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Original Research Article

Normal tissue complication probability model for severe radiation-induced lymphopenia in patients with pancreatic cancer treated with concurrent chemoradiotherapy

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ABSTRACT

Background and purpose: Radiation-induced lymphopenia (RIL) may be associated with a worse prognosis in pancreatic cancer. This study aimed to develop a normal tissue complication probability (NTCP) model to predict severe RIL in patients with pancreatic cancer undergoing concurrent chemoradiotherapy (CCRT).
Materials and methods: We reviewed pancreatic cancer patients treated at our facility for model training and internal validation. Subsequently, we reviewed data from three other facilities to validate model fit externally. An absolute lymphocyte count (ALC) of $< 0.5 \times 10^3/\mu L$ during CCRT was defined as severe RIL. An NTCP model was trained using a least absolute shrinkage and selection operator (LASSO)-based logistic model. The model's predictive performance was evaluated using the receiver operating characteristic area under the curve (AUC), scaled Brier score, and calibration plots.
Results: Among the 114 patients in the training set, 78 had severe RIL. LASSO showed that low baseline ALC, large planning target volume, and high percentage of bilateral kidneys receiving $\geq$ 5Gy were selected as parameters of the NTCP model for severe RIL. The AUC and scaled Brier score were 0.91 and 0.49, respectively. Internal validation yielded an average AUC of 0.92. In the external validation with 68 patients, the AUC and scaled Brier score was 0.83 and 0.30, respectively. Calibration plots showed good conformity.
Conclusions: The NTCP model for severe RIL during CCRT for pancreatic cancer, developed and validated in this study, demonstrated good predictive performance. This model can be used to evaluate and compare the risk of RIL.

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1. Introduction

Concurrent chemoradiotherapy (CCRT) is commonly employed as neoadjuvant or definitive treatment for non-metastatic pancreatic cancer. However, the median survival time for unresectable cases remains between 12 and 18 months [1], emphasizing the need for better strategies to improve these outcomes.

Severe lymphopenia frequently occurs as an unintended consequence of radiotherapy, possibly due to irradiation of the lymphoid organs and circulating lymphocytes, as lymphocytes are highly radiosensitive cells within the hematopoietic system [2]. Radiation-induced lymphopenia (RIL) has been reported to be related to poor prognosis in various malignant tumors, including pancreatic cancer [3]. A systematic review has demonstrated that higher levels of tumor-infiltrating CD3+, CD4+, and CD8 + T cells are associated with improved survival outcomes in patients with resected pancreatic cancer [4]. Since the circulating lymphocyte pool consists of cells that eventually become tissue-resident lymphocytes [5], it is indeed beneficial to explore lymphocyte-sparing radiotherapy as an additional effort to improve outcomes for pancreatic cancer patients.

An unintentional splenic dose was reported to increase the risk of severe lymphopenia during CCRT, marking the first study to investigate the association between RIL and splenic dose parameters for locally advanced pancreatic cancer [6]. Several other studies have reported an association between organs surrounding the pancreas and lymphopenia [7,8]. Recently, Kim et al. developed a Normal Tissue Complication Probability (NTCP) model based on whole-blood dose parameters to estimate severe RIL after abdominal radiotherapy in patients with hepatocellular carcinoma [9]. An NTCP model that could predict severe RIL during radiotherapy planning would be valuable, as it could potentially improve the prognosis of pancreatic cancer. However, studies that developed an NTCP model specifically for predicting severe RIL in pancreatic cancer remain lacking.

The least absolute shrinkage and selection operator (LASSO) is a regression technique that improves a model's predictive accuracy and interpretability by performing variable selection and regularization when developing a predictive model. Variable selection and regularization improve interpretability by simplifying the model and reducing overfitting. Several studies have reported that shrinkage methods, such as LASSO, provides better predictive performance than conventional stepwise methods [10–12]. When new predictive models are developed, they should be validated internally and externally to assess their performance and suitability.

This study aimed to develop a LASSO-based multivariable NTCP model to predict severe RIL based on clinical factors and dose parameters during CCRT in patients with pancreatic cancer. Subsequently, internal validation with the same data and external validation with data from other institutions were conducted to evaluate the validity of the developed model.

