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# Novel machine-learning model for predicting lymph node metastasis in resectable pancreatic ductal adenocarcinoma

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## Abstract

**Aim:** Lymph node metastasis is an adverse prognostic factor in pancreatic ductal adenocarcinoma. However, it remains a challenge to predict lymph node metastasis using preoperative imaging alone. We used machine learning (combining preoperative imaging findings, tumor markers, and clinical information) to create a novel prediction model for lymph node metastasis in resectable pancreatic ductal adenocarcinoma.

**Methods:** The data of patients with resectable pancreatic ductal adenocarcinoma who underwent surgery between September 1991 and October 2022 were retrospectively examined. Machine-learning software (Statistical Package for the Social Sciences Modeler) was used to create a prediction model, and parameter tuning was performed to improve the model's accuracy. We also analyzed the contribution of each feature to prediction using individual conditional expectation and partial dependence plots.

**Results:** Of the 331 cases included in the study, 241 comprised the training cohort and 90 comprised the test cohort. After parameter tuning, the areas under the receiver operating characteristic curves for the training and test cohorts were 0.780 and 0.795, respectively. Individual conditional expectation and partial dependence plots showed that larger tumor size and carbohydrate antigen 19–9 and Duke pancreatic monoclonal antigen type 2 levels were associated with positive lymph node metastasis prediction in this model; neoadjuvant treatment was associated with negative lymph node metastasis prediction.

**Conclusion:** Machine learning may contribute to the creation of an effective predictive model of lymph node metastasis in pancreatic ductal adenocarcinoma. Prediction models using machine learning may contribute to the development of new treatment strategies in resectable pancreatic ductal adenocarcinoma.

KEYWORDS
adenocarcinoma, early diagnosis, lymphatic metastasis, machine learning, pancreatic neoplasms

## 1 | INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is a gastrointestinal cancer associated with poor prognosis with increasing prevalence worldwide. Approximately 500 000 patients were diagnosed with PDAC in 2018.[1] The 5-y overall survival (OS) rate of PDAC is 11%; however, it may be completely cured if complete surgical resection is achieved.[2] According to the National Comprehensive Cancer Network (NCCN) guidelines, PDAC is classified by resectability before determining the treatment strategies.[3] Patients with resectable PDAC who underwent standard surgical treatment are expected to have a better prognosis than those with borderline resectable and unresectable PDAC. Several studies have revealed that the 5-y OS for patients without lymph node metastasis (LNM) is 40%, whereas the OS for those with LNM is <10%.[4,5] Therefore, for a more accurate prognosis of resectable PDAC, LNM must be appropriately diagnosed before the operation. However, meta-analyses of the diagnostic accuracy of conventional radiological methods for LNM in resectable PDAC revealed poor sensitivity and specificity.[6] With the current technology, it remains a challenge to predict LNM using preoperative imaging alone. Therefore, improved prediction methods with higher accuracy are required to preoperatively diagnose LNM.

Recently, artificial intelligence (AI)-based prediction models have garnered attention owing to their potential roles in various fields of medicine.[7] In particular, it has demonstrated its utility in predicting postoperative recurrence after adjuvant chemotherapy and pathological response to neoadjuvant chemotherapy (NAC) based on computed tomography (CT) imaging in PDAC.[8,9] Machine learning (ML) is a type of AI technology powered by large-scale data (Big Data). It is a data analysis technique in which a computer inputs large amounts of historical data (features), learns the hidden patterns, and develops rules for identifying unknown data. Several ML models exist, including decision tree models, random forests, and support vector machines.[10] Ensemble learning is a learning algorithm that trains multiple ML models with insufficient accuracy (weak learners) and combines them to create a learner with superior prediction accuracy (strong learner). Boosting, one of the major ensemble algorithms, is a method of improving the overall prediction results by repeating the iterative process on weak learners; it is generally characterized by a reduced difference between the actual and predicted values in the model. Extreme Gradient Boosting (XGB) is a novel boosting method, which was reported by Chen and Guestrin[11]; it is an algorithm that builds decision trees one by one, weights wrong data in the majority vote of the previous decision trees, and proceeds with learning to check the mistakes in the subsequent decision tree. In this algorithm, models are trained sequentially through a boosting process. Each new model is trained to correct errors in the previous model. Gradient boosting refers to a method of training new models to improve the difference between the predictions and the actual values of the previous model. To improve performance, it uses the number of boosts, learning rate, subsampling, and maximum read depth to control overlearning, which involves overfitting the training data. XGB is widely utilized in Big Data analysis, and its usefulness has been reported in clinical research.[12] Kaissis et al[13] reported the usefulness of ML based on MRI information using XGB to predict subtypes of PDAC that were significantly associated with disease-free survival, OS, and response to chemotherapy.

