Individualized Prediction of Acute Pancreatitis Recurrence Using a Nomogram

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Objectives: The objective of this study was to develop and validate a model, based on the blood biochemical (BBC) indexes, to predict the recurrence of acute pancreatitis patients.

Methods: We retrospectively enrolled 923 acute pancreatitis patients (586 in the primary cohort and 337 in the validation cohort) from January 2014 to December 2016. Aiming for an extreme imbalance between recurrent acute pancreatitis (RAP) and non-RAP patients (about 1:4), we designed BBC index selection using least absolute shrinkage and selection operator regression, along with an ensemble-learning strategy to obtain a BBC signature. Multivariable logistic regression was used to build the RAP predictive model.

Results: The BBC signature, consisting of 35 selected BBC indexes, was significantly higher in patients with RAP ($P < 0.001$). The area under the curve of the receiver operating characteristic curve of BBC signature model was 0.6534 in the primary cohort and 0.7173 in the validation cohort. The RAP predictive nomogram incorporating the BBC signature, age, hypertension, and diabetes showed better discrimination, with an area under the curve of 0.6538 in the primary cohort and 0.7212 in the validation cohort.

Conclusions: Our study developed a RAP predictive nomogram with good performance, which could be conveniently and efficiently used to optimize individualized prediction of RAP.

Key Words: recurrent acute pancreatitis, blood biochemistry indexes, nomogram, least absolute shrinkage and selection operator

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Acute pancreatitis (AP), an inflammatory disease, is the most common gastrointestinal illness leading to hospitalization.[1,2] The worldwide annual incidence of AP is thought to range from 13 to 45 per 100,000 people, and the incidence is increasing yearly.[3,4] The overall mortality of AP patients is approximately 2%.[4] In terms of etiology, gallstones, alcohol abuse, and hypertriglyceridemia are the most important risk factors for AP.[5–7] Patients with type 2 diabetes may have 1.86 to 2.89 times greater risk of pancreatitis than nondiabetic patients.[8–11] Smoking plays an important role in increasing the risk of non–gallstone-related AP.[12,13] Other possible causes of AP are genetics or medication usage (eg, azathioprine, 6-mercaptopurine, didanosine, and mesalamine)[4,14]; up to 36.5% of cases are idiopathic.[15]

Recurrent acute pancreatitis (RAP), which is defined as recurrence after the first attack of AP, is positively associated with alcoholic AP, necrotizing pancreatitis, hyperlipidemic AP, male sex, smoking.[7,16–19] The incidence of RAP has been noted to have a wide range, from 17% to 35%.[16–18,20–22] Prior studies have shown that RAP is a strong risk factor for development of chronic pancreatitis (CP),[21,23] which increases the risk of pancreatic cancer.[24,25] Importantly, RAP patients had a significantly higher (approximately 3-fold) overall mortality than AP patients without RAP episodes.[20] Thus, accurate prediction and prevention of AP relapses are central to improving patient health after an initial episode of AP. However, to the best of our knowledge, there are no convenient and economic methods available to predict RAP.

There are several published works regarding statistical prediction models that have been used for AP prediction. For example, the harmless AP score model and C-reactive protein model were established to predict and differentiate patient disease severity.[26,27] Recently, a radiomics model,[28] based on contrast-enhanced computed tomography, was used to predict RAP successfully with an area under the curve (AUC) of >0.9. Blood biochemical (BBC) indexes are collected from a patient's blood test, which is a routine examination, implying that an accurate prediction model using the BBC indexes could be more practical in clinical applications. Until now, no statistical model using BBC indexes for RAP prediction has been reported.

In this study, we first investigated the possibility of predicting RAP based on the BBC indexes and then created a nomogram model, based on the BBC signature, to predict the risk of RAP. This model could help clinicians choose appropriate therapeutic approaches, to provide timely intervention for patients with a high risk of RAP.

MATERIALS AND METHODS

Patient Population

Patients with AP in Dazhou Central Hospital from January 2014 to December 2016 were enrolled in this retrospective study. Clinical information on all AP patients, including sex, age, drinking and smoking status, hypertension, diabetes, gallstone history, hyperlipemia, and blood-test results were obtained from electronic medical records. Patients with missing data were excluded. In addition, patients with the following characteristics were excluded: (1) age under 18 years, (2) extra-abdominal tumors, (3) CP, (4) pancreatitis that recurred within 3 months,[29–31] (5) abdominal trauma or surgeries, or (6) organ failure caused by underlying

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diseases (such as bee stings and diabetic ketoacidosis). In total, data from 923 patients were included in the analysis.

