A simple prediction algorithm for bacteraemia in patients with acute febrile illness

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Summary

Background: Existing prediction models for the risk of bacteraemia are complex and difficult to use. Physicians are likely to use a model only if it is simple and sensitive.

Aim: To develop a simple classification algorithm predicting the risk of bacteraemia.

Design: Hospital-based study.

Methods: We enrolled 526 adult consecutive patients with acute febrile illness (40 with bacteraemia) presenting to the emergency department at a community hospital in Okinawa, Japan. Recursive partitioning analysis was used to build the classification algorithm with V-fold cross-validation. We used two clinical scenarios: in the first, laboratory tests were not available; in the second, they were.

Results: The two prediction algorithms generated three different risk groups for bacteraemia. In the first scenario, the important variables were chills, pulse, and physician diagnosis of a low-risk site. The low-risk group from this first algorithm included 68% of the total patients; sensitivity was 87.5% and the misclassification rate was 1.4% (5/358). In the second scenario, the important variables were chills, C-reactive protein, and physician diagnosis of a low-risk site. The low-risk group for the second algorithm included 62% of the total patients; sensitivity was 92.5% and misclassification rate 0.9% (3/328). The algorithms had negative predictive values of 98.6% (first scenario) and 99.1% (second).

Discussion: This simple and sensitive prediction algorithm may be useful for identifying patients at low risk of bacteraemia. Prospective validation is needed in other settings.

Introduction

Bacteraemia patients show high mortality and morbidity.¹,² Blood cultures are the gold standard test for proving bacteraemia, and for identifying bacteria and their antibiotic sensitivities.³ Therefore, most physicians have a low threshold for ordering blood cultures for patients with acute febrile illness,⁴ and consequently the yield of blood cultures is relatively low, frequently showing many false positives from bacterial contaminants. These false positive reports may lead to unnecessary antibiotic therapy and longer hospitalization.⁵

Several previous studies have suggested clinical prediction rules to estimate the risk of bacteraemia using logistic regression analysis.⁴⁻⁷ These studies used linear combinations of weighted scoring for a number of variables based on logistic regression models. However, it is not practically convenient to calculate total weighted scores from a large number
of variables. Moreover, these rules were only partially successful for predicting bacteraemia, they showed inconsistent results, depending on setting. Consequently, physicians have shown little willingness to adopt them.

A recursive partitioning analysis is well-suited to the construction of a simple clinical decision algorithm. This method can maximize the overall sensitivity, to reduce the misclassification rate of a particular outcome. In addition, this is potentially useful for identifying the interactions of multiple predictors as they influence disease probability. Thus our objective was to derive and validate internally a simple and sensitive prediction algorithm for excluding bacteraemia in patients with acute febrile illness, using recursive partitioning rather than logistic regression analysis.

**Methods**

**Patient enrolment and data collection**

We enrolled consecutive patients (15 years and older) who presented with acute febrile illness and were admitted to the emergency department (ED) in Okinawa Chubu Hospital of Japan during the 6-month study period. The hospital is a community teaching hospital, and provides primary to tertiary care to a population of approximately 400,000. The patient inclusion criteria were: (i) axillary or oral temperature \(\geq 38^\circ\text{C}\) by patient self-report (prior to admission) or at admission to the hospital; (ii) febrile illness of \(<2\) weeks’ duration before presenting to the ED; (iii) admitted through the out-patient division to the admission division of the ED for workup of possible bacterial infection. These criteria were based on the study method of Leibovici et al.

We excluded the following: (i) patients who provided self-report of fever prior to admission but were not confirmed as having febrile illness by the physicians at the ED; (ii) patients who had only incomplete information for the presence of fever prior to admission and no fever at admission to the hospital.

We analysed clinical characteristics including patient demographics, comorbidity, antibiotic use in the 4 days prior to hospital arrival, vital signs, blood leukocyte count, and serum C-reactive protein concentrations. Serum C-reactive protein concentrations were measured by quick test (latex agglutination kit). For medical comorbidity, we used the classification based on the Charlson comorbidity index, and we defined major comorbidity when the index was one or more. We considered presence or absence of chills during the 24 h prior to presenting to the ED. We defined positive chills when patients had the feeling of cold with the equivalent of a need for a thick blanket, or feeling very cold with generalized bodily shaking.

