Risk Factors for Mortality in Patients with *Serratia marcescens* Bacteremia

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**Purpose:** Over the last 30 years, *Serratia marcescens* (*S. marcescens*) has emerged as an important pathogen, and a common cause of nosocomial infections. The aim of this study was to identify risk factors associated with mortality in patients with *S. marcescens* bacteremia. **Materials and Methods:** We performed a retrospective cohort study of 98 patients who had one or more blood cultures positive for *S. marcescens* between January 2006 and December 2012 in a tertiary care hospital in Seoul, South Korea. Multiple risk factors were compared with association with 28-day all-cause mortality. **Results:** The 28-day mortality was 22.4% (22/98 episodes). In a univariate analysis, the onset of bacteremia during the intensive care unit stay (*p*=0.020), serum albumin level (*p*=0.011), serum C-reactive protein level (*p*=0.041), presence of indwelling urinary catheter (*p*=0.023), and Sequential Organ Failure Assessment (SOFA) score at the onset of bacteremia (*p*<0.001) were significantly different between patients in the fatal and non-fatal groups. In a multivariate analysis, lower serum albumin level and an elevated SOFA score were independently associated with 28-day mortality [adjusted odds ratio (OR) 0.206, 95% confidential interval (CI) 0.044–0.960, *p*=0.040, and adjusted OR 1.474, 95% CI 1.200–1.810, *p*<0.001, respectively]. **Conclusion:** Lower serum albumin level and an elevated SOFA score were significantly associated with adverse outcomes in patients with *S. marcescens* bacteremia.

**Key Words:** *Serratia marcescens*, bacteremia, mortality, risk factors

**INTRODUCTION**

*Serratia marcescens* (*S. marcescens*) is a Gram-negative *Enterobacteriaceae* species, initially considered non-pathogenic due to its low virulence in healthy populations.1 Over the last 30 years, however, this species has emerged as an important pathogen, and a common cause of nosocomial infections.2 *S. marcescens* has been shown to cause a wide range of infectious diseases, including urinary, respiratory, and biliary tract infections, peritonitis, wound infections, and intravenous catheter-related infections, which can also lead to life-threatening bacteremia.1,2 Risk fac-
tors associated with these infections include prolonged immunosuppressive therapy, previous antimicrobial agents, indwelling catheterization, and underlying diseases such as chronic pulmonary disease and diabetes mellitus.3

Recent epidemiologic analyses have shown an increase in the rate of antimicrobial resistance among S. marcescens isolates.4,6 Furthermore, multidrug-resistant (MDR) strains of S. marcescens have been associated with serious outcomes.7,9 The overall mortality rate of S. marcescens bacteremia remains high, ranging from 25–58%.2,9,10 However, despite this high mortality rate, the risk factors associated with mortality in S. marcescens bacteremia have not been well established since 2008 regardless of MDR strains.10–13

Therefore, we aimed to identify the risk factors associated with mortality in patients with S. marcescens bacteremia during the last 6 years.

MATERIALS AND METHODS

Study population and design
A retrospective cohort study was conducted to investigate risk factors associated with mortality in S. marcescens bacteremia at Severance Hospital, a 2000-bed, tertiary-care teaching hospital, Seoul, South Korea. Inclusion criteria for this study included patients with 18 years of age or older, identified as having one or more blood cultures positive for S. marcescens between January 2006 and December 2012. For subjects reporting more than one episode of S. marcescens bacteremia, only the first episode was accepted. Demographic and clinical variables were evaluated using microbiological laboratory records and clinical data gained from electronic medical records; these included age, gender, length of hospital stay, underlying diseases, predisposing conditions, portal of entry, appropriateness of antimicrobial agents, appropriateness of definitive therapy, results of antimicrobial susceptibility testing, laboratory data at the time of bacteremia onset, Sequential Organ Failure Assessment score (SOFA), and 28-day all-cause mortality. This study was approved by our Institutional Review Board. Informed consent was exempt from our local ethics committee because this study was concerned to cause minimal harm on persons.