Previous studies have reported that several factors, such as tumor size and tumor markers, are associated with LNM in PDAC.[14] Therefore, ML, which uses these factors as learning features, may enable a more accurate preoperative diagnosis of LNM. In this study we aimed to develop a novel predictive model for LNM in resectable PDAC using XGB by combining preoperative imaging findings, tumor markers, and clinical information.

## 2 | METHODS

### 2.1 | Patient selection

This was a retrospective, two-center, observational study. The clinical records of patients with resectable PDAC who underwent surgery at the Yokohama City University Hospital or Yokohama City University Medical Center were retrospectively examined. The resectability of each case was retrospectively classified according to the NCCN Clinical Practice Guidelines in Oncology, version 2.2021.

The eligibility criteria were: (1) patients aged ≥18 y, (2) patients with preoperatively diagnosed PDAC, (3) patients with resectable PDAC according to the NCCN classification, and (4) patients who underwent radical resection with lymph node dissection.[3] Patients with unmeasured tumor markers were excluded from the study.

### 2.2 | Machine learning

We used the ML software Statistical Package for the Social Sciences (SPSS; SPSS, Chicago, IL, USA), which provides a variety of modeling methods based on ML, AI, and conventional statistics, including XGB. We used an XGB tree to create a model for predicting LNM in PDAC; the patients' preoperative clinical data were used as the learning features. The study samples were randomly divided into training and test sets at a ratio of 3:1.[15,16] The number of learning iterations and boost rounds was set to 1000. In addition, Bayesian optimization was performed using the open-source programming language Python 3.11 and Optuna to tune the hyperparameters that determined the accuracy of the model and to maximize the area under the curve (AUC) as a performance metric.[17] Hyperparameter tuning prevents overfitting and improves the predictive accuracy for unknown test data. Bayesian optimization is an algorithmic hyperparameter search method that is reportedly superior to other search methods, such as grid and random searches.[18,19] Bayesian optimization was based on a 10-fold cross-validation method, and the derived hyperparameter values were used to calculate the accuracy of the prediction model. The software used anonymized patient information. Figure 1 shows a schematic diagram of the study flow.