We also recorded the initial physicians’ diagnosis for the specific infective site. We defined as low-risk sites the following initial physicians’ diagnoses: (i) acute pharyngitis; (ii) acute bronchitis, including acute exacerbation of chronic obstructive pulmonary disease; (iii) acute infectious diarrhoea; (iv) acute viral syndromes, e.g. influenza; (v) pelvic inflammatory disease; (vi) acute otitis media; (vii) acute sinusitis; and (viii) non-infectious processes, e.g. allergic reaction.

**Definition of bacteraemia**

Our primary outcome was a positive blood culture indicating bacteraemia. The physicians drew blood cultures within 12 h of patient admission to the ED. They collected 10 ml venous blood aseptically and inoculated it into two sets of aerobic and anaerobic bottles, respectively. This procedure was repeated 10 min later, drawing another blood sample from a different site. As a result, we obtained two sets of blood cultures for each patient. The bottles were incubated at \(37^\circ\text{C}\), sub-cultured daily, and inspected for bacterial growth for 7 days. Microbiological techniques provided bacterial identification and antibiotic sensitivity testing.

Bacteraemia was defined as growth of bacteria with recognized pathogenic capacity in at least one blood culture bottle in patients with acute febrile illness and clinical findings suggesting infectious disease. Bacterial contaminants were counted as negative blood cultures. The contaminant bacteria were: (i) *Corynebacterium* species, *Propionibacterium* species, or *Bacillus* species; and (ii) *Staphylococcus epidermidis* and alpha-haemolytic streptococci, unless they were identified on two sets of blood cultures in patients with intravascular device and no apparent infectious focus.

**Statistical analysis**

We used a recursive partitioning analysis to build a prediction algorithm. This technique generates a classification tree with series of binary splits, in which patients are assigned to mutually exclusive subgroups according to a set of predictors. When applied to our group data, each binary split in a tree produced two subgroups, one containing a relatively high proportion of bacteraemia patients, and the other, a relatively high proportion of non-bacteraemia patients. We then interpreted the combination of these binary splits as a prediction algorithm for classifying patients according to the
probability of bacteraemia. A recursive partitioning analysis uses the following three steps: (i) generates an initial large tree to choose the predictors; (ii) prunes this tree backwards to produce a nested sequence of smaller trees; and (iii) selects an optimum tree from this sequence, using a cross-validation technique.\(^{12}\)

The construction of the algorithm considered the following predictor variables: (i) age; (ii) gender; (iii) major comorbidity; (iv) prior antibiotic use; (v) chills; (vi) systolic and diastolic blood pressure; (vii) pulse; (viii) respiratory rate; (ix) consciousness disturbance; (x) physician diagnosis of low risk sites; (xi) blood leukocyte count; and (xii) serum C-reactive protein concentrations. To obtain the best separation of the study cohort into bacteraemia and non-bacteraemia patients, the recursive partitioning determined appropriate cut-off points for each variable to produce two sub-groups of the greatest purity. For continuous variables, potential cut-off points are all values contained in the data. For dichotomous variables, the cut-off point is made between the integer values that represent its two categories. A sub-group is at its most pure when it includes only one class (bacteraemia or non-bacteraemia patients).

A Gini index, a measure of impurity of a node, was used as the node splitting criterion to identify the cut-off point for the best separation of the two subgroups. This index selects the partition with the greatest purity by measuring the amount of variance in the proportion of bacteraemia patients between each potential pair from the partition. It reaches a value of zero when only one class is present at a subgroup node.\(^{12}\) The partitioning starts after evaluating each predictor for its potential to separate subgroups and selects the best predictor with the most pure division for the first split. This procedure is then repeated for each of the two subgroups that are generated from the first split, again evaluating all potential cut-off points of each variable to identify the predictor that provides the best separation. This process is repeated for subsequent subgroups to grow the initial large tree.

