Diagnostic Microbiology and Infectious Disease 87 (2017) 180–187

Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

Tree-structured survival analysis of patients with *Pseudomonas aeruginosa* bacteremia: A multicenter observational cohort study

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ARTICLE INFO

Article history:
Received 3 June 2016
Received in revised form 13 September 2016
Accepted 3 October 2016
Available online 7 October 2016

Keywords:
Pseudomonas aeruginosa
Bacteremia
Mortality

ABSTRACT

This study aimed to construct a prediction algorithm, which is readily applicable in the clinical setting, to determine the mortality rate for patients with *P. aeruginosa* bacteremia. A multicenter observational cohort study was performed retrospectively in seven university-affiliated hospitals in Korea from March 2012 to February 2015. In total, 264 adult patients with monomicrobial *P. aeruginosa* bacteremia were included in the analyses. Among the predictors independently associated with 30-day mortality in the Cox regression model, Pitt bacteremia score >2 and high-risk source of bacteremia were identified as critical nodes in the tree-structured survival analysis. Particularly, the empirical combination therapy was not associated with any survival benefit in the Cox regression model compared to the empirical monotherapy. This study suggests that determining the infection source and evaluating the clinical severity are critical to predict the clinical outcome in patients with *P. aeruginosa* bacteremia.

1. Introduction

Pseudomonas aeruginosa, first isolated by Gessard in 1882, causes many human infections. Particularly, *P. aeruginosa* is the third most common gram-negative pathogen causing bacteremia. In 1997, a cross-sectional study performed in North and Latin America showed that it is associated with a high mortality rate ranging from 26% to 39% (Al-Hasan et al., 2008; Diekema et al., 1999; Parkins et al., 2010; Wisplinghoff et al., 2004). The poor outcomes associated with *P. aeruginosa* bacteremia may be attributed to both host and microbial factors. Therefore, it is imperative to consider several factors that can influence patient outcomes, such as optimal antibiotic treatment, widespread antibiotic resistance and host immunity (Gellatly and Hancock, 2013; Lodise et al., 2007; Sadikot et al., 2005).

In order to improve the clinical outcome and to accurately predict the prognosis, it is essential to identify the predictors associated with mortality. In previous studies, the risk factors associated with adverse outcomes in patients with *P. aeruginosa* bacteremia included severe underlying diseases, neutropenia, pneumonia, severe sepsis, septic shock, an increasing Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) score, prolonged length of hospital stay prior to the blood culture, and inadequacy of the initial empirical antimicrobial therapy (Bisbe et al., 1988; Hilf et al., 1989; Ibrahim et al., 2000; Kang et al., 2003; Kim et al., 2014; Kuikka and Valtonen, 1998; Sadikot et al., 2005).

Antibiotic combination therapy is a common therapeutic approach implemented for decades against infections with *P. aeruginosa* (Bodey et al., 1985; Mutlu and Wunderink, 2006). Combination therapy for *P. aeruginosa* bacteremia provides an increased possibility of adequate empirical coverage, prevention of the emergence of bacterial resistance during antibiotic therapy, and in vitro antibiotic synergy (Micek et al., 2005; van Delden, 2007). However, despite the anticipatable advantages of combination antibiotic therapy, it has not been clearly established whether empirical combination antibiotic therapy essentially improves survival in patients with *P. aeruginosa* bacteremia (Bowers et al., 2013; Hu et al., 2013; Park et al., 2012).

The most widely used models for identification of risk factors of mortality have been the Cox proportional hazard or multivariate logistic regression analyses. However, tree-structured survival analysis is considered an alternative to these traditional models. Its final output is expressed by a tree-structured diagram, which is understood and

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http://dx.doi.org/10.1016/j.diagmicrobio.2016.10.008
0732-8893/

Table 1
Demographic and clinical characteristics of 264 patients with bacteremia caused by *Pseudomonas aeruginosa* according to the treatment outcomes on admission day 30.

Variables	All (n = 264)	Non-survivors (n = 84, 31.8%)	Survivors (n = 180, 68.2%)	*P*-value*
Male sex, n (%)	168 (63.6)	54 (64.3)	114 (63.3)	0.881
Age ≥70 years, n (%)	120 (45.5)	46 (54.8)	74 (41.1)	0.038
Admission to diagnosis of Bacteremia (days), median (IQR)	2 (0–19)	1 (0–17)	3 (0–20)	0.390
Category of infection, n (%)				
Community-acquired	70 (26.5)	22 (26.2)	48 (26.7)	
Healthcare-associated†	54 (20.5)	20 (23.8)	34 (18.9)	0.639
Nosocomial	140 (53.0)	42 (50.0)	98 (54.4)	
Comorbidity, n (%)				
Cardiovascular	118 (44.7)	36 (42.9)	82 (45.6)	0.681
Central nervous system	39 (14.8)	14 (16.7)	25 (13.9)	0.554
Malignancy	111 (42.0)	34 (40.5)	77 (42.8)	0.724
Renal	42 (15.9)	12 (14.3)	30 (16.7)	0.622
Hepatic	31 (11.7)	8 (9.5)	23 (12.8)	0.444
Respiratory	16 (6.1)	4 (4.8)	12 (6.7)	0.546
Metabolic	55 (20.8)	16 (19.0)	39 (21.7)	0.626
Charlson comorbidity index‡, median (IQR)	3 (1–6)	3 (2–6)	3 (1–6)	0.482
Predisposing factors, n (%)				
Prior admission	155 (58.7)	50 (59.5)	105 (58.3)	0.855
Prior surgical operation	42 (15.9)	15 (17.9)	27 (15.0)	0.554
Neutropenia	161 (61.0)	61 (72.6)	100 (55.6)	0.008
Prior antibiotic use	87 (33.0)	27 (32.1)	60 (33.3)	0.848
Primary focus of bacteremia, n (%)				
Low risk	158 (59.8)	66 (78.6)	92 (51.1)	<0.001
CR-BSI	22 (8.3)	5 (8.0)	17 (9.4)	0.339
Urinary tract infection	51 (19.3)	13 (15.5)	38 (21.1)	0.280
Biliary tract infection	33 (12.5)	0	33 (18.3)	<0.001
High risk	106 (40.2)	18 (21.4)	88 (48.9)	<0.001
Pneumonia	68 (25.8)	35 (41.7)	33 (18.3)	<0.001
Surgical wound infection	9 (3.4)	3 (3.6)	6 (3.3)	1.000
Skin and soft tissue infection	7 (2.7)	3 (3.6)	4 (2.2)	0.683
Bone and joint infection	1 (0.4)	0	1 (0.6)	1.000
Cardiovascular infection	4 (1.5)	0	4 (2.2)	0.310
Intra-abdominal infection	14 (5.3)	13 (15.5)	1 (0.6)	<0.001
Central nervous system infection	1 (0.4)	0	1 (0.6)	1.000
Unknown	77 (29.2)	23 (27.4)	54 (30.0)	0.663
Clinical severity, n (%)				
Development of severe sepsis	23 (8.7)	8 (9.5)	15 (8.3)	0.749

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