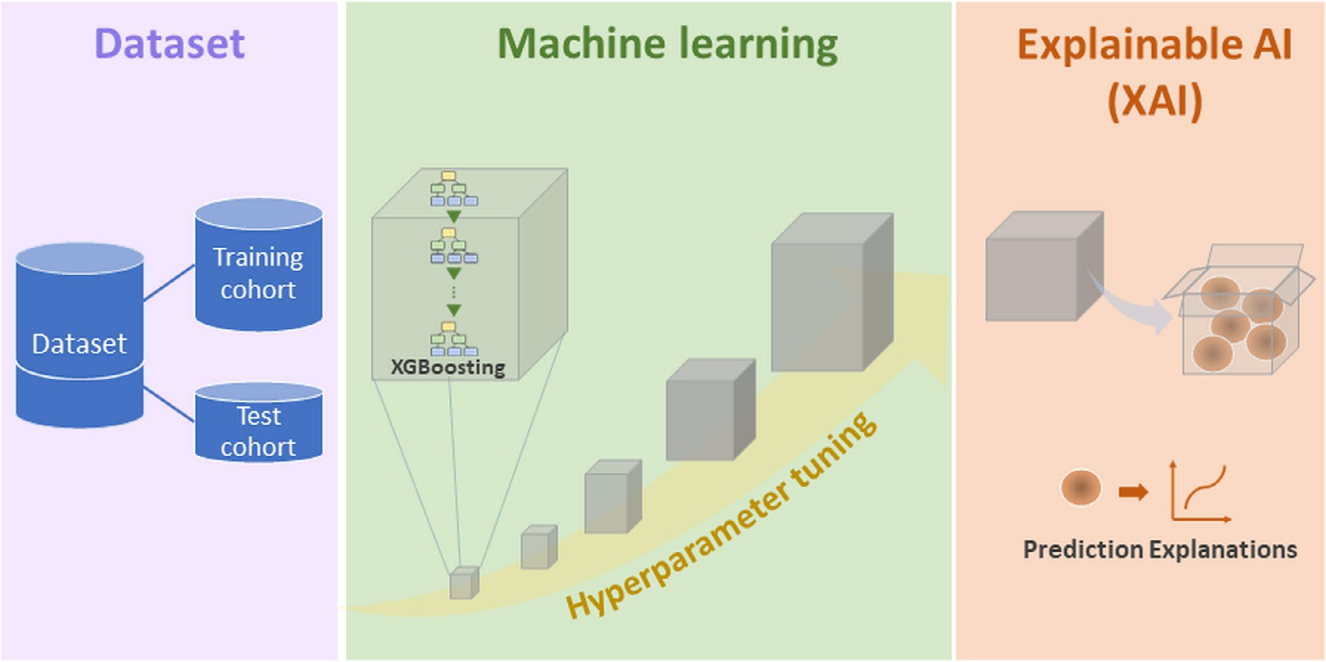


FIGURE 1 Flowchart of machine learning used in this study. The training and test cohorts were used to create a prediction model with the XGB algorithm. After maximizing the prediction performance by hyperparameter tuning, the prediction model was interpreted using the ICE plot and PDP. ICE, individual conditional expectation; PDP, partial dependence plot; XGB, Extreme Gradient Boosting.

### 2.3 | Learning features and interpretation of a novel prediction model

To develop a model for predicting the presence of LNM in resectable PDAC, only clinicopathological data collected from preoperative examinations were used as learning features. Since tumor size, tumor markers, tumor localization, and NAC have been reported to be related to postoperative pathological LNM-positive, we decided to create a prediction model using these factors.[20–25] Learning features included tumor location (pancreatic head, body, or tail), maximum tumor size (mm), carcinoembryonic antigen (CEA; ng/mL) level, carbohydrate antigen 19–9 (CA19-9; U/mL) level, Duke pancreatic monoclonal antigen type 2 (DUPAN-2; U/mL) level, and neoadjuvant treatments such as NAC or neoadjuvant chemoradiotherapy (NACRT). The maximum tumor size was measured using preoperative CT. Tumor markers such as CEA, CA19-9, and DUPAN-2 were data at the initial examination.

An individual conditional expectation (ICE) plot and a partial dependence plot (PDP) were used to analyze the contribution of each feature to the prediction. The ICE plot showed the predicted change for each data instance of the learning feature, and the PDP showed the mean of the variables.

### 2.4 | Statistical analyses

Data are presented as the median and interquartile range (IQR). The Mann–Whitney *U* test was performed to test the differences between continuous variables. Pearson's chi-square test was used to test for differences between categorical variables. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan). The receiver operating characteristic (ROC) curve and AUC were measured to determine the discriminative power of the predictive model.

## 3 | RESULTS

A total of 347 patients with resectable PDAC who underwent radical resection between September 1991 and October 2022 were included in this study. After excluding cases with unmeasured tumor markers, 331 cases were included in the analysis; 241 and 90 comprised the training and test cohorts, respectively (Figure 2). Table 1 summarizes the patients' characteristics across all cohorts. A total of 149 cases (45%) were pathologically LNM-positive; 102 (42%) of these were in the training cohort, and 47 were (52%) in the test cohort, with no significant difference between the two cohorts. Moreover, the median number of harvested lymph nodes was 22 in the training cohort and 20 in the test cohort, and the median number of metastatic lymph nodes was one in both cohorts, with no significant differences between the two cohorts. Similarly, no significant differences were observed between the two cohorts for any of the learning features.

