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Original Contribution

Validation of a prediction rule for endocarditis in febrile injection drug users ☆,☆☆,★

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ABSTRACT

Background: Infectious endocarditis (IE) in febrile injection drug users (IDUs) is a critical diagnosis to identify in the emergency department (ED). A decision tool that identifies patients at very low risk for endocarditis using readily available clinical data could reduce admissions and cost.
Objective: To evaluate the diagnostic performance of a previously derived decision instrument to rule out endocarditis in febrile IDUs (Prediction Rule for Endocarditis in Injection Drug Users [PRE-IDU]) and to develop a prediction model for likelihood of endocarditis for those who are not ruled out by PRE-IDU.
Methods: Febrile IDUs admitted to rule out endocarditis were prospectively enrolled from 2 urban EDs in June 2007 to March 2011. Clinical data from ED presentation (first 6 hours) and outcome data from inpatient records were recorded and reviewed by 2 independent investigators. Diagnosis of IE was based on modified Duke criteria and discharge summaries. The diagnostic performance of PRE-IDU, which combines tachycardia, cardiac murmur, and absence of skin infection, was determined using recursive partitioning and logistic regression modeling.
Results: Of the 249 subjects, 18 (7%) had IE. Recursive partitioning yielded an instrument with 100% sensitivity (95% confidence interval [CI], 84%-100%) and 100% negative predictive value (95% CI, 91%-100%), but low specificity (13%; 95% CI, 12%-13%). Multiple logistic regression modeling with the 3 clinical predictors allowed risk stratification with posttest probabilities ranging from 3% to 20%.
Conclusion: The PRE-IDU instrument predicted IE with high sensitivity and ruled out IE with high negative predictive value. Our logistic regression model provided posttest probabilities ranging from 3% to 20%. The PRE-IDU instrument and the associated model may help guide hospital admission and diagnostic testing in evaluation of febrile IDUs in the ED.

1. Introduction

Infective endocarditis (IE) has an incidence of 1 to 20 cases per 10 000 injection drug users (IDUs) every year and accounts for 5% to 20% of hospital admissions in this population [1-3]. Given its associated complications as well as a 5% to 10% mortality rate, accurate diagnosis of IE is imperative [1,3]. However, diagnosis of IE in the emergency department (ED) remains challenging. Although previous studies have suggested an association between IE and clinical criteria such as urine sediment, higher median temp, recent intravenous drug use within the last 5 days, and mild hyponatremia [1,4-6], attempts to risk stratify febrile IDUs based on these criteria and clinical assessment in the ED were unsuccessful [2-5,7]. Therefore, current standard of practice mandates admission for IDUs with fever of unclear etiology for blood cultures and echocardiography [3-5]. A decision instrument (DI) that could reliably identify IDUs at low risk for IE using clinical and laboratory criteria available in the ED could spare admissions and guide further testing for more efficient resource use.

To this end, we previously developed a DI based on ED clinical data using recursive partitioning modeling techniques: Prediction Rule for Endocarditis in Injection Drug Users (PRE-IDU). We identified tachycardia, lack of skin infection, and cardiac murmur as 3 criteria whose combination into a DI yielded 100% sensitivity (95% confidence interval [CI], 84%-100%) and 100% negative predictive value (95% CI, 88%-100%) for IE [8]. Our initial model was designed to generate a "directive" yes/no algorithm to identify very-low-risk patients who may be safe for discharge, maximizing sensitivity at the price of low specificity (14%, 95% CI, 10%-20%). Alternatively, an "assistive" modeling approach using logistic modeling to obtain posttest likelihood ratios to guide medical decision making may be useful to

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provide risk stratification for patients who do not meet low-risk criteria [9]. The objectives of our study were (1) to validate PRE-IDU for the prediction of IE in an independent, prospectively enrolled cohort of IDUs admitted to rule out endocarditis, and (2) to generate a logistic model with likelihood of IE ratios for those patients explicitly not meeting PRE-IDU low-risk criteria.

2. Methods

2.1. Study design and patient enrollment

From June 2007 to March 2011, we prospectively enrolled patients from 2 urban, county EDs, each with an approximate annual census of 60 000 patients. We used the following inclusion criteria: (1) history of injection drug use, (2) age >17 years, (3) fever (temperature ≥ 38.0°C), (4) admission to the hospital, and (5) ED diagnosis of "rule out endocarditis," "shooter with a fever," "fever without source," or "IDU with fever." Patients were excluded from analysis if they left against medical advice prior to diagnostic workup (blood cultures and echocardiograms). Study protocols were approved by the respective institutional review boards. We calculated a target sample size of 588 patients to generate a narrow CI for our sensitivity point estimate, but due to funding constraints and loss of one study site, we were unable to meet our target enrollment and terminated the study at the halfway point of enrollment.