2. Materials and methods

2.1. Patients

The training set of this study included all consecutive patients with localized pancreatic cancer who underwent CCRT with three-dimensional conformal radiotherapy (3DCRT) at the coordinating institution between April 2013 and March 2021. The exclusion criteria were as follows: patients with distant metastasis, patients who did not complete radiotherapy because of tumor progression or refusal to undergo treatment, patients without absolute lymphocyte count (ALC) measurements within 1 month before CCRT initiation, or those not monitored at least every two weeks during treatment. Patients' medical records were retrospectively reviewed, and clinical and laboratory data were collected for analysis. Internal validation was carried out using data from the training set.

As shown in Supplementary Fig. 1, data of 114 patients were analyzed as the training set. Table 1 presents patient and treatment characteristics. Irradiation could not be completed in seven patients (two patients had gastric hemorrhage grade 2, and one each had grade 3 gastric hemorrhage, grade 3 cholangitis, grade 3 sepsis, grade 3 nausea, and grade 3 rash). Pancreatectomy was performed after irradiation in 49 patients (43.0 %).

As an external validation set, we retrospectively reviewed the medical records of consecutive patients with localized pancreatic cancer who underwent CCRT at three other institutions between April 2013 and March 2021. The exclusion criteria were identical to those used for the training set. A total of 68 patients were included. Radiotherapy was performed using 3DCRT in all patients. In the external validation set, we reviewed only the data necessary for external validation of the predictive model, along with basic patient information such as age, radiation dose, and concurrent chemotherapy regimens. Supplementary Table 1 presents patient and treatment characteristics of the external validation

Table 1
Patient and treatment characteristics (n = 114).

Characteristics	N (%) or median (range)
Age (years)	67 (42–84)
Sex	
Male	61 (53.5 %)
Female	53 (46.5 %)
Karnofsky performance status (%)	
90	93 (81.6 %)
70–80	21 (18.4 %)
Pathology	
Adenocarcinoma	109 (95.6 %)
Adenosquamous carcinoma	1 (0.9 %)
Unknown	4 (3.5 %)
Maximum tumor size (mm)	28 (14–63)
T factor (JPS 7th)	
T1–T2	4 (3.5 %)
T3	33 (28.9 %)
T4	71 (62.3 %)
Postoperative recurrence	6 (5.3 %)
Regional lymph node swelling (JPS 7th)	
N0	96 (84.2 %)
N1–N2	12 (10.5 %)
Postoperative recurrence	6 (5.3 %)
Resectability classification (JPS 7th)	
R	18 (15.8 %)
BR	55 (48.2 %)
UR-LA	35 (30.7 %)
Postoperative recurrence	6 (5.3 %)
CA19-9 (U/ml)	75.7 (< 1.0–17767.8)
Neutrophils ($\times 10^3/\mu L$)	3.60 (1.27–14.16)
Lymphocytes ($\times 10^3/\mu L$)	1.44 (0.52–3.50)
NLR	2.4 (0.8–13.2)
Baseline Lymphopenia Grade	
0	86 (75.4 %)
1	22 (19.3 %)
2	6 (5.3 %)
Charlson Comorbidity Index	
0	91 (79.8 %)
≥1	23 (20.2 %)
Radiation dose (Gy)	50.4 (16.2–50.4)
Dose per fraction (Gy)	1.8 (1.8–1.8)
Regional lymph nodes area	
Yes	38 (33.3 %)
No	76 (66.7 %)
Concurrent chemotherapy	
S-1	82 (71.9 %)
Gemcitabine	32 (28.1 %)
Induction chemotherapy	
Yes	33 (28.9 %)
No	81 (71.1 %)
PTV size (cm^3)	330.3 (86.3–1079.3)

JPS = Japan pancreas society, R = resectable, BR = borderline resectable, UR-LA = unresectable-locally advanced, CA19-9 = carbohydrate antigen 19–9, NLR = neutrophil-to-lymphocyte ratio, S-1 = tegafur/gimeracil/oteracil, PTV = planning target volume.

set. Similar treatment methods were employed in the training and external validation sets, and the treatment details are described in Supplementary Materials.

