**Original Article**

**Advanced Age is not a Risk Factor for Mortality in Patients with Bacteremia Caused by Extended-Spectrum β-Lactamase-Producing Organisms: a Multicenter Cohort Study**

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**SUMMARY:** A 5-year multicenter retrospective cohort study was conducted across six hospitals in Niigata, Japan. Patients (n = 179) with bacteremia due to extended-spectrum β-lactamase (ESBL)-producing organisms were included in the study. The rates of appropriate carbapenem prescription were 61% (n = 41) in patients aged 65–84 years and 89% (n = 31) in those aged ≥ 85 years. Patients aged ≥ 85 years were significantly more likely to receive carbapenem than their younger counterparts. After propensity score matching, 65 patients were assigned to two groups based on age (65–84 years or ≥ 85 years). Multivariate regression analysis showed that other sites of infection had a positive association with 30-day mortality (odds ratio [OR], 27.50; 95% confidence interval [CI], 2.90–260.00) and biliary tract infection tended to have a positive association with 30-day mortality (OR, 8.90; 95% CI, 0.88–89.90) compared with urinary tract infection. However, an age ≥ 85 years was not associated with 30-day mortality. Elderly patients aged ≥ 85 years were more likely to be treated with carbapenem; however, old age was not associated with 30-day mortality when bacteremia was caused by ESBL-producing organisms. These results may help clinicians justify withholding carbapenem in patients aged ≥ 85 years.

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**INTRODUCTION**

The proportion of elderly individuals is increasing in communities worldwide, and this trend is expected to continue (1–3). Elderly patients with infectious diseases have a high mortality rate because of immunosenescence, and diagnosis is difficult in those with atypical presentations (4,5).

The global incidence of infections caused by extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae is also increasing (6,7). Bloodstream infections (BSIs) caused by these bacteria are associated with high mortality rate and increased hospital costs (8). Patients with comorbidities and institutionalized elderly individuals are at particularly high risk of contracting a BSI caused by ESBL-producing Enterobacteriaceae and have a high mortality rate (5,9,10). Moreover, the number of centenarians is increasing, and several previous studies on bacteremia caused by ESBL-producing organisms have defined “elderly” as age ≥ 65 years (5,9,11).

A recent study suggested that carbapenem antibiotics have a mortality benefit when compared with piperacillin-tazobactam (12). We hypothesized that patients aged ≥ 85 years would have a high mortality rate due to increasing immunosenescence. Although there are no data suggesting that “elderly” should be defined as age ≥ 85 years in patients with BSI caused by ESBL-producing Enterobacteriaceae, patients in this age group who develop Clostridium difficile infection or urinary tract infection (UTI) are at higher risk of a complicated course (13,14). The high mortality rate in these patients might justify the empirical use of carbapenem antibiotics. However, it is important to define the requirements for empirical use of these agents because of the need to combat antimicrobial resistance (15). Japan has one of the highest elderly...
populations worldwide (11). In this study, we evaluated the association between ESBL-producing Enterobacteriaceae bacteremia and 30-day mortality in patients aged ≥85 years admitted to general hospitals in Japan.

**MATERIALS AND METHODS**

Data collection and ethical approval: This multicenter retrospective cohort study included all patients with bacteremia caused by ESBL-producing Escherichia coli, Klebsiella pneumonia, or Proteus mirabilis from January 2012 to December 2016 across six hospitals in Niigata, Japan (Kaetsu Hospital, 261 beds; Niigata Kouseiren Sado General Hospital, 354 beds; Kashiwazaki General Hospital and Medical Center, 400 beds; Saiseikai Niigata Daini Hospital, 425 beds; Niigata City General Hospital, 676 beds; and Nagaoka Red Cross Hospital, 649 beds). Patient demographic and clinical characteristics were reviewed and recorded (Table 1). The severity of illness was determined using the quick Sequential Organ Failure Assessment (qSOFA) tool (16). Only the first episode of bacteremia for each patient was included. Patients aged <65 years, those in whom the outcome was unknown, and those who died within 24 h of admission were excluded. The study was approved by the institutional review board of each participating hospital (approval numbers: H29-014, sgh20170920-0186, 2017-001, E17-16, 18-007, and 2762, respectively, in the order of the abovementioned hospitals).

Outcomes and definitions: The main outcome was 30-day mortality from any cause. BSI was defined as infection caused by ESBL-producing E. coli, K. pneumonia, or P. mirabilis confirmed by blood culture. The primary site of infection was identified from the physician’s diagnosis recorded on the medical chart and classified as UTI, biliary tract infection, or “others.”
Antimicrobial susceptibility and confirmatory testing for ESBL was performed using the microdilution or disk diffusion method according to the recommendations of the Clinical and Laboratory Standards Institute (17). Isolates categorized as intermediate by antimicrobial susceptibility testing were considered resistant. Antimicrobial therapy was classified as empirical or definitive. Empirical therapy was defined as the initiation of antimicrobial therapy before the results of blood culture were available. Definitive therapy was defined as antimicrobial therapy administered after the start of empirical therapy. Appropriate therapy was defined as the use of carbapenem antibiotic or other antimicrobial agents, such as quinolone, cefmetazole, or piperacillin-tazobactam, based on the results of in vitro susceptibility testing. Infections developing ≥ 48 h after hospital admission were defined as hospital-acquired infections.