This study was approved by the Institutional Research Ethics Board of Dazhou Central Hospital (IRB00000003-19007). Written informed consent requirement was waived.

Reference Standard

The diagnosis of AP was confirmed based on the American College of Gastroenterology guidelines, which requires 2 or 3 of the following features: (1) typical abdominal pain, (2) increased serum amylase and/or lipase >3 times the upper limit of normal, and (3) computed tomography or ultrasound-imaging features of AP.[32] The RAP was defined as AP occurring at least 3 months after the initial episode. The number of prior attacks was determined based on the admitting history and medical records.

BBC Indexes

The BBC index data were obtained within 24 hours after diagnosis. A total of 48 BBC indexes were detected. The detailed names for all indexes are presented in the Supplemental Digital Content (http://links.lww.com/MPA/A887). In particular, another 4 designed indexes, including the platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, calcium-to-phosphorus ratio, and red blood cell distribution width-to-platelet ratio, were calculated as follows: the absolute platelet count divided by the absolute lymphocyte count, the absolute neutrophil count divided by the absolute lymphocyte count, the calcium divided by the absolute lymphocyte count, and the red cell distribution width divided by the absolute lymphocyte count, respectively, based on laboratory BBC results for each patient.

Group Design

Our study divided a total of 923 patients into 2 cohorts: the primary cohort, for training the model and development of the nomogram, and the validation cohort for evaluating the trained model. The primary cohort included 586 patients seen from January 2014 to December 2015. The validation cohort included 337 patients seen from January 2016 to December 2016.

Patients with AP recurrence at least 3 months after the first episode were assigned to the Recurrent AP group (RAP group), whereas those without recurrent AP were assigned to the non-recurrent AP group (non-RAP group).

BBC Indexes Selection With LASSO Along With the Technique of Bagging

The BBC index includes 52 indexes from patient blood tests. An assumption of this study is that (only) some of the 52 indexes are related to RAP, and we need feature selection that identifies those indexes that were good predictors for RAP. The least absolute shrinkage and selection operator (LASSO) method is currently the most simple and popular method for the task of feature selection. Here, we adopted an R package ("glmnet," https://cran.r-project.org/web/packages/glmnet/index.html) to construct the LASSO model.

In the current study, we adopted the technique of bootstrap aggregation or "bagging" (a kind of ensemble learning) to train our LASSO model (Supplemental Fig. 1, http://links.lww.com/MPA/A887). Specifically, for the extremely imbalanced data set of 103 positives versus 483 negatives in the primary cohort (Table 1), bagging made multiple resamples of 103 negatives, without replacement, from the total of 483 negatives. Each resample of 103 negatives together with 103 positives (1:1) was fitted with a LASSO model, and thus, multiple resamples fitted multiple LASSO models. An ensemble score, obtained as the average of the predicted scores of the multiple trained LASSO models, was eventually produced for each sample. Importantly, a parameter called the "number of bagging," that is, the optimal number of resamples, had to be determined. That was addressed via a 10-fold cross-validation (10-fold-CV).

Development and Validation of an Individualized Prediction Model Based on the BBC Signature

Using the LASSO method, together with the bagging technique, we could assign an ensemble score (the "BBC signature") from the BBC data to each sample in the primary cohort via a 10-fold-CV. In greater detail, the BBC signature was computed as a composite index for a representative subset of the total of 52 indexes and was considered to reflect some kind of tendency of occurrence of RAP.

In the development of an individualized prediction model, the BBC signature was directly used for receiver operating characteristic analysis and thus for computing AUC values. The AUC was used for discriminating between positives and negatives with a decision threshold of 0.5. All of the samples with a BBC signature >0.5 were considered positives; all the rest were negatives. Accordingly, the accuracy of the prediction model could be computed.