This study was approved by the Institutional Review Board of the coordinating institution (IRB number: 022–0359) and received implementation permission from the participating institutions in accordance with the Helsinki Declaration of 1975, as revised in 2013. Although the requirement for written informed consent was waived because of the retrospective nature of the study, participants were informed about the study, and an opt-out procedure was available to decline participation.

2.2. Lymphocyte count

Baseline ALC was defined as the ALC within 1 month before the start of CCRT, which was the closest to the treatment initiation date. Blood tests were performed every 1–2 weeks during CCRT. The ALC was recorded until the end of CCRT. The minimum ALC during CCRT was used as the nadir [7]. Lymphopenia during CCRT was graded according to the Common Terminology Criteria for Adverse Events version 5.0. Grade 3 or more ($<0.5 \times 10^3/\mu L$) was defined as severe RIL.

2.3. Predictor selection

For the patients of our facility used as a predictive model training set, clinical predictors known before treatment and dose parameters for the surrounding organs associated with RIL, were selected based on published literature. The selected clinical predictors were age, sex, Karnofsky Performance Status, carbohydrate antigen (CA) 19–9 level before radiotherapy, baseline ALC, and PTV size. The dose parameters were assessed using the actual delivered number of fractions, rather than the initially planned fractions, to account for the incomplete treatment cases. Dose parameters from the spleen, vertebrae, liver, bilateral kidneys, and gastrointestinal tract (including the stomach, duodenum, small intestine, and large intestine) were extracted for inclusion in the analysis. The contours were reviewed or retrospectively created by two radiation oncologists. The dose parameters V5–V45 (%) and V5–V45 (cm^3), defined as the percentage and absolute volume receiving 5–45 Gy or more, were obtained for each organ every 5 Gy. The spleen, liver, and bilateral kidneys were delineated and evaluated based on the relative volume (%). As not all contours could be delineated due to the limited imaging range of the treatment planning CT, the vertebrae and the entire gastrointestinal tract were evaluated in absolute volume (cm^3) by delineating all slices plus 2 cm from the CTV in the cephalocaudal direction, confirming that the irradiated area was adequately included. All dose parameters are listed in Supplementary Table 2.

2.4. Statistical analyses

The probability of severe RIL was predicted using a logistic regression model. All candidate predictors were selected using LASSO method. The hyperparameter in LASSO model was optimized by searching a grid of tuning parameter values. The variables were standardized before being input into LASSO model, but the regression coefficients were reported on the original scale. A multivariable logistic analysis was performed using the limited factors selected by LASSO. We analyzed the selected parameters using the multivariate logistic model with severe RIL as the dependent variable. Receiver operating characteristic (ROC) curves were drawn, and the predictive performance of the model was evaluated by the area under the curve (AUC) and scaled Brier score [13], both of which approached 1 as the predictive performance improved. Brier score is described in Supplementary Materials.

We conducted an internal validation using data from the training set with 1,000 bootstrap resamples that repeated all modeling steps for each imputed dataset to assess the optimality of the predictive models created by overlearning or intentional selection. The average AUC obtained by bootstrapping was compared to the original predictive model. Furthermore, the prediction model was applied to an external dataset, yielding an externally validated AUC and a scaled Brier score. Calibration of the model reflecting the agreement between the predicted and observed (actual) outcomes was visualized using a calibration plot for the training and external validation sets. Supplementary Fig. 2 shows an overview of the study design.

Survival analyses are described in Supplementary Materials. Statistical analyses were performed using JMP Pro version 16.0 (SAS Institute Japan Co., Ltd., Minato-ku, Tokyo, Japan). Statistical significance was set at $p < 0.05$.

3. Results

3.1. Survival outcome

The median follow-up time from the start date was 20.6 months (range, 0.4–108.0). Fig. 1 shows the Kaplan–Meier curves for overall survival (OS) and progression-free survival (PFS). The median OS and PFS were 21.2 months and 11.2 months, respectively. Multivariable analysis for OS showed that severe RIL was one of the statistically significant predictors of poor OS (hazard ratio [HR] = 1.93, 95 % confidence interval [CI]: 1.15–3.21, p = 0.01, Supplementary Table 3). All treatment-related toxicities during CCRT are listed in Supplementary Table 4.

