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Original Contribution

Prognostic factors of *Streptococcus pneumoniae* infection in adults

Toru Hifumi, MD [a,*], Seitaro Fujishima, MD, PhD [b], Takayuki Abe, MD, PhD [c], Nobuaki Kiriu, MD, PhD [d], Junichi Inoue, MD, PhD [e], Hiroshi Kato, MD, PhD [d], Yuichi Koido, MD, PhD [d], Kenya Kawakita, MD, PhD [a], Yasuhiro Kuroda, MD, PhD [a], Junichi Sasaki, MD, PhD [f], Shingo Hori, MD, PhD [f]

[a] *Emergency Medical Center, Kagawa University Hospital, Miki, Kita, Kagawa, Japan*
[b] *Center for General Internal Medicine and Education, Keio University Hospital, Shinjuku-ku, Tokyo, Japan*
[c] *Center for Clinical Research, Department of Preventive Medicine and Public Health, Keio University School of Medicine, Shinjuku-ku, Tokyo, Japan*
[d] *Division of Critical Care Medicine and Trauma, National Hospital Organization Disaster Medical Center, Tachikawa, Tokyo, Japan*
[e] *Division of Critical Care Medicine and Trauma, Yamanashi Prefectural Central Hospital, Kofu, Yamanashi, Japan*
[f] *Department of Emergency Medicine and Critical Care Medicine, Keio University Hospital, Shinjuku-ku, Tokyo, Japan*

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ABSTRACT

Objectives: The mortality of severe sepsis has markedly decreased since the implementation of the Surviving Sepsis Campaign guidelines. The next logical step is to examine the necessity of individualized management guidelines for targeted therapy against specific bacteria. *Streptococcus pneumoniae* is the leading cause of community-acquired severe sepsis; however, little is known regarding the prognostic factors in adult patients with *S pneumoniae* sepsis. We aimed to identify prognostic factors in patients with *S pneumoniae* sepsis and to explore a subgroup of patients at high risk for death with detailed Sequential Organ Failure Assessment (SOFA) score analysis.
Methods: We retrospectively reviewed the records of patients with *S pneumoniae* infection treated between 1st January 2006 and 31st July 2012. We identified prognostic factors for 28-day mortality using univariate and multivariate logistic regression models.
Results: Of 171 patients (median age, 72 years) with *S pneumoniae* infection who were included in this study, the 28-day mortality was 17% (29/171). The SOFA score (odds ratio, 2.25; 95% confidence interval, 1.60-3.18; $P < .001$) and bacteremia (odds ratio, 19.0; 95% confidence interval, 4.06-90.20; $P < .001$) were identified as prognostic factors for the 28-day mortality. In a subgroup analysis with a cutoff value of the SOFA score determined by receiver operating characteristic analysis, patients with bacteremia and a SOFA score of at least 7 had a significantly higher mortality than did patients without bacteremia and a SOFA score lower than 7 (84% vs 0%, respectively).
Conclusions: Bacteremia and a SOFA score at least 7 were independent prognostic factors of poor outcome in *S pneumoniae* sepsis.

1. Introduction

The mortality of severe sepsis has markedly decreased from greater than 50% to less than 30% since the implementation of the Surviving Sepsis Campaign guidelines [1,2]. In addition to these standard management guidelines, researchers have considered associations between the source of infection, the pathogenic species, and the mortality [3,4], particularly for sepsis because of fatal conditions such as *Neisseria meningitidis* [5], *Vibrio vulnificus* [6], *Clostridium perfringens* [7], and *Streptococcus pneumoniae* [8]. Therefore, the next logical step is to examine the necessity of individualized management guidelines for targeted therapy against specific bacteria.

S pneumoniae causes a broad spectrum of illnesses, ranging from mild upper respiratory tract infection to fatal septic shock [9], and is the leading cause of community-acquired severe sepsis [4,10]. *S pneumoniae* infection can be broadly grouped into invasive disease and noninvasive (mucosal) disease [11]. Invasive pneumococcal disease is usually diagnosed when *S pneumoniae* is identified in normally sterile body fluids, such as the blood, cerebrospinal fluid, synovial fluid, pericardial fluid, pleural fluid, or peritoneal fluid [12]. Invasive pneumococcal disease is associated with a high mortality [9,13]; however, some studies report that the presence of *S pneumoniae* bacteremia did not increase the risk of poor outcomes in patients with community-acquired pneumonia [14,15]. Thus, the prognostic factors and the mechanism underlying fatal outcomes are unknown. However, timely and accurate diagnosis of pneumococcal disease and the identification of patients at high risk for poor outcomes are both essential if adequate treatment is to be initiated as early as possible [16].

The Sequential Organ Failure Assessment (SOFA) score is a simple and objective score that enables the calculation of both the number and severity of organ dysfunction in 6 organ systems (pulmonary, hematologic, hepatic, cardiovascular, central nervous system, and renal) [17]. The SOFA score will be widely introduced in the intensive care

* Corresponding author at: Emergency Medical Center, Kagawa University Hospital, 1750-1 Ikenobe, Miki, Kita, Kagawa 761-0793, Japan. Tel.: +81 87 891 2392; fax: +81 87 891 2393.
E-mail address: hifumitoru@gmail.com (T. Hifumi).

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unit and emergency department because of its potential availability of prognosis of mortality in septic patients [18]. Thus, we considered that detailed analysis of SOFA score is the principle for early determination of prognostic factors in *S pneumoniae* infection.

This study aimed to identify the prognostic factors associated with mortality in adult patients with *S pneumoniae* sepsis and to explore a subgroup of patients at high risk for death with detailed SOFA analysis.