TABLE 1. Patients' Characteristics in Primary and Validation Cohorts

	Primary Cohort			Validation Cohort		
Characteristic	RAP (n = 103)	Non-RAP (n = 483)	*P*	RAP (n = 70)	Non-RAP (n = 267)	*P*
Age, mean (SD), y	52.62 (13.23)	54.29 (14.62)	0.287	48.71 (13.60)	54.7 (15.07)	0.002*
Sex, female, n (%)	46 (44.7)	244 (50.5)	0.058	29 (41.4)	146 (54.7)	0.048*
Hypertension, n (%)	8 (7.8)	61 (12.6)	0.339	2 (2.9)	52 (19.5)	0.001*
Diabetes, n (%)	12 (11.7)	43 (8.9)	0.620	11 (15.7)	32 (12.0)	0.405
Gallstone, n (%)	13 (12.6)	107 (22.2)	0.082	8 (11.4)	87 (32.6)	<0.001*
Hyperlipemia, n (%)	8 (7.8)	22 (4.6)	0.530	10 (14.3)	8 (3.0)	<0.001*
Smoking, n (%)	25 (24.3)	112 (23.2)	0.789	25 (35.7)	53 (20.0)	0.005*
Alcohol, n (%)	16 (15.5)	93 (19.3)	0.605	5 (7.1)	45 (16.9)	0.042*
BBC signature, n (%)	0.55 (0.79)	0.49 (0.92)	<0.001*	0.56 (0.17)	0.49 (0.11)	<0.001*

P value is derived from the univariable association analyses between each of the clinicopathologic variables and RAP status.

**P* value <0.05.

For an objective validation of the trained model, we used the validation cohort to externally test the model's generalizability and applicability. Specifically, all 52 indexes for each sample in the validation cohort were input into the trained LASSO model, which output a BBC signature of the sample. Subsequently, a receiver operating characteristic analysis was performed using the BBC signature of 337 samples in the validation cohort, and the corresponding AUC value was taken as the evaluation index for the external validation of the trained LASSO model.

Development and Validation of the RAP Predictive Nomogram in the Primary Cohort

For convenient use, a nomogram that gives the clinician a quantitative tool to predict individual probability of RAP was required. To construct a RAP predictive nomogram, we first fitted a multivariable logistic regression model with 4 clinical candidate predictors: BBC signature, age, hypertension, and diabetes. A RAP predictive nomogram was then constructed with the fitted logistic regression model, using the R package of "rms" (https://cran.r-project.org/web/packages/rms/index.html).

For objective evaluation of the established RAP predictive nomogram, 2 calibration curves were plotted. The curves were used to assess the consistencies between the actual RAP rates and the nomogram-predicted probabilities of RAP, both in the primary cohort and in the validation cohort. Perfect consistency will be declared if the calibration curve is close to the straight line $y = x$.

Clinical Use

For clinical utility of the RAP predictive model, a decision-curve analysis was performed, to provide a tool to evaluate the value of using a risk prediction instrument to decide on treatment or intervention (versus no treatment or intervention). Decision curves display estimates of the net benefit over a range of probability thresholds used to categorize observations as "high risk." In this study, we performed decision-curve analyses using 2 groups of predictors: one with only the BBC signature and the other with the 4 predictors (BBC signature, age, hypertension, and diabetes) used in the development of the RAP predictive nomogram. Two decision curves were plotted with the R package of "rmda" (https://lib.ugent.be/CRAN/web/packages/rmda/index.html).

RESULTS

Patient Characteristics

A total of 923 patients with AP were included in this study (Fig. 1). In our data, the mean follow-up period was 40.14 months for all subjects, and the median recurrence time of AP was 11.6 months for patients with RAP in Dazhou Central Hospital in the past 10 years. Among those in the primary cohort, 103 of 586 patients were classified as RAP (57 males and 46 females; mean age, 52.62 years [standard deviaion {SD}, 13.23 years]; range, 23–86 years), and the remaining 483 patients were non-RAP (239 males and 244 females; mean age, 54.29 years [SD, 14.26 years]; range, 19–92 years). In the validation cohort, 70 of 337 patients were classified as RAP (41 males and 29 females; mean age, 48.71 years (SD, 13.60 years); range, 20–86 years), and the remaining 267 patients were non-RAP (121 males and 146 females; mean age, 54.70 years [SD, 15.07 years]; range, 19–88 years) (Table 1). There were no differences between the 2 cohorts in terms of age or sex distribution, or rates of hypertension, diabetes, gallstones, hyperlipemia, smoking, or alcohol use (Supplemental Table 1, http://links.lww.com/MPA/A887).