An initial prediction model with default settings was created using XGB, and the AUCs for the training and test cohorts were 1.000 and 0.680, respectively. Hyperparameter tuning through Bayesian optimization was performed using Optuna. Each

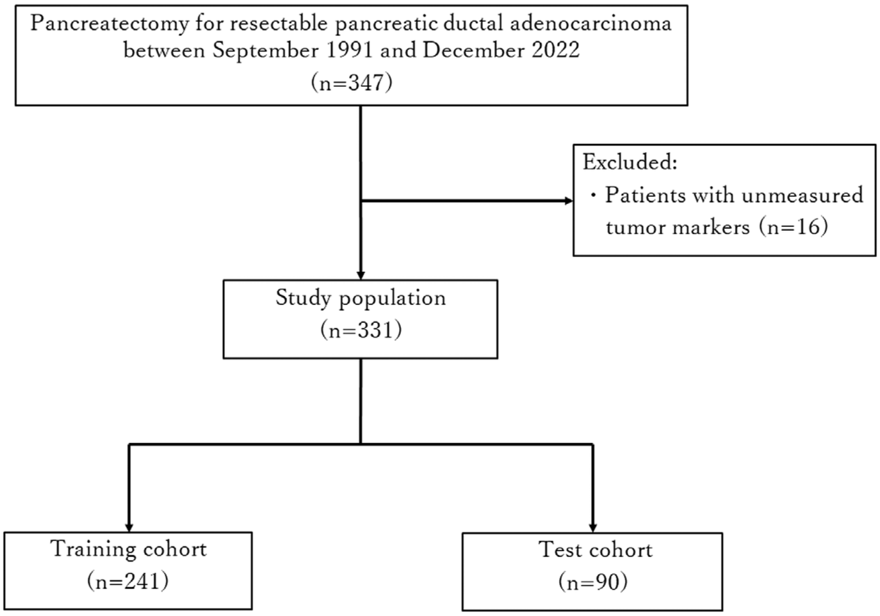


**FIGURE 2** Patient selection process.

**TABLE 1** Patient and tumor characteristics.

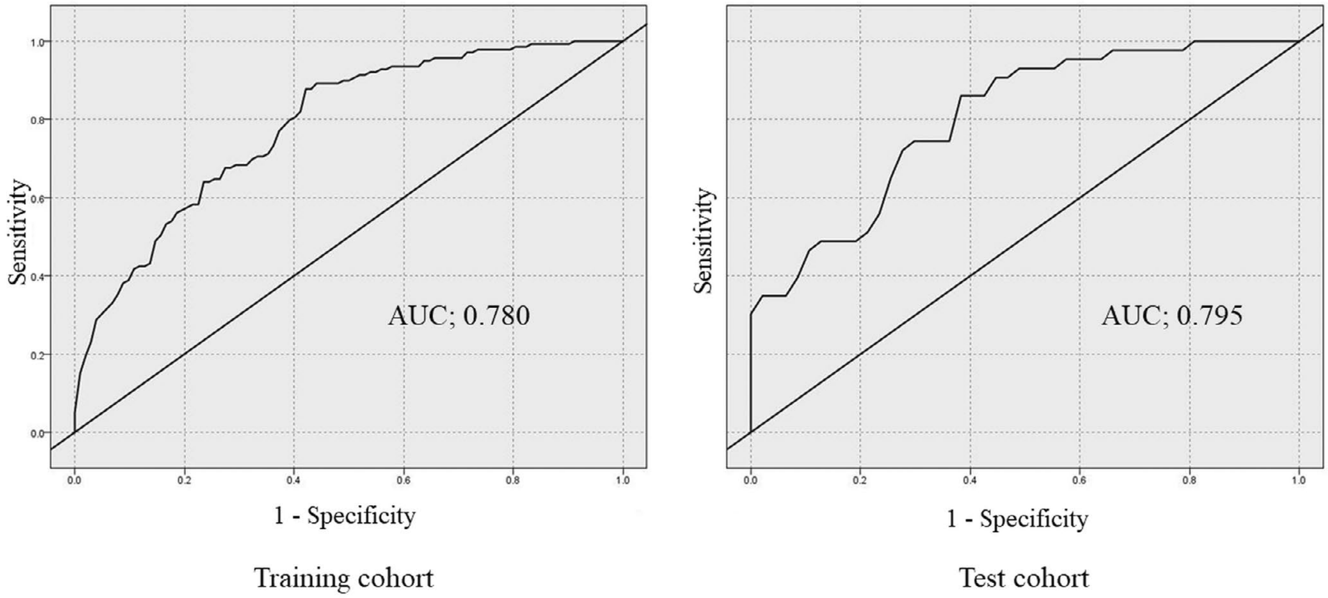
| Variable | Training cohort<br>*n* = 241 | Test cohort<br>*n* = 90 | *p* Value |
|---|---|---|---|
| Age (y) | 71 [65–76] | 72 [65–76] | 0.85 |
| Sex | | | |
| Male | 136 (56.4) | 49 (54.4) | 0.75 |
| Female | 105 (43.6) | 41 (45.6) | |
| CEA (ng/mL) | 3.1 [2.1–4.6] | 2.8 [1.7–4.4] | 0.10 |
| CA19-9 (U/mL) | 57 [21–165] | 78 [20.5–255.5] | 0.38 |
| DUPAN-2 (U/mL) | 120 [38.3–500] | 125 [52.3–326.3] | 0.31 |
| Tumor size(cm) | 2.2 [1.7–3] | 2.5 [1.7–3] | 0.61 |
| Tumor location | | | |
| Pancreatic head | 138 (57.3) | 51 (56.7) | 0.87 |
| Pancreatic body | 62 (25.7) | 27 (30.0) | |
| Pancreatic tail | 41 (17.0) | 12 (13.3) | |
| Neoadjuvant treatment | 44 (18.3) | 21 (23.3) | 0.30 |
| Operative procedure PD/DP/TP | 141/92/8 | 53/37/0 | 0.78 |
| Pathological LNM −/+ | 102/139 | 47/43 | 0.11 |
| Number of dissected lymph nodes | 22 [14–29] | 20 [12–29] | 0.55 |
| Number of metastasis lymph nodes | 1 [0–2] | 1 [0–2] | 0.29 |