Definitions
Significant S. marcescens bacteremia was defined as S. marcescens isolates cultured from one or more blood samples obtained from a patient, combined with clinical symptoms compatible with systemic inflammatory response syndrome.13 Hospital-acquired bacteremia was defined as a positive blood culture taken from a patient no sooner than 48 h after hospital admission, whereas healthcare-associated bacteremia was defined as a positive blood culture taken from a patient receiving home and/or ambulatory intravenous therapy, hemodialysis, wound care, chemotherapy, or nursing care, or who had attended a hospital clinic within the last 30 days; patients hospitalized in an acute care hospital for ≥2 days within the last 90 days; or those living in a nursing home or long-term care facility.16 The primary site of infection was presumed to be the source of bacteremia if S. marcescens was identified from any culture specimens at the time of bacteremia onset; if S. marcescens was not identified from any culture other than the blood, the source presumed to be primary bacteremia. Polymicrobial bacteremia was defined as bacteremia where more than one organism were isolated from the same blood culture specimen. Septic shock was defined as sepsis-induced organ hypoperfusion, combined with either a systolic blood pressure <90 mm Hg or <40 mm Hg less than baseline, or a mean arterial pressure <65 mm Hg after a fluid resuscitation, eventually leading to require the vasopressor use.17 Underlying chronic diseases included hemato-oncological disease, chronic renal disease, chronic liver disease, chronic lung disease, cardiovascular disease, and cerebrovascular disease, as defined by the International Classification of Disease, 10th Revision.18 Prior use of antimicrobial agent was defined as receipt for at least 48 h within 1 month prior to the bacteremic episode. Appropriateness of initial empirical antimicrobial agents was defined as the use of at least one in vitro susceptible antimicrobial agent within 24 h of positive blood culture before the susceptibility was known.19 Definitive therapy was defined as antibiotic therapy given properly according to the results of final blood culture.20 Hypoalbuminemia was defined as a serum albumin of less than 3.0 g/dL at the time of bacteremia.21,22 Twenty-eight-day all-cause mortality was investigated to confirm the primary outcome.

Microbiological tests
Clinical isolates were evaluated using either conventional techniques or the ATB 32 GN system (bioMérieux, Marcy l’ Etoile, France). Antimicrobial susceptibility testing was performed by microbiology laboratory staff using the disk-diffusion method or a VITEK-2 N131 card (bioMérieux,
and underlying conditions of all patients with *S. marcescens* bacteremia. Sixty patients (61.2%) were male, and the ages of patients ranged from 26 to 92 years (median age, 63.5 years). Of 98 bacteremic episodes, hospital-acquired bacteremia accounted for 73.5% of the episodes (72 patients), whereas healthcare-associated bacteremia accounted for 18.4% of the episodes (18 patients). The remaining 8 episodes (8.1%) were defined as community-acquired bacteremia. The most common underlying condition was malignancy (46.9%), which included conditions such as solid organ and hematologic malignancy; and diabetes mellitus (30.6%) were also common. The most frequent portal of entry was the lower respiratory tract (50%). Other portals of entry included the urinary tract (20.4%), abdomen (11.2%), skin and soft tissue (10.2%), and intra-venous catheter (5.1%). Half of the patients had central venous catheters (CVCs), including chemo-ports, and urinary catheters. 56.1% of the patients showed bacteremia during the intensive care unit (ICU) stay. Among them, the fatal group showed a greater incidence of bacteremia during the ICU stay (77.3%) than the non-fatal group (50%) (\(p=0.020\)).

### Risk factors for 28-day all-cause mortality

The 28-day all-cause mortality was 22.4% (22/98). Univariate analysis revealed significant differences in the number of important clinical covariates including the onset of bacteremia during the ICU stay (\(p=0.020\)), serum albumin level (\(p=0.011\)), serum C-reactive protein level (\(p=0.041\)), presence of indwelling urinary catheter (\(p=0.023\)), and SOFA score at the onset of bacteremia (\(p<0.001\)) between patients in the fatal and non-fatal groups (Table 1). In a multivariate analysis, lower serum albumin level [adjusted odds ratio (OR) 0.206, 95% confidential interval (CI) 0.044–0.960, \(p=0.040\)], and elevated SOFA score (adjusted OR 1.474, 95% CI 1.200–1.810, \(p<0.001\)) were all found to be inde-
Table 1. Clinical Characteristics of the Patients with *Serratia marcescens* Bacteremia