Development and Validation of the BBC Signature Model

We first investigated the possibility of RAP prediction based on the BBC indexes. To this end, we used the LASSO method, along with the technology of bagging, on the primary cohort to construct the prediction model. As described in the Materials and Methods, a parameter of the number of bagging must be

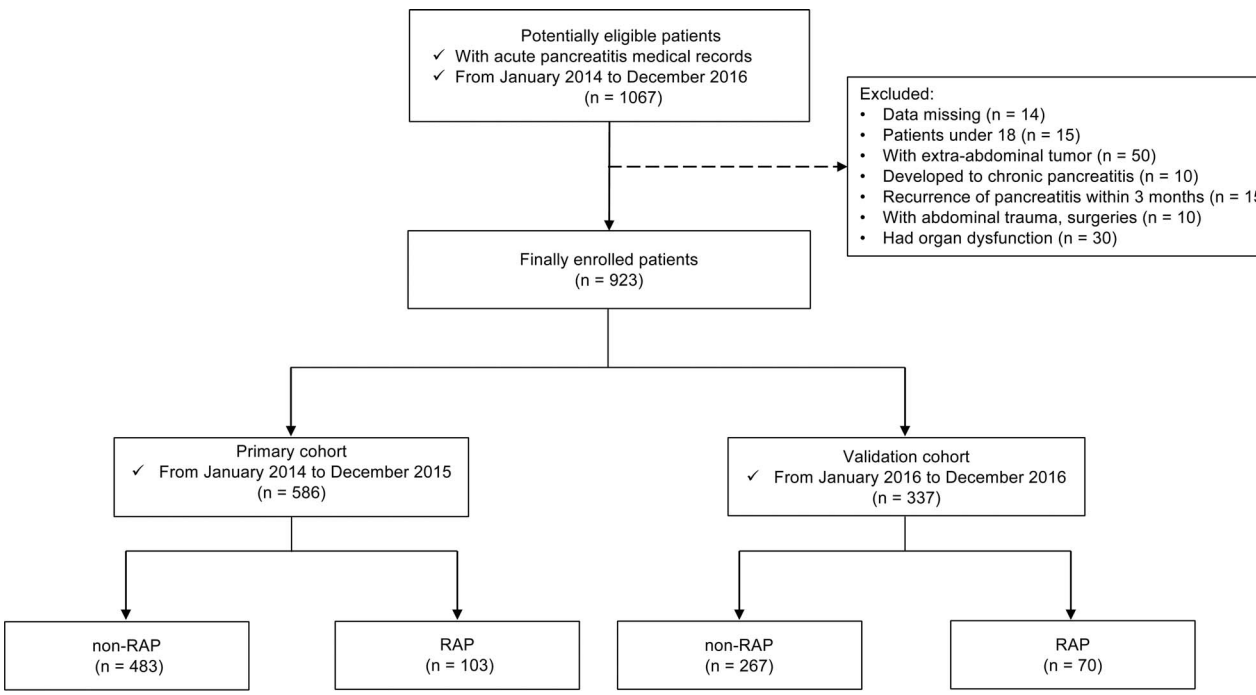

FIGURE 1. Flowchart of inclusion and exclusion criteria for this study.

determined. We used a 10-fold-CV to evaluate prediction performance at each value of the number of bagging from 1 to 20, with a step size of 1. According to these efforts, a maximal AUC value of 0.6534 was achieved at the optimal bagging number of 18 (Supplemental Fig. 2, http://links.lww.com/MPA/A887).

