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LETTER TO THE EDITOR Open Access

Machine learning-aided risk stratification in Philadelphia chromosome-positive acute lymphoblastic leukemia

Satoshi Nishiwaki[1*], Isamu Sugiura[2], Daisuke Koyama[2], Yukiyasu Ozawa[3], Masahide Osaki[3], Yuichi Ishikawa[4] and Hitoshi Kiyoi[4]

Abstract

We used the eXtreme Gradient Boosting algorithm, an optimized gradient boosting machine learning library, and established a model to predict events in Philadelphia chromosome-positive acute lymphoblastic leukemia using a machine learning-aided method. A model was constructed using a training set (80%) and prediction was tested using a test set (20%). According to the feature importance score, *BCR-ABL* lineage, polymerase chain reaction value, age, and white blood cell count were identified as important features. These features were also confirmed by the permutation feature importance for the prediction using the test set. Both event-free survival and overall survival were clearly stratified according to risk groups categorized using these features: 80 and 100% in low risk (two or less factors), 42 and 47% in intermediate risk (three factors), and 0 and 10% in high risk (four factors) at 4 years. Machine learning-aided analysis was able to identify clinically useful prognostic factors using data from a relatively small number of patients.

Keywords: eXtreme gradient boosting algorithm, Machine learning, Philadelphia chromosome-positive acute lymphoblastic leukemia, Prognostic factor, Survival stratification

To the Editor

Several prognostic factors for Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph + ALL) have been identified, such as minimal residual disease (MRD) [1, 2], chromosomal abnormalities [3], and genetic lesions [4]. However, further exploration is needed to identify the high-risk group in Ph + ALL The eXtreme Gradient Boosting (XGBoost) algorithm draws attention as an interpretable machine learning model [5], and is considered to be useful for identifying new prognostic factors for Ph + ALL.

XGBoost model

Using a dataset of 59 adult Ph + ALL patients [6], we attempted to identify further risk factors using the XGBoost model [7] (TableS1 and S2). When the trained model was applied to the test set, the mean accuracy was 0.67, and the macro-average precision, recall, and f1-scores were 0.71, 0.78, and 0.66, respectively. The cross-validated accuracy was 0.66 (standard deviation 0.072). The area under the receiver operating characteristic curve (AUC) of the test set was 0.76.

In multivariate analysis using the conventional Cox model, *BCR-ABL* lineage and age were identified as significant risk factors [6]. According to the feature importance score, two more factors, polymerase chain reaction (PCR) value and white blood cell (WBC) count, were also identified as important features, and the XGBoost decision tree used these four factors as nodes, which

* Correspondence: n-3104@tf7.so-net.ne.jp
[1]Department of Advanced Medicine, Nagoya University Hospital, 65 Tsurumai-cho Showa-ku, Nagoya 466-8560, Japan
Full list of author information is available at the end of the article

suggested these four features were important for the model construction (Fig. 1a and b). There were no strong correlations between the features: the absolute value of the correlation coefficients was between 0.016 (*BCR-ABL* value and PCR value) and 0.27 (PCR value and WBC count). The mean variance inflation factor for checking multicollinearity between WBC count and another feature was 1.06 (range 1.01–1.09). The permutation feature importance also showed that PCR value, age, and *BCR-ABL* lineage were important features, which was indicative of how much the prediction using the test set depended on these features (Fig. 1c). The AUC, sensitivity, and specificity were 0.77 [Standard error (SE) 0.06], 0.59, and 0.89 when using parameters identified in the XGBoost model, and 0.72 (SE 0.06), 0.50, and 0.81 when using those identified in the conventional COX model. In the XGBoost model for predicting an event within 2 years from diagnosis, *BCR-ABL* lineage, PCR value, age, and WBC count were also identified as important features according to the feature importance score (Fig.S1A). The permutation feature importance also identified these four features as important (Fig.S1B).