2.2. Data collection, criteria, and outcome

Study personnel reviewed medical records and abstracted data according to the guidelines proposed by Gilbert et al [10]. Multiple quality assurance measures, including standardized data abstraction forms and protocols, double data entry checking, regular meetings of abstractors, and interrater assessments of abstractors, were implemented. With blinding to subjects' criteria data, we determined the outcome classification of subjects. Discrepancies in data after abstraction, which were less than 2% of data elements, were resolved by consensus of the authors.

The following ED clinical, laboratory, and radiography data were collected using template medical records and confirmed through review of computer records: (1) history of IE, (2) HIV status, (3) presence or absence of tachycardia (heart rate >100 beats/min at any time during the first 6 hours of ED stay), (4) cardiac murmur (as assessed by the ED provider), (5) skin infection (abscess or cellulitis) on physical examination, (6) leukocytosis (>11.7 × 1000 cells/mm^3), (7) hyponatremia (<136 miliequivalents/L), (8) thrombocytopenia (<150 × 1000 platelets/mm^3), and (9) presence of infiltrates or cavitations on ED chest x-ray (based on blinded final radiologist reading). These criteria for the logistic model were chosen on the basis of our pilot study and review of past studies [8]. Missing and unrecorded data elements, which were less than 1% of the total, were excluded from analysis.

Outcome data pertaining to the final diagnosis of IE including microbiology, echocardiogram, and discharge diagnoses were abstracted from discharge summaries and final signed reports. Diagnosis of IE was confirmed if a patient received a diagnosis of endocarditis in their discharge summaries and if they met the modified Duke criteria [11]. Discrepancies in outcomes were resolved by consensus of investigators.

2.3. Data analysis and statistical methodology

All data were entered into Microsoft Access (Microsoft Corp, Seattle, WA) and analyzed using Stata 12 (Stata Corporation, College Station, TX) and SAS v. 9.2 (SAS institute Inc, Cary, NC). We evaluated the screening performance (sensitivity, specificity, and odds ratio) of PRE-IDU and individual clinical criteria using standard formulae and Clopper-Pearson binomial method for 95% CIs.

To generate an alternative predictive model using logistic regression, we analyzed the original derivation data from the pilot study to identify independent variables with adequate predictive power [8]. We then derived odds ratios and the logistic coefficients for each of these variables using the logistic regression formula.

Model selection was performed in a stepwise fashion with potential predictor variables added and retained if the associated *P* value was less than .2. We found no significant 2- and 3-way interactions between variables. We generated a receiver operating characteristic (ROC) curve from the selected optimal model using both derivation (Fig. 1A) and validation data (Fig. 1B) by generating sensitivity and specificity values for a prespecified range of probabilities. The area under the curve for the ROC curve was generated using the trapezoidal method, and the SE was generated using the equations set forth by Hanley and McNeil [12].

3. Results

Of the 296 patients initially identified for possible enrollment, 43 subjects were excluded because they did not have any of the inclusion diagnoses on their list of ED diagnoses. Four subjects left the hospital against medical advice prior to receiving their endocarditis workup and were also excluded. Subject characteristics are summarized in Table 1.

Of the 249 subjects included in the analysis, 18 (7.2%) were diagnosed as having endocarditis. Among the 18 subjects with IE, 16 had positive blood cultures, half of which grew methicillin-resistant *Staphylococcus aureus*. Sixteen patients had abnormal echocardiograms consistent with endocarditis. Echocardiograms in 2 subjects were initially reported to be normal, but both subjects had evidence of septic emboli to multiple organs and methicillin-resistant *S aureus* bacteremia.

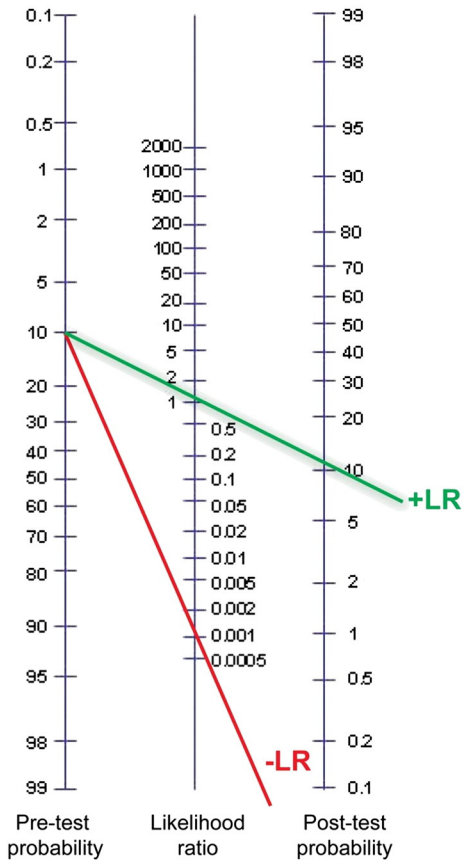

Fig. 1. Receiver operator characteristic curves for the logistic regression model. A, ROC curve for derivation data. B, ROC curve for validation data.