Since an initial large tree model using the large number of parameters usually has an over-fitting problem, a pruning technique is used to eliminate several branches of the initial tree and to form a sequence of nested candidate subtrees. A cross-validation technique then identifies the subtree to minimize the misclassification rate by a sample reuse method. Since we used five-fold cross-validation, the entire group is randomly partitioned into five samples, each containing 20% of all patients. With the first 20% sample set aside, the other 80% sample is used to select the best subtree. The 20% sample is then run down this subtree as a validation sample, and the misclassification rate is calculated. This process is repeated for all five validation partitions, and identifies the most complex subtree while minimizing the misclassification rate.

We constructed two classification algorithms using two different clinical scenarios. In the first scenario, we could use data from history, physical examination and initial physician diagnosis. In the second scenario, we could also include laboratory data such as blood leukocyte count and serum C-reactive protein concentrations. Recursive partitioning was also used to rate the relative importance of each of the predictor variables in terms of their ability to discriminate between bacteraemia and non-bacteraemia. The relative importance score was calculated by scoring the relative importance of the predictor variables compared to the variable with highest rank (score = 100).

We grouped the several terminal nodes into three different risk levels (high, intermediate and low risk groups), based on the prevalence of bacteraemia within each terminal node. The Gini index can assign the costs of misclassifying each category. Since our goal was to generate a prediction algorithm that would accurately exclude bacteraemia patients, we set the misclassification cost for labelling bacteraemia patients as non-bacteraemia at 15 times higher than for labelling non-bacteraemia patients as bacteraemia. Varying misclassification costs in this manner tends to result in a final model with higher sensitivity in the recursive partitioning analysis.

We evaluated the classification performance of the final algorithm by calculating the prevalence (with 95%CIs) within each classified group. We also assessed the classification characteristics of the final algorithm by calculating the sensitivity, specificity, and positive and negative predictive value with 95% CIs within each group. We used a cut-off point for the high–intermediate vs. the low-risk group classifications, and calculated the classification characteristics, since our goal was to generate a prediction algorithm that would accurately exclude bacteraemia patients by identifying the low-risk group.

We also calculated positive and negative likelihood ratios with 95%CIs to assess clinical usefulness of the prediction algorithms. The positive likelihood ratio is defined as sensitivity/(1 – specificity) (the probability of a positive test result in bacteraemia patients divided by the probability of a positive test result in patients without bacteraemia). The negative likelihood ratio is defined as (1 – sensitivity)/specificity (the probability of a negative test result in bacteraemia patients divided by the probability of a negative test result in patients...
without bacteraemia). A likelihood ratio >1 indicates an increased probability that the bacteraemia is present, and a likelihood ratio <1 indicates a decreased probability that the bacteraemia is present. The magnitude of likelihood ratios correlates with the magnitude of decrease (or increase) in the likelihood of bacteraemia.

We used CART version 5.0 (Salford Systems) for recursive partitioning analysis, and SAS version 9.0 (SAS Institute) for general statistical calculation. All p values were two-sided and considered statistically significant at <0.05. The study received prior approval from the institutional review board of the Okinawa Chubu Hospital.

**Results**

We enrolled total 526 consecutive patients. Mean age was 57 years (range 15–106); 278 (53%) were women. Of these 526, 40 had bacteraemia (7.6%, 95%CI 5.5–10.2%). Table 1 shows the clinical characteristics in patients with and without bacteraemia. In univariate analysis, the continuous variables significantly associated with bacteraemia were old age (p = 0.015), high body temperature (p = 0.001), and high C-reactive protein concentrations (p = 0.001). Similarly, the significant binary variables were cancer (p = 0.027) and chills (p = 0.001).

Of the 40 bacteraemia episodes, Gram-negative micro-organisms were responsible in 25 patients, while Gram-positive micro-organisms were recognized in 15 patients. The pathogenic bacteria found in two or more patients were *Escherichia coli* (n = 13), *Klebsiella* sp. (n = 5), *Staphylococcus aureus* (n = 5), *Streptococcus pneumoniae* (n = 4), and *Enterococcus* sp (n = 2). One patient had polymicrobial bacteraemia.

Table 2 shows the initial diagnosis of the infective site in patients with and without bacteraemia. Over all the patients, the most frequent diagnoses were pneumonia (n = 114), urinary tract infection (n = 74) and acute bronchitis (n = 67). In the bacteraemia patients, the most frequent diagnoses were urinary tract infection (n = 14), pneumonia (n = 8) and...
biliary tract infection ($n = 6$). The proportions of bacteraemia episodes were 35.3% in patients with biliary tract infection, 18.9% in patients with urinary tract infection, and 7.0% in patients with pneumonia.