3.2. Development of NTCP model for severe RIL and internal validation

The median ALC nadir during CCRT was $0.39 \times 10^3/\mu L$ (range, 0.09–1.31) among the 114 patients in the training set. A total of 78 patients (68.4 %) experienced severe RIL. Supplementary Tables 5 and 6 present patient and treatment characteristics, and dose parameters, respectively, for severity of RIL.

Table 2 presents the results of univariable analysis of all factors predicting severe RIL. LASSO showed that baseline ALC ($\times 10^3/\mu L$) (standard error [SE] = 0.0003, p = 0.009), PTV size (cm^3) (SE = 0.001, p = 0.03), and kidney V5 (%) (SE = 0.02, p = 0.03) were selected as predictors of severe RIL among all factors (Table 3). The results of multivariable logistic analysis using these factors revealed an AUC and scaled Brier scores of 0.91 and 0.49, respectively. Fig. 2 shows the ROC curve obtained using the proposed model of training set. Supplementary Fig. 3 presents the profile of the developed model.

Based on the developed model, the probability of severe RIL during CCRT was calculated using the formula in Supplementary Materials. As a result of internal validation by the bootstrap method, the average AUC was 0.92 (95 % CI, 0.83–0.95).

3.3. External validation

A total of 55 patients (80.9 %) experienced severe RIL. The AUC for predicting severe RIL by applying the prediction model to the external validation set was 0.83, and the scaled Brier score was 0.30. The ROC curve obtained by fitting the predictive model to the external validation set is shown in Supplementary Fig. 4. Calibration plots for the training and external validation sets are shown in Fig. 3. In the external validation set (Fig. 3B), model misalignments were mild, with a tendency for misalignments to increase with higher prediction probabilities; however, the overall model fit was considered good. Errors were generally mild, although the model may have been underestimated in groups with high prediction probabilities. The 95 % CI (shaded area in Fig. 3B) mainly included results from the training set, and the visual inspection was similarly good.

4. Discussion

We developed a prediction model using pretreatment data to predict severe RIL in CCRT for pancreatic cancer, and performed internal and

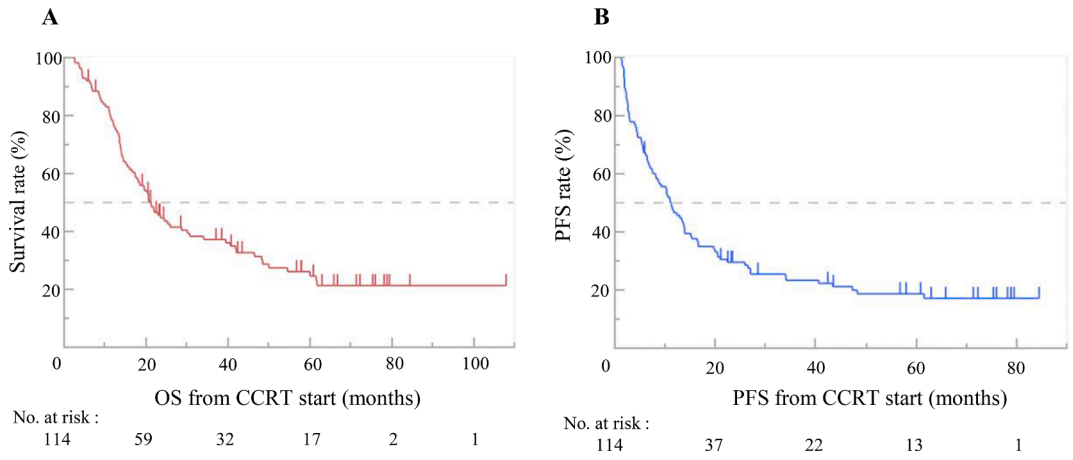


Fig. 1. Kaplan–Meier analysis for overall survival (A) and progression-free survival (B) for patients treated with concurrent chemoradiotherapy for pancreatic cancer.

external validations, which revealed good model performance and satisfactory fit. The NTCP model developed in this study enabled us to identify patients at high risk of severe RIL during radiotherapy planning.