**Statistical analysis:** Initially, we assessed 30-day mortality by dividing the patients into two groups based on age: 65–84 years and ≥ 85 years. Next, we performed propensity score analysis to adjust for treatment selection bias. Propensity scores were calculated based on multivariate logistic regression modeling of sex, body weight, primary site of infection, total duration of antibiotic therapy, whether or not empirical carbapenem therapy was prescribed, hospital-acquired infection, cardiovascular disease, liver disease, neurological disease, diabetes mellitus, and hematologic malignancy. Univariate analysis was performed using the Mann-Whitney U test or Fisher’s exact test. Multivariate analysis was performed using logistic regression to identify independent risk factors for 30-day mortality. Age ≥ 85 years, qSOFA score ≥ 2, and the primary site of infection were tested as variables for inclusion in the analysis. Only qSOFA score ≥ 2 and primary site of infection were included in the final model because they were determined to be highly relevant to 30-day mortality after propensity score analysis (16,18).

Continuous variables are reported as median and range, and categorical variables as frequency and percentage. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated in the multivariate analyses. All analyses were performed with R 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria). A P-value < 0.05 was considered statistically significant.

**RESULTS**

Of 221 patients with BSI due to ESBL-producing bacteria, 41 were excluded because they were aged ≤ 64 years, had received short-duration antimicrobial treatment, or had an unknown outcome. Of the 179 patients included in the study, 110 (61%) were aged 65–84 years, and 69 (39%) were aged ≥ 85 years. Baseline characteristics and outcomes according to age group are shown in Table 1. The univariate analysis showed that body weight and rates of hospital-acquired infection and liver disease were significantly higher in the group aged 65–84 years than in the group aged ≥ 85 years. Furthermore, the proportion of patients with neurological disease was significantly lower in those aged 65–84 years than in those aged ≥ 85 years.

There was a significant difference in the primary site of infection between the two age groups. Approximately 50% of patients received appropriate empirical therapy in both age groups. However, although patients aged ≥ 85 years received carbapenem therapy at a significantly higher rate than those aged 65–84 years, the rates of appropriate carbapenem prescription were 61% (n = 41) in patients aged 65–84 years and 89% (n = 31) in those aged ≥ 85 years.

Patient characteristics are presented in Table 2 based on the 30-day mortality. The univariate analysis revealed that body weight and incidence of pulmonary disease were significantly lower in patients who died within 30 days. Furthermore, a significantly greater number of patients in this group had a qSOFA score ≥ 2, hospital-acquired infection, and solid or hematologic malignancy. There were also significant between-group differences in the causative pathogen and primary site of infection.

After propensity score matching, 65 patients were assigned to each age group. The univariate analysis found no significant difference between the two groups other than age. The findings of the multivariate regression analysis of factors potentially associated with 30-day mortality are shown in Table 3. Other sites of infection had a positive association with 30-day mortality (OR, 27.50; 95% CI, 2.90–260.00), and biliary tract infection tended to have the most positive association (OR, 8.90; 95% CI, 0.88–89.90). However, age ≥ 85 years and qSOFA score ≥ 2 were not associated with 30-day mortality.

**DISCUSSION**

In this study, carbapenem antibiotics were prescribed at a significantly higher rate in patients aged ≥ 85 years than in those aged 65–84 years. However, our findings also suggest that advanced age was not associated with higher 30-day mortality rate in patients with bacteremia caused by ESBL-producing organisms and should not be a criterion in the selection of antibiotic therapy. Although one previous study suggested a high mortality rate in patients aged ≥ 85 years requiring treatment of infection in the intensive care unit (ICU) (19), it did not assess the relationship between carbapenem use and patient age. This difference is likely because patients who require admission to the ICU have comorbidities and more severe condition than those who do not require ICU admission. However, the present study included several patients who were not admitted to the ICU and adjusted for underlying disease by propensity score analysis. Furthermore, life expectancy varies, even in individuals with similar age, depending on genetic, lifestyle, and environmental factors (21). Therefore, an age ≥ 85 years is not necessarily an indication for empirical carbapenem therapy.

Although age-related immunosenescence may be associated with infection-related mortality, it is also associated with diseases such as diabetes mellitus and chronic kidney disease (22,23). Moreover, there may be a difference between biological age and chronological age. The influence of biological age on the likelihood of developing cardiovascular, respiratory, nervous, renal, liver, or hematological disease and on life expectancy
is stronger than that of chronological age (21), and the estimated biological age is higher in patients with multiple comorbidities. This suggests that underlying disease affects mortality more than chronological age, and our findings support this concept.