| Characteristics                              | Total cases (n=98) | Fatal group (n=22) | Non-fatal group (n=76) | p value |
|----------------------------------------------|-------------------|-------------------|-----------------------|---------|
| Age, yr, median (range)                      | 63 (26–92)        | 62.5 (26–92)      | 63 (26–88)            | 0.692   |
| Age >65 yrs, n (%)                           | 46 (46.9)         | 10 (45.5)         | 36 (47.4)             | 0.871   |
| Male, n (%)                                  | 60 (61.2)         | 10 (50)           | 50 (64.1)             | 0.253   |
| BMI (kg/m²)                                  | 22.36 (12.17–40.09) | 21.77 (12.17–40.09) | 23.27 (14.79–33.42) | 0.139   |
| Polymicrobial, n (%)                         | 27 (27.6)         | 5 (22.7)          | 22 (28.9)             | 0.573   |
| Acquisition of bacteremia, n (%)             |                   |                   |                       | 0.651   |
| Hospital-acquired                            | 72 (73.5)         | 18 (81.8)         | 54 (71.1)             |         |
| Healthcare-associated                        | 18 (18.4)         | 3 (13.6)          | 15 (19.7)             |         |
| Community-acquired                           | 8 (8.1)           | 1 (4.5)           | 7 (9.2)               |         |
| Underlying diseases, n (%)                   |                   |                   |                       |         |
| Malignancy                                    |                   |                   |                       |         |
| Solid organ malignancy                       | 36 (36.7)         | 11 (50)           | 25 (32.9)             | 0.144   |
| Hematologic malignancy                       | 10 (10.2)         | 1 (4.5)           | 9 (11.8)              | 0.450   |
| Diabetes mellitus                            | 30 (30.6)         | 5 (22.7)          | 25 (32.9)             | 0.360   |
| Chronic renal disease                        | 26 (26.5)         | 4 (18.2)          | 22 (28.9)             | 0.308   |
| Cerebrovascular disease                      | 24 (24.5)         | 5 (22.7)          | 19 (25)               | 0.829   |
| Cardiovascular disease                       | 11 (11.2)         | 3 (13.6)          | 8 (10.5)              | 0.714   |
| Chronic liver disease                        | 6 (6.1)           | 3 (13.6)          | 3 (3.9)               | 0.132   |
| Congestive heart failure                     | 5 (5.1)           | 1 (4.5)           | 4 (5.3)               | 1.000   |
| Neuromuscular disease                        | 5 (5.1)           | 0 (0)             | 5 (6.6)               | 0.592   |
| Chronic lung disease                         | 4 (4.1)           | 0 (0)             | 4 (5.3)               | 0.571   |
| Solid organ transplantation                   | 3 (3.1)           | 1 (4.5)           | 2 (2.6)               | 0.540   |
| Rheumatologic disease                        | 3 (3.1)           | 0 (0)             | 3 (3.9)               | 1.000   |
| Predisposing conditions, n (%)               |                   |                   |                       |         |
| Prior anti-biotic use (within 1 month)       | 49 (50)           | 11 (50)           | 38 (50)               | 1.000   |
| Immunosuppressive therapy                    | 19 (19.4)         | 4 (18.2)          | 15 (19.7)             | 1.000   |
| Inappropriate empirical antimicrobial therapy | 17 (17.3)         | 4 (18.2)          | 13 (17.1)             | 1.000   |
| Inappropriate definitive therapy              | 3 (3.1)           | 1 (4.5)           | 2 (2.6)               | 0.544   |
| CVC indwelling                               | 49 (50)           | 15 (68.2)         | 34 (44.7)             | 0.052   |
| Urinary catheter indwelling                  | 54 (55.1)         | 17 (77.3)         | 37 (48.7)             | 0.023   |
| Onset of bacteremia during the ICU stay      | 55 (56.1)         | 17 (77.3)         | 38 (50)               | 0.020   |
| Laboratory data                              |                   |                   |                       |         |
| Leukocyte count (>1000/µL) (range)           | 9.08 (0.45–60.95) | 9.94 (0.45–60.95) | 8.80 (0.71–51.96)     | 0.345   |
| Serum CRP (mg/L) (range)                     | 93.84 (4.19–346)  | 76.44 (4.19–346)  | 125.01 (12.1–335)     | 0.041   |
| Serum albumin (g/dL) (range)                 | 3.1 (2.0–4.4)     | 2.7 (2.0–4.1)     | 3.2 (2.1–4.4)         | 0.011   |
| SOFA                                         | 4 (0–19)          | 3 (0–13)          | 9.5 (3–19)            | <0.001  |

BMI, body mass index; CRP, C-reactive protein; CVC, central venous catheter; SOFA, Sequential Organ Failure Assessment; ICU, intensive care unit.

Values are given as n (%) or range.
dependent risk factors for mortality in patients with *S. marcescens* bacteremia (Table 2).

**DISCUSSION**

A number of recent reports have shown that *S. marcescens* bacteremia may arise from both community-acquired as well as healthcare-associated exposures.\(^{10,12,13,24,25}\) Furthermore, an increase in the number of multidrug-resistant *S. marcescens* strains has been reported worldwide.\(^{26-28}\) As these factors can substantially influence the outcome of *S. marcescens* bacteremia, we sought to identify the risk factors associated with *S. marcescens*-related mortality during recent 6 years. In our study, the 28-day all-cause mortality rate was 22.4%, similar to that in a previous report from South Korea.\(^{12}\)