Recursive partitioning analysis provided the important variables based on the two different clinical scenarios. In the first scenario using variables except laboratory tests, the important predictors of bacteraemia were chills (relative importance score = 100), pulse (score = 45.9), physicians’ diagnosis of a low-risk site (score = 36.7), respiratory rate (score = 3.7), body temperature (score = 1.7), and systolic blood pressure (score = 0.2). In the second scenario, using all available variables, the important predictors of bacteraemia were chills (relative importance score = 100), C-reactive protein (score = 54.3), physicians’ diagnosis of a low-risk site (score = 36.2), systolic blood pressure (score = 4.7), respiratory rate (score = 3.1), age (score = 2.4), diastolic blood pressure (score = 1.1), body temperature (score = 0.5), and blood leukocyte count (score = 0.1).

Figure 1 shows the optimal algorithm in the first scenario. A recursive partitioning analysis identified three classification splits that predicted the high, intermediate and low risk groups. The high-risk group were those with chills and without physician diagnosis of a low-risk site. The intermediate-risk group were those without chills but with tachycardia (pulse $>120$/min). Finally, the low-risk group patients included (i) those with chills but with physician diagnosis of a low-risk site, and (ii) those without chills and with pulse $\leq 119$/min.

Figure 2 shows the optimal algorithm in the second scenario, including laboratory data. A recursive partitioning also identified three classification splits. The high-risk group were those with chills and without a physician diagnosis of a low-risk site. The intermediate-risk group were those without chills but with increased C-reactive protein concentration ($>10$ mg/dl). Finally, the low-risk group patients included (i) those with chills but with a physician diagnosis of a low-risk site, and (ii) those without chills and with C-reactive protein concentration $\leq 10$ mg/dl.
The number of patients classified as low risk was 358 (68%) in the first scenario and 328 (62%) in the second scenario (Table 3). Misclassification rate was low in the low-risk groups. In the first scenario, there were five bacteraemia patients (1.4%, 95%CI 0.5–3.2%) in the 358 patients classified as low risk. In the second scenario, there were three bacteraemia patients (0.9%, 95%CI 0.2–2.7%) in the 328 classified as low risk. There was no significant difference of proportions of bacteraemia patients in the low risk group between the first and second scenarios (two-tailed \( p \) value for Fisher’s exact test = 0.73). Finally, in the high-risk group, there were 29 bacteraemia patients (25.7%, 95%CI 17.9–34.7%) of 113 in both scenarios.

Table 4 shows classification characteristics for bacteraemia between the high–intermediate groups and the low-risk group. Using this cut-off point for identifying the low-risk group vs. other groups, we observed high sensitivities of 87.5% (first scenario) and 92.5% (second scenario). Further, the algorithms showed high negative predictive values of 98.6% (first scenario) and 99.1% (second scenario).

**Discussion**

We have developed a simple and sensitive algorithm predicting bacteraemia using recursive partitioning with V-fold cross-validation. The algorithm has a simple structure. It should be easy to remember and use quickly at the bedside. When we used a cut-off point between the low-risk group and the intermediate–high-risk group to attempt to identify the low-risk group, we obtained high sensitivity as well as high negative predictive value. This risk-aversive prediction algorithm seems clinically reasonable, since it is crucial to avoid misclassifying bacteraemia patients as non-bacteraemia. Nevertheless, since sepsis is often a fatal condition, we should also consider other

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**Table 3  Classification performance for bacteraemia among low, intermediate and high-risk groups**

