European Journal of Internal Medicine 25 (2014) 914–918

Contents lists available at ScienceDirect

European Journal of Internal Medicine

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

Original Article

A predictive rule for mortality of inpatients with *Staphylococcus aureus* bacteraemia: A classification and regression tree analysis

Daiki Kobayashi [a,b,c,*,1], Kyoko Yokota [d,2], Osamu Takahashi [a,b,3], Hiroko Arioka [a,3], Tsuguya Fukui [a,3]

[a] Division of General Internal Medicine, Department of Medicine, St. Luke's International Hospital, Tokyo, Japan
[b] Center for Clinical Epidemiology, St. Luke's Life Science Institute, Japan
[c] Department of Infectious Disease, Faculty of Medicine, Kagawa University, Kagawa, Japan
[d] Department of Infectious Disease, Faculty of Medicine, Kagawa University, Kita-gun, Japan

ARTICLE INFO

Article history:
Received 14 August 2014
Received in revised form 29 September 2014
Accepted 1 October 2014
Available online 14 October 2014

Keywords:
Staphylococcus aureus
Bacteraemia
Sepsis
CART analysis
Predictive rule
Mortality

ABSTRACT

Objective: To create a predictive rule to identify risk factors for mortality among patients with *Staphylococcus aureus* bacteraemia (SAB).
Design, setting and patients: This was a retrospective cohort study of all adult patients with SAB at a large community hospital in Tokyo, Japan, from April 1, 2004 to March 31, 2011. Baseline data and clinically relevant factors were collected from electronic charts. The primary outcome was in-hospital mortality. All candidate predictors were included in a classification and regression tree (CART) analysis. A receiver operating characteristic (ROC) curve was drawn, and the area under the curve (AUC) was obtained. A cross-validation analysis was performed.
Measurements and main results: A total of 340 patients had SAB during the study period. Of these, 118 (34.7%) patients died in hospital. Among 41 potential variables, the CART analysis revealed that underlying malignancy, serum blood glucose level, methicillin resistance, and low serum albumin were predictors of mortality. The AUC was 0.73 (95% CI: 0.67–0.79). For validation, the estimated risk was 0.26 (±SE: 0.02) in the resubstitution analysis and 0.33 (±SE: 0.03) in the cross-validation analysis.
Conclusion: We propose a predictive model for the mortality of patients with SAB consisting of four predictors: underlying malignancy, low serum albumin, high glucose, and methicillin resistance. This model may facilitate appropriate preventative management for patients with SAB who are at high risk of mortality.

1. Introduction

Staphylococcus aureus bacteraemia (SAB) is one of the most common types of bacteraemia in both community and healthcare settings. In the United States, the National Nosocomial Infections Surveillance System of the Centers for Disease Control and Prevention showed that the rate of SAB had increased by 122% to 283% over a 10-year period since the late 1980s [1]. Likewise, in European countries, the incidence of SAB increased by 55% from 1995 to 2001 [2]. Some patients acquired SAB in community settings; the others acquired SAB in healthcare settings. Recently, some patients have acquired methicillin-resistant *S. aureus* (MRSA) bacteraemia even in community settings, because the number of MRSA strains carried from hospitals is increasing [3–5]. As a result, patients with SAB have different disease severity levels and clinical outcomes [6].

The mortality caused by SAB is significant. Previous studies have reported that the mortality ranges from 20 to 40% [7,8]. Another study showed that MRSA bacteraemia has higher mortality than methicillin-sensitive *S. aureus* (MSSA) bacteraemia. In a recent meta-analysis about SAB, the mortality of patients with MSSA bacteraemia was found to be from 3.6% to 51.7%, while that with MRSA bacteraemia was from 0.0% to 83.3% [9]. Because the prevalence of MRSA infections has been increasing rapidly [10], the mortality rate is also likely to increase in the future. Therefore, because of its high incidence and mortality, being able to stratify patients with SAB into risk categories is important.

Although mortality is high, the risk factors for the mortality among patients with SAB have not been sufficiently evaluated. For patients with SAB that is not methicillin resistant [11], a limited number of other factors have been examined such as interleukin-10 [6] and sensitivity to vancomycin [12,13]. According to a previous study, an elevated ratio of the anti-inflammatory cytokine interleukin-10 to cytokine tumour necrosis factor alpha is predictive of increased mortality for patients with fever [14]. To provide the best treatment and care, we have to identify other risk factors for mortality among patients with

* Corresponding author at: Division of General Internal Medicine, Department of Internal Medicine, St. Luke's International Hospital, Tokyo, Japan. Tel./fax: +81 3 5550 2426.
E-mail addresses: daikoba@luke.ac.jp (D. Kobayashi), kyoyokota@hotmail.com (K. Yokota), otakahas@luke.ac.jp (O. Takahashi), arihiro@luke.ac.jp (H. Arioka), fkts@luke.ac.jp (T. Fukui).
[1] Tel./fax: +81 3 3541 5151.
[2] Tel./fax: +81 87 832 1000.
[3] Tel./fax: +81 3 5550 2426.

http://dx.doi.org/10.1016/j.ejim.2014.10.003
0953-6205/

SAB. The goal of this study was to predict the mortality of patients with SAB based on relevant patient demographic and clinical factors.

2. Methods

A retrospective cohort study of all adult patients who had SAB from April 2004 through March 2011 was conducted at St. Luke's International Hospital, a large academic hospital in Tokyo, Japan. The study was approved by the Research Ethics Committee of St. Luke's International Hospital, Tokyo, Japan and the Committee on Clinical Investigation at Beth Israel Deaconess Medical Center.