*Note*: Numerical data are indicated as medians. Values in parentheses are percentages and values in brackets are IQR: first quartile – third quartile.

Abbreviations: CA19-9, carbohydrate antigen 19–9; CEA, carcinoembryonic antigen; DP, distal pancreatectomy; DUPAN-2, Duke pancreatic monoclonal antigen type 2; LNM, lymph node metastasis; PD, pancreaticoduodenectomy; TP, total pancreatectomy.

parameter (subsample = 0.3, learning_rate = 0.01, max_depth = 4, min_child_weight = 1.0, gamma = 1.4, colsample_bytree = 0.75, colsample_bylevel = 0.2, reg_lambda = 5.0, and reg_alpha = 0.047) was defined as the best. This tuning improved overlearning with AUCs for the training and test cohorts to 0.780 and 0.795, respectively (Figure 3). Table 2 shows the sensitivity, specificity, accuracy, and positive and negative predictive values of each model.

Figure 4 shows the ICE plot (blue lines) and PDP (orange line) for each feature in the prediction model. The ICE plot and PDP were used to evaluate the relationships between the model and each feature. The vertical axis shows the prediction of the model, wherein



Training cohort

Test cohort

**FIGURE 3** ROC curves of the prediction model in the training and test cohorts. AUC, area under ROC curves; ROC, receiver operating characteristic.