Survival stratification

Based on the index of dichotomy in the XGBoost decision tree, we considered the following four features as risk factors: uni-lineage Ph leukemia (uni-Ph), a *BCR-ABL* PCR value≥14500copies/μgRNA, age ≥ 65 years, and WBC count ≥5300/μl. The cohort was divided into three risk groups according to the number of risk factors: low-risk group (Low; two or less factors), intermediate-risk group (Int; three factors), and high-risk group (High; four factors) (TableS3). The event-free survival (EFS) and overall survival (OS) were compared among the three risk groups using conventional statistical techniques (TableS4). The EFS and OS were 80 and 100% in Low, 42 and 47% in Int, and 0 and 10% in High, respectively at 4 years (Fig. 2). The same trend was also confirmed in the stratification using only the test set: EFS at 4 years was 100% in Low, 80% (20–97%) in Int, and 0% in High ($P = 0.046$).

Discussion

The advantage of extracting risk factors using machine learning is that it can reduce the influence of artificial variable selection that can occur in conventional statistical analyses. In addition, new factors that go unnoticed by humans may be extracted. In this study, the PCR value of *BCR-ABL* was identified as an important feature. The PCR value of *BCR-ABL* is considered to be important for following MRD in Ph + ALL [2, 8–11], so it is not common to consider PCR value at diagnosis as a risk factor in conventional analyses. It is interesting that such a new factor was identified as being useful for prognostic stratification.

In this study, the XGBoost algorithm could extracted clinically valid features using a small dataset comprising 59 cases. Since the small number of cases was one of the major limitations of this study, additional confirmation

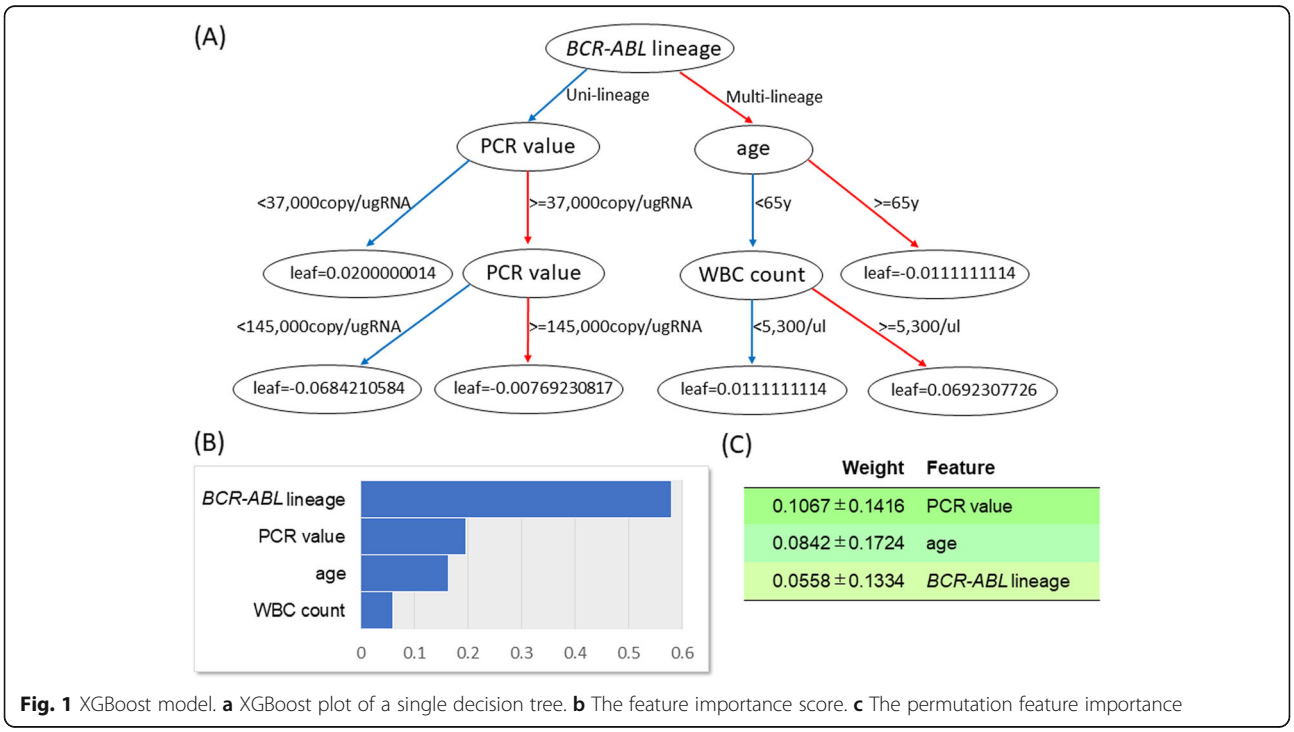

Fig. 1 XGBoost model. **a** XGBoost plot of a single decision tree. **b** The feature importance score. **c** The permutation feature importance