In pancreatic cancer, RIL is associated with poor prognosis [14,15], and lymphocytes in particular play an important role in mediating the immune response against tumor cells. However, as pancreatic cancer forms a characteristic microenvironment with few effector T cells responsible for the immune response [16,17], preserving lymphocytes during radiotherapy might be particularly important.

We used ROC curves, Brier scores, and calibration plots as each metric evaluates different aspects of the model's performance. Specifically, ROC curves assess the model's discriminative ability, visualizing the balance between sensitivity and specificity. The Brier score quantifies the accuracy of probabilistic predictions by measuring the difference between predicted probabilities and actual outcomes. Meanwhile, the calibration plots evaluate the validity of the predicted probabilities by comparing them to observed event rates. By combining these metrics, we can provide a more comprehensive evaluation of the model's overall performance.

Patients with low baseline ALC, large PTV size, and high kidney V5 were found to have a high probability of developing severe RIL during CCRT for pancreatic cancer. While a correlation exists between PTV size and kidney V5 (Supplementary Fig. 5), selecting predictor variables for predictive models should prioritize those most closely related to the objective variable over the correlation between factors. LASSO mitigates the effects of multicollinearity, making it useful when multicollinearity is present, as with dose parameters. We posit that LASSO is a valid option for developing predictive models; however, it does not completely eliminate multicollinearity, thereby requiring caution when interpreting the selected variables.

Several factors that contributed to the development of this model were considered. First, all patients received relatively similar radiotherapy and chemotherapy compared with previous reports on pancreatic cancer. Another factor is that the inclusion of 114 patients, a relatively large number, may have contributed to the good model performance. Therefore, the NTCP model may be a clinically useful indicator for treatment planning.

Considering that no patient had severe lymphopenia before the start of CCRT and 78 patients (68.4 %) developed it during treatment, CCRT likely frequently induces severe lymphopenia. Baseline ALC is an important predictor of severe RIL in various organs, including pancreatic, head and neck, and brain tumors [6,18–26]. This study also showed a significant correlation between baseline ALC and the incidence of severe RIL, demonstrating the importance of maintaining pretreatment immune function. Several studies have found no difference in the occurrence of severe RIL among the various concurrent chemotherapy regimens used and induction chemotherapy [6,14,20,21,27–30]. In this study, the incidence of severe RIL was higher in patients treated with CCRT with Gemcitabine (96.9 %) than with S-1 (57.3 %), and in those without induction chemotherapy (74.1 %) than with it (54.5 %). However, neither factor was selected as a predictor by LASSO.

Univariable analysis in Table 2 showed significant correlations between specific doses and RIL in the spleen, liver, vertebrae, and gastrointestinal tract in addition to kidney. Subsequent variable selection by LASSO resulted in kidney V5 being selected as the most significant predictor. However, few reports have shown an association between renal dose and RIL. The mechanism by which irradiation of these organs correlates with RIL is hypothesized to be related to the irradiation of lymphoid organs and circulating lymphocytes. Jin et al. modeled that 60 % of total blood affecting RIL flows through the aorta, and divides into five interspersed organs (15 % in the liver, 15 % in the kidneys, 5 % in the bowels, 5 % in the other abdominal organs, and 20 % in the non-abdominal organs), and merges into the IVC [31]. The kidneys are blood-rich organs and irradiation of the kidneys may be associated with a decrease in circulating lymphocytes.

Our study showed that a large PTV size is associated with severe RIL, which is consistent with the findings of other studies [15,25,32,33]. In another study where 48 % of the patient cohort had pancreatic cancer, each 100 cm^3 increase in PTV was associated with a 20 % increase in the risk of grade 3 or higher lymphopenia [8]. Reducing the PTV through rigorous motion management and precise patient set-up is expected to reduce severe RIL.

Previous studies have reported that irradiation with particle beam therapy reduces RIL risk [22,30,34,35]. A recent report on locally advanced pancreatic cancer also reported a significantly lower degree of RIL with carbon ion beam therapy compared to photon beam therapy [35]. The model developed using 3DCRT in this study could be adaptable because similar dose fractionation and combination chemotherapy are often used in proton therapy, which may reduce the kidney dose and potentially preserve lymphocyte function. However, further research is necessary to determine how proton beam therapy directly affects clinical outcomes.