**TABLE 2** Diagnostic performance of model in predicting lymph node metastasis in PDAC.

| | AUC | Sensitivity (%) | Specificity (%) | Positive predictive value (%) | Negative predictive value (%) | Accuracy (%) |
|---|---|---|---|---|---|---|
| Training cohort | 0.78 | 93.5 | 42.2 | 68.8 | 82.7 | 71.8 |
| Test cohort | 0.795 | 95.3 | 34 | 56.9 | 88.9 | 63.3 |

Abbreviations: AUC, area under the curve; PDAC, pancreatic ductal adenocarcinoma.

the positive and negative values correspond to the positive and negative prediction of LNM, respectively. This model revealed that, as tumor size increased, positive prediction of LNM also increased. Similarly, high levels of CA19-9 and DUPAN2 were related to the positive prediction of LNM. However, tumor localization in the pancreatic head and CEA level did not significantly affect the predictions, and neoadjuvant treatment was associated with the negative prediction of LNM.

## 4 | DISCUSSION

In this study we created a novel ML model using an XGB tree to predict postoperative pathological LNM in patients with resectable PDAC. This novel ML model is a valuable tool because it can improve the accuracy of predicting LNM using available clinical information instead of lymph node imaging findings. To our knowledge, this is the first study to demonstrate the usefulness of ML in predicting LNM in patients with PDAC.

Previous studies have examined the prediction of LNM using cutoff values for CA19-9, tumor size, and clinical T stage on CT.[5,21] Yamada et al[5] reported the prediction of LNM in resectable pancreatic cancer using preoperative CA19-9 and tumor size; the cutoff values for CA19-9 and tumor size were determined to be 120 U/mL and 30 mm using ROC curve analysis, with AUC values of 0.662 and 0.677, respectively. Additionally, Coppola et al[21] evaluated the AUC for each clinical T stage in resectable pancreatic adenocarcinoma with a cutoff value 37 of CA19-9, and the results revealed an AUC 0.600–0.712. Conversely, the AUC for our new model was 0.780 in the training cohort and 0.795 in the test cohort, indicating the superiority of this novel model and the usefulness of ML with XGB in this setting.

Several recent studies have reported the factors associated with positive postoperative LNM in PDAC.[20,22–24] In this study we used an ICE plot and PDP to interpret the contribution of each feature to the predictions of this model. The results showed that a larger tumor size and higher levels of CA19-9 and DUPAN2 were associated with a positive prediction of LNM, and this finding is similar to those of previous reports.[20,22] However, as shown in the ICE plot and PDP of tumor size, predicting the optimal cutoff value when it changed linearly proves difficult. In contrast, setting a previously reported cutoff value may be useful when it reaches a plateau, as in the cases of CA19-9 and DUPAN-2. However, as indicated by the blue lines in the ICE plot, each learning feature was influenced by variations in the other features. This indicates that, even if predictive models are created with features that exclude strongly correlated factors, it is difficult to completely remove the influence of other features when determining the cutoff value for