Accordingly, a total of 18 LASSO models were trained on each resample. Each trained LASSO model had selected some BBC indexes, and the average of all 18 models eventually selected a total of 35 features of the 52 indexes to be potential predictors, on the basis of the 586 patients in the primary cohort (Supplemental Fig. 3, http://links.lww.com/MPA/A887). The features with nonzero coefficients in each LASSO model are represented in the BBC signature calculation formula (Supplemental Digital Content, http://links.lww.com/MPA/A887). There was a significant difference in the BBC signatures between RAP and non-RAP patients in both the primary and validation cohorts ($P < 0.001$, Table 1). As a result, the BBC signature model yielded an AUC value of 0.6534 in the primary cohort, with a sensitivity of 67.96%, specificity of 62.32%, positive predictive value (PPV) of 27.78%, and negative predictive value (NPV) of 90.12% (Fig. 2, Table 2). More importantly, the BBC signature model achieved a higher AUC value of 0.7173 in the validation cohort, with a sensitivity of 75.71%, specificity of 59.92%, PPV of 33.13%, and NPV of 90.39% (Fig. 2, Table 2), indicating the good generalizability of the trained model.

A RAP Nomogram and Evaluations

We next wanted to build a RAP nomogram for convenient use. To this end, a logistic regression analysis was used based on the BBC signature, with the addition of age, hypertension, and diabetes status as independent predictors (Supplemental Table 2, http://links.lww.com/MPA/A887). A novel predictive model that incorporated these 4 independent predictors was developed and displayed as a RAP predictive nomogram (Fig. 3A). It is apparent that the BBC signature contributes the most to the construction of the RAP nomogram, and the other 3 predictors make some contribution as well. Similarly, when we included the 4 predictors, the maximal AUC value was again achieved at a bagging number of 18 (Supplemental Fig. 4, http://links.lww.com/MPA/A887). This

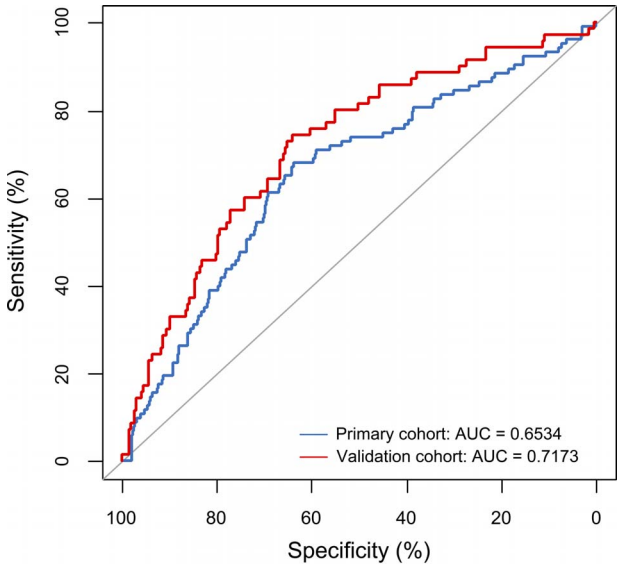

FIGURE 2. Receiver operating characteristic curve of the BBC signature model in the primary and validation cohorts. **Editor's note:** A color image accompanies the online version of this article.

TABLE 2. Prediction Performance of the Trained Model in Primary and Validation Cohorts

	BBC Signature Model		RAP Predictive Nomogram	
Outcome	Primary Cohort	Validation Cohort	Primary Cohort	Validation Cohort
AUC	0.6534	0.7173	0.6538	0.7212
ACC	0.6331	0.6320	0.6280	0.6261
Sensitivity	0.6796	0.7571	0.6796	0.7143
Specificity	0.6232	0.5993	0.6170	0.6030
PPV	0.2778	0.3313	0.2745	0.3205
NPV	0.9012	0.9040	0.9003	0.8895

ACC indicates accuracy.

RAP predictive nomogram reached an incremental AUC of 0.6538 (sensitivity, 0.6796; specificity, 0.6170; PPV, 27.45%; NPV, 90.03%) and 0.7212 (sensitivity, 0.7143; specificity, 0.6030; PPV, 32.05%; NPV, 88.95%) in predicting RAP positive patients in the primary and validation cohorts, respectively (Fig. 3B, Table 2). The RAP predictive nomogram did not show significantly improved prediction performance compared with the BBC signature model. However, the higher AUC values observed for the BBC signature model including age, hypertension, and diabetes in the primary and validation cohorts imply that age, hypertension, and diabetes are potential risk factors for RAP.

The calibration curves of the nomograms in the primary cohort (Fig. 3C) and validation cohort (Fig. 3D) showed good agreements between the predicted values and the true values. The decision-curve analysis for the BBC signature with and without clinical data (age, hypertension, and diabetes) is presented in Figure 4, which shows that, if the threshold probability of a patient is larger than 0.22, the RAP predictive nomogram has more benefit than either the none scheme or the all scheme.