This study had several limitations. First, this was a retrospective analysis of patients with pancreatic cancer treated with CCRT. Several factors are inconsistent across the cohort, such as the concurrent chemotherapy regimens and treatments received prior to or after CCRT. Although the NTCP model for severe RIL developed and validated in this study demonstrated good predictive performance, further research is warranted to evaluate this model prospectively for utilization in treatment planning. Second, the databases in the training and external validation sets of this study contain only 3DCRT treatments. Notably although these results are based solely on 3DCRT, there has been no previous NTCP model for severe RIL in pancreatic cancer. This study, therefore, provides a potentially valuable basis for establishing

Table 2
Univariable analysis for predictors of severe RIL.

Factor	Univariable analysis		
	OR	95 %CI	P
Age (years)	0.98	0.94–1.02	0.38
Sex (male vs female)	2.22	0.97–5.05	0.06
Karnofsky performance status (%)	0.70	0.26–1.88	0.48
Maximum tumor size (mm)	1.06	1.01–1.11	0.01
CA19-9 (U/ml)	1.00	1.00–1.00	0.79
Baseline ALC ($\times 10^3/\mu L$)	1.00	1.00–1.00	< 0.001
PTV size (cm^3)	1.01	1.01–1.02	< 0.001
Spleen V5 (%)	1.05	1.02–1.09	0.004
Spleen V10 (%)	1.05	1.01–1.10	0.02
Spleen V15 (%)	1.06	1.00–1.11	0.03
Spleen V20 (%)	1.05	0.99–1.10	0.09
Spleen V25 (%)	1.04	0.98–1.10	0.15
Spleen V30 (%)	1.04	0.96–1.14	0.34
Spleen V35 (%)	1.02	0.95–1.10	0.54
Spleen V40 (%)	1.01	0.95–1.09	0.71
Spleen V45 (%)	1.01	0.94–1.10	0.72
Vertebrae V5 (cm^3)	1.01	1.01–1.02	0.001
Vertebrae V10 (cm^3)	1.01	1.00–1.02	0.002
Vertebrae V15 (cm^3)	1.01	1.00–1.02	0.006
Vertebrae V20 (cm^3)	1.01	1.00–1.02	0.02
Vertebrae V25 (cm^3)	1.01	1.00–1.01	0.08
Vertebrae V30 (cm^3)	1.01	1.00–1.01	0.009
Vertebrae V35 (cm^3)	1.01	1.00–1.03	0.006
Vertebrae V40 (cm^3)	1.06	1.03–1.10	< 0.001
Vertebrae V45 (cm^3)	1.08	1.03–1.13	< 0.001
Liver V5 (%)	1.04	1.01–1.06	0.01
Liver V10 (%)	1.04	1.00–1.07	0.02
Liver V15 (%)	1.04	1.00–1.07	0.03
Liver V20 (%)	1.02	0.98–1.06	0.32
Liver V25 (%)	1.01	0.97–1.06	0.52
Liver V30 (%)	1.13	1.03–1.25	0.01
Liver V35 (%)	1.24	1.08–1.42	0.003
Liver V40 (%)	1.27	1.07–1.51	0.006
Liver V45 (%)	1.33	1.06–1.67	0.01
Kidney V5 (%)	1.10	1.06–1.14	< 0.001
Kidney V10 (%)	1.12	1.07–1.17	< 0.001
Kidney V15 (%)	1.14	1.07–1.20	< 0.001
Kidney V20 (%)	1.14	1.07–1.21	< 0.001
Kidney V25 (%)	1.15	1.07–1.24	< 0.001
Kidney V30 (%)	1.30	1.14–1.50	< 0.001
Kidney V35 (%)	1.44	1.16–1.79	< 0.001
Kidney V40 (%)	1.87	1.25–2.81	0.002
Kidney V45 (%)	2.41	1.28–4.56	0.007
GI tract V5 (cm^3)	1.00	1.00–1.00	0.006
GI tract V10 (cm^3)	1.00	1.00–1.00	0.006
GI tract V15 (cm^3)	1.00	1.00–1.00	0.006
GI tract V20 (cm^3)	1.00	1.00–1.00	0.06
GI tract V25 (cm^3)	1.00	1.00–1.00	0.04
GI tract V30 (cm^3)	1.01	1.00–1.01	0.001
GI tract V35 (cm^3)	1.01	1.00–1.02	< 0.001
GI tract V40 (cm^3)	1.01	1.00–1.02	0.002
GI tract V45 (cm^3)	1.01	1.00–1.02	0.002

RIL = radiation induced lymphopenia, OR = odds ratio, CI = confidence interval, CA19-9 = carbohydrate antigen 19–9, ALC = absolute lymphocyte count, PTV = planning target volume, GI = gastrointestinal.