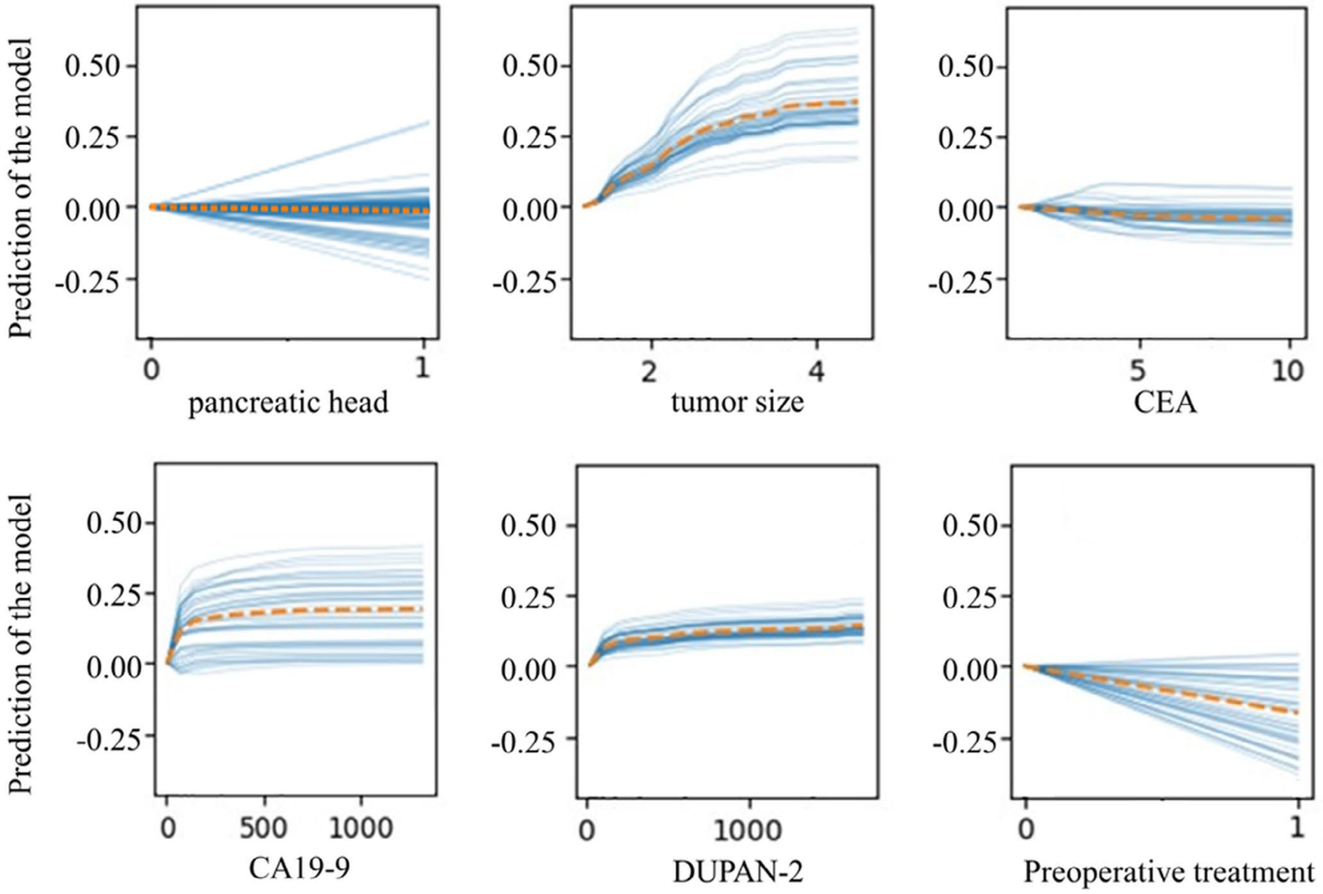


**FIGURE 4** ICE plot and PDP of the prediction model. The average of each ICE plot (blue line in the graph) is the PDP (orange line). The ICE plot and PDP were used to evaluate the relationships between the model and each feature. The vertical axis shows the prediction of the model, with positive and negative values on the vertical axis corresponding to the positive and negative prediction of LNM, respectively. CA19-9, carbohydrate antigen 19–9; CE, individual conditional expectation; CEA, carcinoembryonic antigen; DUPAN-2, Duke pancreatic monoclonal antigen type 2; PDP, partial dependence plot.

each learning feature. Therefore, when using multiple learning features it is necessary to coordinate them simultaneously; however, conventional methods have limitations. ML is considered to overcome this difficulty through a large number of learning steps and trials, which is reflected in the improvement of the prediction accuracy demonstrated in this study.