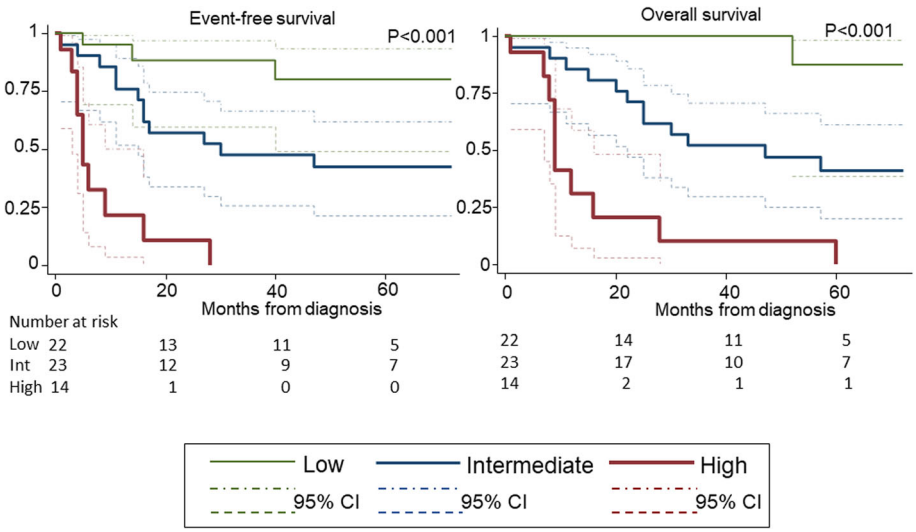

Fig. 2 Survival stratification. Survival was stratified by risk groups using four important features (*BCR-ABL* lineage, PCR value, age and WBC count) identified by the XGBoost model. Low, two or less factors; Int, three factors; High, four factors. **a** Event-free survival (EFS). **b** Overall survival (OS). The EFS and OS were 88% (95%CI 60–97%) and 100% in Low, 57% (34–75%) and 71% (47–86%) in Int, and 11% (0.6–38%) and 21% (3–49%) in High at 2 years, and 80% (49–93%) and 100% in Low, 42% (21–62%) and 47% (25–66%) in Int, and 0 and 10% (0.6–37%) in High, respectively at 4 years

is required to validate the methodology. Although the difference in predictive indices was small between conventional and machine learning-aided methods, it was suggested that the new parameters could contribute to improving each index.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40364-021-00268-x.

Additional file 1: Fig.S1. Important feature for event within 2 years. (A) The feature importance score. (B) The permutation feature importance.

Abbreviations

AUC: area under the receiver operating characteristic curve; EFS: event-free survival; High: high-risk group; Int: intermediate-risk group; Low: low-risk group; MRD: minimal residual disease; OS: overall survival; Ph + ALL: Philadelphia chromosome-positive acute lymphoblastic leukemia; PCR: polymerase chain reaction; SE: Standard error; uni-Ph: uni-lineage Ph leukemia; WBC: white blood cell; XGBoost: eXtreme Gradient Boosting

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Not applicable.

Authors' contributions

S.N., I.S. and H.K. designed the research and interpreted the data; D.K., Y.O., M.O., and Y.I. collected specimens and provide the data of patients; S.N. performed statistical analyses, and wrote the manuscript. All authors reviewed and approved the final draft.

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Availability of data and materials

All data generated or analysed during this study are included in this published article.

Ethics approval and consent to participate

Each hospital's institutional review board approved the study. Written informed consent was obtained upon treatment and sample collection.

Consent for publication

Not applicable.

Competing interests

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Author details

[1]Department of Advanced Medicine, Nagoya University Hospital, 65 Tsurumai-cho Showa-ku, Nagoya 466-8560, Japan. [2]Division of Hematology and Oncology, Toyohashi Municipal Hospital, Toyohashi, Japan. [3]Department of Hematology, Japanese Red Cross Nagoya Daiichi Hospital, Nagoya, Japan. [4]Department of Hematology and Oncology, Nagoya University Graduate School of Medicine, Nagoya, Japan.

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