In previous studies, a wide array of independent risk factors have been found to be associated with mortality in patients with *S. marcescens* bacteremia, including old age (>65 years), pneumonia, hemorrhage, shock, inappropriate treatment, leukocytosis (leukocyte count >20000/mm\(^3\)), thrombocytopenia (platelet count <50000/mm\(^3\)), hyperbilirubinemia (serum total bilirubin >18 µmol/L), ICU stay, rapidly fatal or ultimately fatal disease, existence of poly-microorganisms, and unknown portal of entry.\(^{7,12,29-31}\) Previous studies reports have directly investigated the association between chronic, fatal conditions and *S. marcescens*-associated bacteremia.\(^{12,31}\) Watanakunakorn reported that both rapidly fatal and ultimately fatal diseases influenced the rate of mortality in *S. marcescens* bacteremia-related patients with no underlying conditions. Similar results were obtained by Choi, et al.\(^{12}\) with rapidly fatal or ultimately fatal diseases serving as independent prognostic factors for *S. marcescens* bacteremia-associated fatality. However, in our study, underlying diseases were not significantly different between the fatal and the non-fatal group.

Herein, we identified significant associations between 28-day all-cause mortality and decreased serum albumin, and elevated SOFA score. Serum albumin level was significant-

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### Table 2. Risk Factors for the Mortality in Patients with *S. marcescens* Bacteremia

| Variables                                  | OR   | 95% CI       | \(p\) value |
|--------------------------------------------|------|--------------|-------------|
| Age                                        | 0.964| 0.917–1.014  | 0.164       |
| ICU stay                                   | 0.939| 0.140–6.289  | 0.950       |
| Serum albumin                              | 0.206| 0.044–0.960  | 0.040       |
| SOFA                                       | 1.474| 1.200–1.810  | <0.001      |
| Presence of indwelling urinary catheter    | 0.886| 0.176–4.447  | 0.880       |
| Presence of 3rd cephalosporin resistance   | 0.896| 0.211–3.804  | 0.882       |

ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment; OR, odds ratio; CI, confidential interval.

Multivariate logistic regression analyses were performed with all statistically significant variables of less than 0.05 of \(p\) value obtained from univariate analyses.

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fig2. *In vitro* antibiotic susceptibility tests for *S. marcescens* isolates cultured from blood.
ly associated with mortality in S. marcescens bacteremia. Hypoalbuminemia was shown in the fatal group although both groups showed evidence of decreased albumin level. Serum albumin levels are used to gauge the general health of a patient, since significant fluctuations are seen during acute illnesses due to changes in vascular permeability and redistribution of fluids. Moreover, hypoalbuminemia can alter pharmacokinetics (PK) and pharmacodynamics of certain antimicrobial agents. Hypoalbuminemia influences PK as a result of decreased binding of the antimicrobial compound to albumin, leading to an increase in the unbound fraction. The relationship between hypoalbuminemia and mortality in acutely ill patients is well established. Herrmann, et al. found that subjects with low serum albumin levels had a higher rate of mortality than the subjects with normal concentrations. The impact of these changes has since been quantified, with mortality risk increasing 137% with each 1 mg/dL decline in serum albumin level.

Elevated SOFA score was also found to be an independent risk factor for mortality in S. marcescens bacteremia. The SOFA score is a grading system that describes the severity of a patient’s illness based on the degree of organ dysfunction, and serves as a useful tool for predicting mortality in bacteremic patients. An elevated SOFA score is indicative of severe organ dysfunction and poor prognosis. Several studies demonstrated correlations between SOFA score and clinical outcomes, such as severe sepsis and septic shock, in patients with bacteremia.

In our study, the fatal group showed a poorer general condition, including a greater presence of indwelling CVC, urinary catheter, and the onset of bacteremia during the ICU stay than the non-fatal group. These conditions might result in decreased serum albumin level and low SOFA score.

The rate of resistance to cefotaxime (46.9%) during this study period was slightly lower than previous investigations in South Korea. In our study, there was no statistically significant difference between the fatal and non-fatal group for the presence of 3rd cephalosporin resistance. Most of the patients received appropriately definitive therapies, which could have affected the result.

Our study has some limitations. First, patients with S. marcescens bacteremia included in this study were enrolled from a single center. Second, there is potential for bias and inaccurate data collection due to retrospective nature of this study. Moreover, evidence of a high proportion (>20%) of polymicroorganisms other than S. marcescens may create a bias when analyzing the data. Further prospective studies, conducted in larger patient populations involving multiple centers, are necessary to more accurately identify the risk factors associated with mortality in S. marcescens bacteremia. Finally, the small sample size of those with S. marcescens bacteremia may possibly influence our results.

In conclusions, lower serum albumin level and an elevated SOFA score were significantly associated with adverse outcomes in patients with S. marcescens bacteremia.

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