All patients with fever (≥38.5 °C) had 2 sets of blood cultures at the time of admission. In addition, afebrile patients who were suspected of having a bacterial infection also had 2 sets of blood cultures at the discretion of their clinical provider. SAB was determined based on at least one positive blood culture. All patients with positive blood cultures were monitored and supported by infectious disease specialists. The main outcome was SAB-specific in-hospital mortality. Patients who died within 90 days after the infection were assessed as to whether the *S. aureus* infection caused the death or contributed to the death based on a previous study [8]. The main cause of the patient's death was evaluated by their physician based on their clinical course.

All potential prognostic prediction parameters were collected at the time of admission and during hospitalization. The parameters collected included 1) demographic data, 2) vital signs, 3) medical devices, 4) medical history, and 5) laboratory test results. For our analyses, we used blood test results and vital sign data collected on the day of admission or the closest day before the blood culture was drawn. If a patient was admitted more than one time with SAB during the study period, only the first data were included.

Potential predictors of interest were identified based on previous studies as well as potential clinical relevance. Demographic data of interest included gender, age, height, weight, and body mass index (BMI). Medical device data included central venous line, ventilation, and haemodialysis before infection day. Clinical factors of interest included the primary site of *S. aureus* infection and underlying diseases. Vital sign data included heart rate, body temperature, systolic/diastolic blood pressure, respiratory rate, and oxygen saturation, and laboratory test results were collected following routine blood draws. In the past medical history, cancer-bearing patients were defined as those who had leukaemia, malignant lymphoma, or a solid tumour based on previous study [15]. A Charlson score was calculated for each patient as a potential parameter for a predictive rule.

3. Statistical analysis

We used descriptive statistics to characterize the subjects' baseline data. For bivariable analysis, Student's t test was used to test differences in continuous variables and the Chi-square test was used for differences in proportions among survivors and deaths.

To create the prediction model for the mortality of patients with SAB, we used the classification and regression tree (CART) methodology to identify patients at different levels of risk. The CART model is well suited to the generation of clinical decision rules and has been used to develop prediction models in various fields, including medical settings [16]. The CART method employs a non-parametric statistical technique that makes no distribution assumptions of any kind, for either dependent or independent variables [17,18]. A decision tree is created by stratifying the initial data set, which contains all potential predictors, into subsets based on the 'impurity' of the model. Branch nodes in the decision are based on the 'impurity' [8] of the model which is represented by the Gini diversity index (GI):

$$\Delta GI(t) = P_t GI(t) - P_L GI(t_L) - P_R GI(t_R)$$

where $\Delta GI(t)$ represents variation of the GI, $GI(t)$ represents the Gini diversity index at node t, P_t represents the ratio of node t before partition, P_L represents the ratio of the left node after partition, and P_R represents the ratio of the right node after partition. The risk factor that maximizes impurity is selected as a branch point. This process is repeated on each derived subset, and it is completed when the impurity value of the subset is not improved by additional splitting.

In this study, the CART algorithm was used to analyse 41 potential variables. Nodes in the CART decision tree were constrained to a minimum size of 50 subjects to consider additional stratification, and each resulting subgroup needed to have at least 20 subjects. A receiver operator characteristic (ROC) curve was drawn from the result of the CART analysis, and the area under the curve (AUC) was calculated to evaluate the accuracy of the tree. After arriving at the final decision tree, to derive the standard error of the branches of our CART model, we performed cross validation.

All analyses were conducted using SPSS software package version 19.0 (IBM, Tokyo, Japan), except for the calculation of the 95% confidence intervals (CIs), which was based on an exact binominal [19] using Stata version 11 (STATA Corp., College Station, USA).

4. Results

A total of 340 patients had SAB and 118 (36%) patients died within 90 days of a positive blood culture. The median survival for the patients who died with SAB was 38.6 days (standard deviation 25.2).

Table 1 shows the patients' characteristics and the results of the bivariable analysis. There were 60 (51%) patients with MRSA in the group who died and 91 (41%) in the group who survived. The patients who died were significantly older. Primary disease involving soft tissue infection, lower BMI, underlying malignancy, higher Charlson score, low oxygen saturation, anaemia, lower serum albumin level, higher lactate dehydrogenase, and low potassium level were all related to mortality.

Using CART analysis, we arrived at the decision tree shown in Fig. 1. Based on the observed results, the patients can be categorized into 3 risk groups, low (<30%), medium (30–60%), and high (>60%).

Of 41 potential variables, the CART decision tree identified underlying malignancy at the time of a positive blood culture as the best single discriminator between death and survival (Fig. 1). For patients without underlying malignancy, the next best predictor was their serum blood glucose level, dichotomized at the level of 167 mg/dl. Patients with a blood glucose level greater than 167 mg/dl had a higher risk of mortality. Methicillin resistance predicted mortality risk only among patients who had a glucose level higher than 167 mg/dl. For patients with malignancy, their serum albumin level was the most important predictor. Patients with less than 3.25 mg/dl of serum albumin were placed in one group (mortality 73%), and those over 3.25 (mg/dl) were placed in the other group (mortality 46%).

The results of the analysis were used to predict the probability of mortality in each group as represented by the ROC curve in Fig. 2. The area under the curve was 0.73. For validation, the risk estimate was 0.26 (±SE: 0.02) in a resubstitution analysis and 0.33 (±SE: 0.03) in a cross-validation analysis.

5. Discussion

In this study, we developed a CART model for estimating the mortality of patients with SAB. The four predictors identified were underlying malignancy, serum glucose level, methicillin resistance and serum albumin level. The area under the ROC curve demonstrated acceptable accuracy.

This is the first study to propose a model to quantitatively estimate the mortality of patients with SAB. Previous studies have identified the importance of methicillin resistance in predicting mortality [8,20]. Our study also identified methicillin resistance as an important risk for patients but only among those without malignancy and with a glucose