DISCUSSION

At present, quantitative methods based on clinical characteristics for predicting the recurrence of AP are lacking. In our study, we established the RAP predictive nomogram model mainly based on 35 blood test signatures, together with age, hypertension, and diabetes status, for predicting the recurrence of AP. The advantage of this model is that it can effectively predict recurrence risk of AP at the baseline of first episodes, using only patient's routine blood tests together with a few clinical characteristics, which is very economical and easy to use. Moreover, it does not need additional tests of patients. It does help clinicians choose more-targeted strategies for patients suspected of being at high risk for RAP to inhibit AP recurrence. When the sensitivity and specificity of the model are constant, the PPV of the model is positively correlated with the RAP prevalence rate of the population. In our data, according to the RAP, prevalence rate was only 18.7% (173/923); the PPV of this model reached 27.45% in primary and 32.05% in validation cohorts, indicating that this model was reliable.

After their initial episode of AP is cured, about 27% of patients will experience another attack,[33] which significantly reduces the quality of life of patients. Up to 36% of RAP patients will progress to CP, and once CP develops, there is a high probability of progression to pancreatic cancer.[21] There were only 10 cases of CP in our data, and 2 cases were chronic recurrent pancreatitis, accounting for 20%. The recurrence rate for CP in our set was roughly consistent with the report of Akshintala et al[34] that

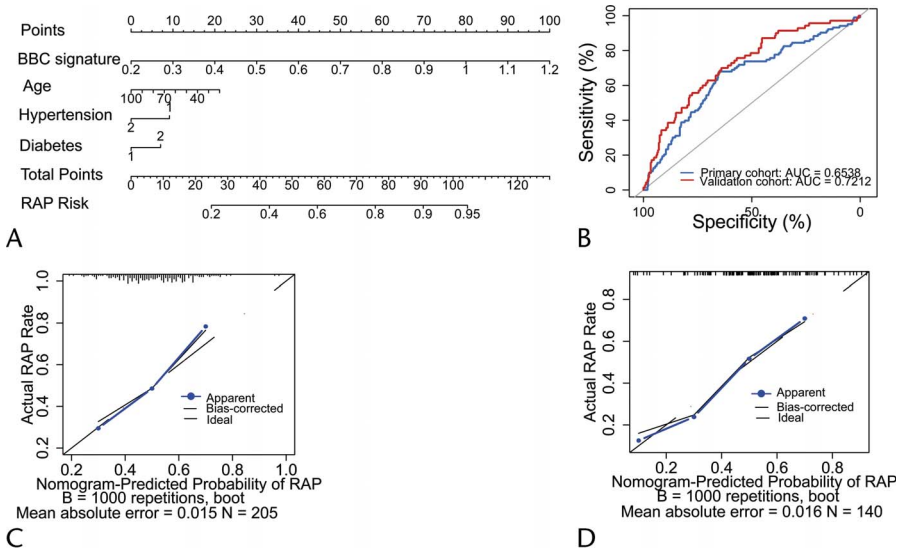

FIGURE 3. The RAP predictive nomogram, ROC curves, and calibration curves. A, Nomogram for RAP predictive model. B, Receiver operating characteristic curves of RAP predictive model in the primary and validation cohorts. C, Calibration curve of the RAP predictive nomogram in the primary cohort. D, Calibration curve of the RAP predictive nomogram in the validation cohort. ROC, receiver operating characteristic. **Editor's note:** A color image accompanies the online version of this article.

the proportion of AP-on-CP discharges doubled during the study period (8.8% to 17.6%; $P < 0.0001$). Early prediction of RAP is helpful for clinical-treatment selection and prompt assessment, but convenient, economic, and quantitative methods for predicting RAP are lacking. Recently, Chen et al[28] developed a radiomics model for predicting the recurrence of AP. The AUC of the radiomics model was as high as 0.929 in their validation cohort. Compared with the radiomics model, the RAP predictive nomogram in our study is easier to use. The BBC indexes and clinical risk factors are easily and economically acquired in clinical cases. In addition, the AUCs of our predictive model in 2 cohorts (grouped by admission time) were adoptable. Of interest, the AUC in our validation cohort was higher than that in the primary cohort, which suggests that our model has good generalizability.