2. Materials and methods

2.1. Study design and setting

This was a single-center study of adult patients hospitalized with a confirmed diagnosis of pneumococcal infection between 1st January 2006 and 31st December 2012 at the National Disaster Medical Center (Tokyo, Japan). The National Disaster Medical Center is a tertiary care center with 450 beds and 33 intensive care beds. All data were collected retrospectively by medical record review. The study was approved by the institutional review board of the National Disaster Medical Center and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The institutional review board waived the requirement for patient consent because of the retrospective study.

2.2. Study participants and inclusion criteria

We included all patients 18 years or older and diagnosed as having *S pneumoniae* sepsis. Patients were excluded if they were referred from another institution where they had received antimicrobial treatment.

Community-acquired pneumonia was diagnosed in accordance with the criteria defined by Fang et al [19], as follows: the presence of new infiltrates on chest x-ray, the presence of at least 1 major criteria (fever ≥38.0°C, hypothermia <35.0°C, cough, or pleuritic pain) or 2 minor criteria (dyspnea, leukocytosis >12 000 cells/mm^3, altered level of consciousness, auscultatory signs of consolidation, or expectoration), and not having been hospitalized for more than 48 hours prior to symptom onset and a positive sputum culture for *S pneumoniae*. *Primary bacteremia* was defined as a positive blood culture with an undetermined focus [20,21].

The presence of systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, or septic shock was defined according to the definitions of the American College of Chest Physicians/Society of Critical Care Medicine consensus conference statement and its 2003 revision [22]. Illness severity was evaluated with the SOFA score [23], in which organ dysfunction was defined as a score of at least 2 for each organ system. The diagnosis of disseminated intravascular coagulation (DIC) was performed according to the Japanese Association of Acute Medicine DIC diagnostic criteria [24,25], with a total score of at least 4 establishing a diagnosis of DIC.

2.3. Data sampling

The following data were collected: age, sex, comorbid illness, primary infection site, blood culture result, white blood cell count, C-reactive protein level, SIRS score, DIC score, SOFA score, presence of severe sepsis and septic shock, the 28-day mortality, and the in-hospital mortality.

2.4. Outcome measures

The primary aim of the study was to determine the prognostic factors associated with *S pneumoniae* sepsis in adults. As a secondary outcome, we aimed to identify the group at highest risk for poor outcomes with *S pneumoniae* sepsis.

2.5. Statistical analysis

The primary end point of this study was 28-day mortality. Demographic factors and baseline characteristics were summarized for participants using descriptive statistics. The distribution of each variable was compared between 2 groups defined by the 28-day mortality, using Mann-Whitney *U* tests or Fisher exact tests, depending on variables. Univariate and multivariate logistic regression analyses (with stepwise variable selection) were performed to explore prognostic factors for the 28-day mortality. Covariates with a *P* value less than .05 in the univariate logistic regression analyses were included in the multivariate analysis.

Receiver operating characteristic (ROC) curve and its area under the curve (AUC) were estimated based on Mann-Whitney *U* test, and null hypothesis on AUC (H0: AUC = 0.5) was tested. Cutoff value for each continuous variable that gives the best combination of sensitivity and specificity was identified. All statistical analyses were performed using IBM SPSS, Version 20.0J (IBM Corp, Armonk, NY) and SAS version 9.3 (Cary, NC). A 2-sided *P* value less than .05 was considered statistically significant.

3. Results

3.1. Demographic factors and clinical characteristics of all study patients

During the 7-year study period, 171 patients were admitted to our hospital with *S pneumoniae* infection. The patient age ranged from 23 to 97 years (median, 72 years). The most common underlying disease was diabetes mellitus followed by chronic obstructive pulmonary disease. Pneumonia was the most common form of infection, causing 86.5% of presentations, followed by pneumococcal meningitis in 7% of patients. In total, 49 patients (28.7%) developed bacteremia, and overall 29 patients (17%) died within 28 days of admission (Table 1).

3.2. Univariate analysis of the association between covariates and 28-day mortality

There were significant differences between survivors and nonsurvivors with regard to the presence of comorbid diabetes mellitus and bacteremia, the infection site and the SIRS, DIC, and SOFA scores. The 28-day mortalities of patients with severe sepsis and septic shock due to *S pneumoniae* were 26.6% and 50.0%, respectively (Table 2).

3.3. Multivariate analysis

Multiple logistic regression analysis showed that the SOFA score (odds ratio [OR], 2.25; 95% confidence interval [CI], 1.60-3.18; $P < .01$) and presence of bacteremia (OR, 19.0; 95% CI, 4.06-90.20; $P < .01$) were independent prognostic factors for the 28-day mortality (Table 3). We, therefore, performed a subcategory analysis of the SOFA scores, using the pulmonary, hematologic, hepatic, cardiovascular, central nervous system, and renal scores as explanatory variables in a further multiple logistic regression analysis (Table 4). Initial cardiovascular (OR, 12.18; 95% CI, 3.27-45.38; $P < .01$) and hematologic dysfunction (OR, 6.80; 95% CI, 1.94-23.81; $P < .01$) were associated with the higher risk of a poor outcome.

3.4. Subgroup analysis of the association between bacteremia and mortality by infection site

Primary bacteremia was associated with a high mortality rate (85.7%), as were invasive fasciitis, osteomyelitis, epidural abscesses, and infectious endocarditis (Table 5).

3.5. Comparing the DIC score between primary bacteremia and other infection sites

Primary bacteremia was complicated by a significantly higher rate of DIC than the other infection sites (6/7 [85.7%] vs 17/164 [10.4%]; $P < .01$). The acute DIC score was also significantly higher in primary bacteremia than in the other infection sites (medians [interquartile range], 6 [5-8] vs 1 [1-2]; $P < .01$).