<table>
<thead>
<tr>
<th></th>
<th>No. of patients</th>
<th>No. with bacteraemia</th>
<th>Bacteraemia % (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The first scenario</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-risk</td>
<td>113</td>
<td>29</td>
<td>25.7 (17.9–34.7)</td>
</tr>
<tr>
<td>Intermediate-risk</td>
<td>55</td>
<td>6</td>
<td>10.9 (4.1–22.3)</td>
</tr>
<tr>
<td>Low-risk</td>
<td>358</td>
<td>5</td>
<td>1.4 (0.5–3.2)</td>
</tr>
<tr>
<td>The second scenario</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-risk</td>
<td>113</td>
<td>29</td>
<td>25.7 (17.9–34.7)</td>
</tr>
<tr>
<td>Intermediate-risk</td>
<td>85</td>
<td>8</td>
<td>9.4 (4.2–17.7)</td>
</tr>
<tr>
<td>Low-risk</td>
<td>328</td>
<td>3</td>
<td>0.9 (0.2–2.7)</td>
</tr>
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</table>
About two-thirds of patients were classified as low risk using our algorithm. If these episodes had been considered as not needing blood cultures, the reduced blood cultures taken would have led to fewer unnecessary antibiotic treatments from the false positive results, and both would have led to cost savings.

Several studies have shown that the presence of chills is one of the most powerful single predictor of bacteraemia. Presence of chills was the most important variable in the recursive partitioning analysis, and was the first separator in both algorithms. For these reasons, it should be mandatory in clinical practice to ask patients with acute febrile illness specifically whether they have chills.

Physicians’ diagnosis of a low-risk site was a powerful predictor in our study. Tentative diagnosis of these conditions would suggest clinically reliable reasons not to obtain blood cultures. Although acute bronchitis, acute diarrhoea, and pelvic inflammatory disease are sometimes of bacterial causes, these locally confined infective processes are unlikely to cause bacteraemia, even with the presence of chills.

To our knowledge, this study is the first to generate a clinical prediction algorithm using recursive partitioning for estimating risk of bacteraemia in patients with acute febrile illness. The overall test performance of our algorithm was comparable with the previous prediction algorithms in considering the test characteristics. The previous models used logistic regression using various clinical variables. However, the validation of these models was only partially successful. One author highlighted the limited usefulness and inconsistency of the previous models. The complex models using a large number of variables may be better for prediction, but may lead to overfitting. Moreover, most physicians are reluctant to use complex models, even if they are shown to be useful. Our simplified algorithms are easily adoptable into pocket cards, personal digital assistants and computerized clinical decision support systems.

We must interpret our results in the light of their clinical application. We performed the study and generated the prediction algorithm in a single institution. Thus, our prediction algorithm would need external validation for its generalizability to other institutional settings and other patient groups such as hospitalized patients.

In summary, we developed a simple clinical prediction algorithm that classified patients with acute febrile illness according to their risk of bacteraemia. This algorithm is simple and seems easy to use, and may provide both clinical and economic benefits in caring for patients with acute febrile illness. External validation is needed to confirm its generalizability. If externally validated, the algorithm could be used in combination with individualized clinical judgment to estimate the risk of bacteraemia.

### Table 4 Classification characteristics for bacteraemia between high–intermediate and low risk groups

<table>
<thead>
<tr>
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<th>High–intermediate risk vs. Low risk</th>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>The first scenario</td>
<td></td>
</tr>
<tr>
<td>Sensitivity, % (95%CI)</td>
<td>87.5 (73.2–95.8)</td>
</tr>
<tr>
<td>Specificity, % (95%CI)</td>
<td>72.6 (68.4–76.6)</td>
</tr>
<tr>
<td>PPV, % (95%CI)</td>
<td>20.8 (15.0–27.8)</td>
</tr>
<tr>
<td>NPV, % (95%CI)</td>
<td>98.6 (96.8–99.5)</td>
</tr>
<tr>
<td>+LR (95%CI)</td>
<td>3.20 (2.62–3.53)</td>
</tr>
<tr>
<td>−LR (95%CI)</td>
<td>0.17 (0.08–0.36)</td>
</tr>
</tbody>
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|                      |                                    |
| The second scenario  |                                    |
| Sensitivity, % (95%CI) | 92.5 (79.6–98.4)                    |
| Specificity, % (95%CI) | 66.9 (62.5–71.1)                    |
| PPV, % (95%CI)        | 18.7 (13.5–24.8)                    |
| NPV, % (95%CI)        | 99.1 (97.4–99.8)                    |
| +LR (95%CI)           | 2.79 (2.36–2.98)                    |
| −LR (95%CI)           | 0.11 (0.04–0.30)                    |

CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; +LR, positive likelihood ratio; −LR, negative likelihood ratio.
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References


