comparison to those reported from other studies, which ranged between 2.7-9.0% [15,19,33,__35-37]. Relatively expressed ICU-BSI incidence of 12.4 ICU-BSIs in elderly and 12.3 in younger adults per 1,000 ICU days in our observed severe infectious disease patients fits among the results of other studies, where that incidence in patients treated at ICU, because of different medical and surgical conditions, was mostly in the range of 5-19/1,000 ICU days [19,35,37]. Exceptionally, the highest recorded incidence, reaching 44/1,000 ICU days, has been reported from Upper Egypt [38]. However, unlike data collected by the Turkish authors who reported a significantly higher incidence of ICU-BSIs among elderly patients in comparison to younger adults (17.37

vs. 11.21/1,000 ICU days), in our study age-based difference was not found [8].

The main shortcomings of this study are the disadvantages associated with its retrospective design. Also, although the signs of infection were carefully monitored in our critically ill infectious disease patients, the possibility of underdiagnosing ICU-acquired infections in elderly patients cannot be completely excluded.

Conclusion

It seems that among adult mechanically ventilated infectious disease patients, borderline significantly higher rate of ICU-BSI among those aged ≥ 65 years was related to longer use of ICU facilities, rather than to their older age itself. The duration of CVC use was identified as the only factor positively related to the development of ICU-BSI.

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