The use of an appropriate method in index selection may explain the robust performance of our BBC signature model. The samples in both the primary and validation cohorts were extremely imbalanced, with ratios between positive and negative samples of nearly 1:4 (1:4.689 in the primary cohort and 1:3.814 in the validation cohort). Based on the knowledge of machine learning with extremely imbalanced data, the classifier tends to predict the majority of samples to be negative if we put all sample data into the training model. An advanced and rational solution is ensemble learning, which aims to construct multiple models to give a predicted probability for each sample.[35] Furthermore, the biggest advantage of LASSO is its ability to select the most-predictive features (indexes) from the primary cohort data by forcing the coefficients of irrelevant features to be zeros. Hence, a technique of bagging was applied to train our LASSO model to address the extremely imbalanced samples in both of our cohorts. These appropriate methods ensure the reliability of our predictive model, and the corresponding strong predictive performance demonstrates the possibility of RAP prediction using the BBC indexes.

Moreover, the combined uses of age, hypertension, and diabetes data further improved the performance of the model. Among the 8 clinical indexes in our study, alcoholic etiology (hazard ratio, 1.58; 95% confidence interval, 1.25–2.23; $P < 0.01$) and smoking (hazard ratio, 1.42; 95% confidence interval, 1.03–1.95; $P = 0.03$) are reportedly the most strongly associated risk factors for RAP.[18] In the present study, the logistic regression analysis revealed age, hypertension, and diabetes as prediction factors for RAP. Our RAP predictive nomogram revealed that age contributes 0 to 20 points and that younger patients have higher risk of developing RAP. Diabetes contributes ranged from 0 to 10 points, and patients with diabetes are more likely to have RAP. However, hypertension is not a risk factor but rather a protective factor for RAP. Patients with hypertension are less likely to have RAP. The reason why hypertension is a protective factor in our cohort is unclear, and to our knowledge, it has not been reported before. Altogether, our results show that incorporating age, hypertension, diabetes, and BBC

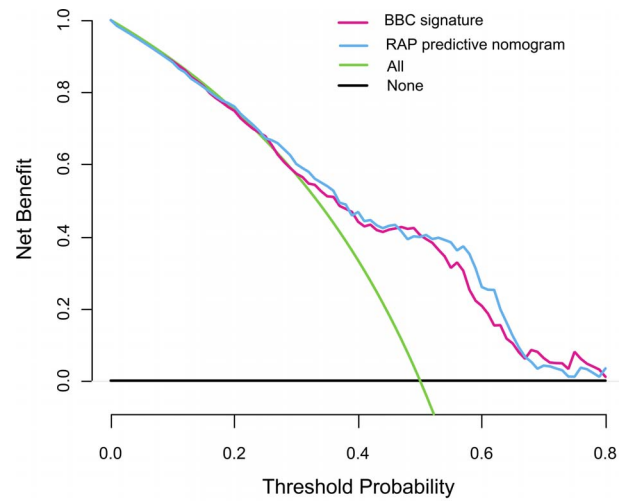

FIGURE 4. Decision-curve analysis for the RAP predictive nomogram. The red line presents the BBC signature, and the blue line presents the RAP predictive nomogram. The *y* axis shows the net benefit. The net benefit was calculated by subtracting the proportion of all patients who were false positives from the proportion who were true positives and weighting by the relative harm of forgoing treatment compared with the negative consequences of an unnecessary treatment. **Editor's note:** A color image accompanies the online version of this article.

signature increased the AUC value compared with the BBC signature model alone in RAP prediction.

Although substantial progress was achieved in our study, several limitations still need addressing in a future study. First, the number of patients in the RAP group was relatively small. Second, although the primary and validation cohorts were assigned by time of treatment, this was a single-center retrospective study. Therefore, increasing the sample size with patients from multiple centers would help strengthen the robustness and reproducibility of our RAP model.

CONCLUSIONS

Our study developed an easy-to-use predictive nomogram incorporating a newly constructed BBC signature, age, hypertension, and diabetes to predict RAP in patients with AP. This novel model could guide doctors in personalized treatment of patients, by predicting possible recurrence based on blood test data and basic information at a lower cost.

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