In contrast, Manen et al[23] found that CEA values were an independent predictor of PDAC progression; however, in this model the CEA levels did not have much relevance to the prediction of LNM. Although no reports have focused on the manner in which CEA levels are related to LNM in PDAC, future studies may reveal useful details. Similarly, in this model the ICE plot and PDP showed that whether the tumor localization was in the pancreatic head or not did not contribute to predicting LNM. Although surgical procedures and the area of lymph node dissection for PDAC are determined according to tumor localization, this predictive model is considered applicable irrespective of tumor localization. In addition, our findings suggested an association between neoadjuvant treatment and LNM. There are several potential benefits of NAC for PDAC, such as the identification of patients who may benefit from surgical resection, improved completion rates of multimodal therapy, and the potential for downstaging of tumors.[26,27] Roland et al[24] revealed that neoadjuvant treatment contributed to the regression of preoperative LNM and confirmed the presence of lymph node fibrosis in patients who underwent NAC, which indicates histopathological tumor regression and supports previous findings on the efficiency of neoadjuvant treatment. Although standardized NAC is currently used, the ability to preoperatively predict LNM may contribute to the development of new treatment strategies that differentiate patients by prognosis, such as enhanced treatment for patients with PDAC and positive prediction of LNM.

Pancreatectomy is a highly invasive surgery, and major postoperative complications are not rare (reported in 23% of cases).[28] In particular, older adult patients with PDAC are more likely to have decreased organ reserve and comorbidities. Several reports indicate that the incidences of postoperative complications and perioperative mortality after pancreatectomy are higher in older adult patients than their younger counterparts.[29,30] In the future, the demand for surgery for PDAC in older adults is expected to increase due to the aging population. Consequently, there will be a growing need for not only radical cure for cancer but also safe and minimally invasive surgical approaches, both considered pivotal factors. Perioperative complications and prolonged operation times are concerning issues associated with standard surgery in patients with reduced physical capacity owing to aging or comorbidities; if LNM can be accurately predicted prior to the operation, it may be feasible to ascertain the extent of lymph node dissection required without compromising curability. In such cases, this new model may be useful as an auxiliary tool when making treatment decisions. The concern in this model is the low specificity and positive predictive value, as shown in Table 2. In this study, ML was employed to maximize the AUC, and while results revealed low specificity, suggesting that it was difficult to increase specificity while maintaining sensitivity with the information available in this study. Adjusting the threshold for predictions could potentially mitigate overdiagnosis; however, this typically leads to reduced sensitivity, with a trade-off relationship. Improving the prediction model's accuracy could be feasible by incorporating factors directly associated with postoperative pathological LNM into the training features.

This study has some limitations. First, it was a retrospective study; resectability was retrospectively classified, and the NAC and NACRT regimens were not uniform. As such, future prospective studies are required. Second, this study was conducted at two institutions, and the number of patients was limited. ML has the advantage of dealing with large amounts of data, which enables the creation of a more accurate model.

In conclusion, ML using XGB may contribute to the development of an effective predictive model for LNM in patients with PDAC. This predictive model demonstrated better predictive power than those of previous studies that did not utilize ML. Furthermore, the use of Big Data in combination with deep learning may facilitate the development of superior prediction models.

## AUTHOR CONTRIBUTIONS

Susumu Daibo, Yuki Homma, and Hiroki Ohya contributed to the study concept and design, and drafting of this article. Susumu Daibo and Yuki Homma contributed to data collection and acquisition. Susumu Daibo, Yuki Homma, and Hiroki Ohya contributed to data analysis and interpretation. Hironori Fukuoka, Kentaro Miyake, Mayumi Ozawa, Norifumi Kumamoto, Ryusei Matsuyama, and Itaru Endo contributed to the drafting and critical revision of this article. Yusuke Saigusa, analyzed the data and validated the Python code. All authors have approved the final version of the article.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest for this article. Itaru Endo is an editorial board member of the *Annals of Gastroenterological Surgery*.

## ETHICS STATEMENTS

Approval of the research protocol: The study protocol was approved by the Ethical Advisory Committee of Yokohama City University Graduate School of Medicine (approval number: F231100004) and the Institutional Review Board of the participating hospital. The study conformed to the provisions of the Declaration of Helsinki.

Informed Consent: Due to the retrospective nature of this study, written informed consent was not required. An opt-out method was used after disclosure of the study information.

Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

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