Infections other than UTI, such as biliary tract infection, were associated with 30-day mortality in this study (many patients had an unknown focus on infection). Generally, biliary tract infection has a higher mortality rate than UTI (18), and our results are

| Characteristics of patients                          | Death within 30 days |   |
|------------------------------------------------------|----------------------|---|
|                                                      | None (n = 155)       | Yes (n = 24) |   |
| Age, years, median (range)                           | 82 (65–100)          | 81 (65–98)  | 0.68 |
| Aged ≥ 85 years, n (%)                               | 60 (39)              | 9 (38)      | 1.00 |
| Sex, n male (%)                                      | 83 (54)              | 18 (75)     | 0.08 |
| Body weight, kg, median (range)                      | 51 (25–85)           | 45 (22–85)  | < 0.01 |
| Pathogen, n (%)                                      |                      |             |   |
| *E. coli*                                            | 136 (88)             | 16 (67)     |   |
| *K. pneumoniae*                                      | 16 (10)              | 6 (25)      | 0.02 |
| *P. mirabilis*                                       | 3 (2)                | 2 (8)       |   |
| Primary site of infection, n (%)                     |                      |             |   |
| Urinary tract                                        | 93 (60)              | 6 (25)      |   |
| Biliary tract                                        | 33 (21)              | 5 (21)      | 0.01 |
| Other                                                | 29 (19)              | 13 (54)     |   |
| Abdominal infections                                 | 7 (5)                | 0 (0)       |   |
| Central venous catheter infection                    | 3 (2)                | 0 (0)       |   |
| Pneumoniae                                           | 1 (1)                | 0 (0)       |   |
| Unknown                                              | 18 (12)              | 13 (54)     |   |
| qSOFA ≥ 2, n (%)                                     | 47 (30)              | 13 (54)     | 0.04 |
| Total duration of antibiotic therapy, days, median (range) | 11 (2–42) | 9 (2–28) | 0.07 |
| Received appropriate empirical therapy, n (%)        | 77 (50)              | 10 (42)     | 0.52 |
| Carbapenem use among appropriate empirical therapy, n (%) | 63 (81) | 9 (90) | 0.83 |
| Received appropriate definitive therapy, n (%)        | 120 (77)             | 17 (71)     | 0.45 |
| Hospital-acquired infection, n (%)                   | 55 (36)              | 15 (63)     | 0.01 |
| Underlying disease, n (%)                            |                      |             |   |
| Cardiovascular disease                               | 28 (18)              | 5 (21)      | 0.78 |
| Pulmonary disease                                     | 15 (10)              | 6 (25)      | 0.04 |
| Renal disease                                        | 32 (21)              | 1 (4)       | 0.09 |
| Liver disease                                        | 16 (10)              | 5 (21)      | 0.17 |
| Neurological disease                                 | 71 (46)              | 7 (29)      | 0.18 |
| Diabetes mellitus                                    | 40 (26)              | 2 (8)       | 0.07 |
| Solid cancer                                         | 37 (24)              | 11 (46)     | 0.045|
| Hematologic malignancy                               | 10 (7)               | 5 (21)      | 0.03 |

Table 3. Multivariate logistic regression analyses of factors associated with 30-day mortality

| Factor                                 | Odds ratio | OR (95% CI) | P |
|----------------------------------------|------------|-------------|---|
| Age < 85 years                         | 1.00 [Reference] |   |   |
| Age ≥ 85 years                         | 1.59       | 0.36–7.02   | 0.54 |
| qSOFA scores < 2                       | 1.00 [Reference] |   |   |
| qSOFA scores ≥ 2                       | 1.27       | 0.27–5.97   | 0.76 |
| Urinary tract infection                | 1.00 [Reference] |   |   |
| Biliary tract infection                | 8.90       | 0.88–89.90  | 0.06 |
| Other sites of infection               | 27.50      | 2.90–260.00 | < 0.01 |

*: Logistic regression analyses.

OR, odds ratio; CI, confidence interval; qSOFA, quick Sequential Organ Failure Assessment.
consistent with this. A possible reason for this finding is that non-antibiotic approaches, such as decompression, are also important in the treatment of biliary infection (18).

Furthermore, several studies have shown that the prognosis is poorer when the focus of infection is unknown. Moreover, patients with biliary tract infections often have severe underlying disease, such as cancer (27). Therefore, empirical carbapenem therapy may be indicated in patients with severe infection and underlying disease regardless of age (28).

Our study has several limitations, which stem mainly from its retrospective observational design and may have introduced a degree of bias. For example, patients who were more severely ill and those who had multiple underlying diseases may have been more likely to be treated with empirical carbapenem therapy by the attending physician. However, we adjusted for qSOFA score and underlying disease status as background factors in this study. Unfortunately, we could not adjust for the criteria used to diagnose sepsis because the necessary blood tests were not performed in a consistent manner across all participating hospitals. Nevertheless, despite these limitations, we believe that this study reflects the real-world experience of treating bacteremia caused by ESBL-producing organisms in the general hospital setting.

Our findings suggest that elderly patients aged ≥ 85 years are more likely to be treated with carbapenem antibiotics. However, patients in this age group with bacteremia caused by ESBL-producing organisms do not have a higher 30-day mortality rate, and thus do not require empirical carbapenem therapy. Our findings may help clinicians justify withholding carbapenem in these patients.

Conflict of interest None to declare.

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