Table 3
Predictors selected by LASSO.

Predictors	SE	coefficients	P
baseline ALC ($x10^3/\mu L$)	0.0003	−0.0008	0.009
PTV size (cm^3)	0.001	0.0024	0.030
kidney V5 (%)	0.02	0.033	0.030

LASSO = least absolute shrinkage and selection operator, SE = standard error, ALC = absolute lymphocyte count, PTV = planning target volume.

lymphocyte-sparing radiotherapy for pancreatic cancer. However, further validation may be needed to adapt the findings to different dose distribution treatments, such as intensity-modulated radiation therapy. Third, ALC at nadir was used as a cut-off value in this study, referring to several previous reports showing an association between worse survival and RIL. However, the interval between the ALC recordings during CCRT was not uniform; therefore, the values may have fluctuated during this period. A more accurate assessment of RIL may be possible by including only patients with ALC measured at least once a week (5–6 times during the treatment period). Moreover, these lymphocyte counts might not be an accurate indicator as they are heavily influenced by baseline ALC, as shown in recent reports. To address this problem, alternative measures of RIL have been proposed, such as lymphocyte depletion kinetics [36,37], logarithmic lymphocyte depletion [38], and lymphocyte recovery at three or six months after treatment [39,40]. Further studies are needed on how to assess RIL. Finally, the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) statement provides guidelines for the development and validation of predictive models. However, this study does not adhere to them in several respects (Supplementary Materials), and caution should be exercised in its interpretation [41].

In conclusion, severe RIL occurred frequently during CCRT for pancreatic cancer, and the NTCP model for severe RIL developed and validated in this study showed good predictive performance. Our NTCP model can be used to evaluate and compare the risk of RIL.

5. Data statement

Due to the ethical review of this study, data sharing is not approved, and therefore, we are unable to provide the research data.

CRediT authorship contribution statement

Fuki Koizumi: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing – original draft, Visualization. **Norio Katoh:** Conceptualization, Methodology, Investigation, Resources, Data curation, Writing – review & editing, Project administration, Funding acquisition. **Takahiro Kanehira:** Methodology, Software, Formal analysis, Resources, Data curation, Writing – review & editing. **Yasuyuki Kawamoto:** Resources, Writing – review & editing. **Toru Nakamura:** Resources, Writing – review & editing. **Tatsuhiko Kakisaka:** Resources, Writing – review & editing. **Miyako Myojin:** Investigation, Resources, Writing – review & editing. **Noriaki Nishiyama:** Investigation, Resources, Writing – review & editing. **Akio Yonesaka:** Investigation, Resources, Writing – review & editing. **Manami Otsuka:** Investigation, Resources, Writing – review & editing. **Rikiya Takashina:** Investigation, Resources, Writing – review & editing. **Hideki Minatogawa:** Investigation, Resources, Writing – review & editing. **Hajime Higaki:** Investigation, Resources, Writing – review & editing. **Yusuke Uchinami:** Resources, Writing – review & editing. **Hiroshi Taguchi:** Resources, Writing – review & editing. **Kentaro Nishioka:** Resources, Writing – review & editing. **Koichi Yasuda:** Resources, Writing – review & editing. **Naoki Miyamoto:** Resources, Writing – review & editing, Funding acquisition. **Isao Yokota:** Methodology, Software, Validation, Formal analysis, Resources, Data curation, Writing – review & editing. **Keiji Kobashi:** Methodology, Software, Validation, Formal analysis, Resources, Data curation, Writing – review & editing. **Hidefumi Aoyama:** Conceptualization, Writing – review & editing, Supervision, Funding acquisition.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: HA reports grants from Hitachi Ltd., outside of the submitted work. KK

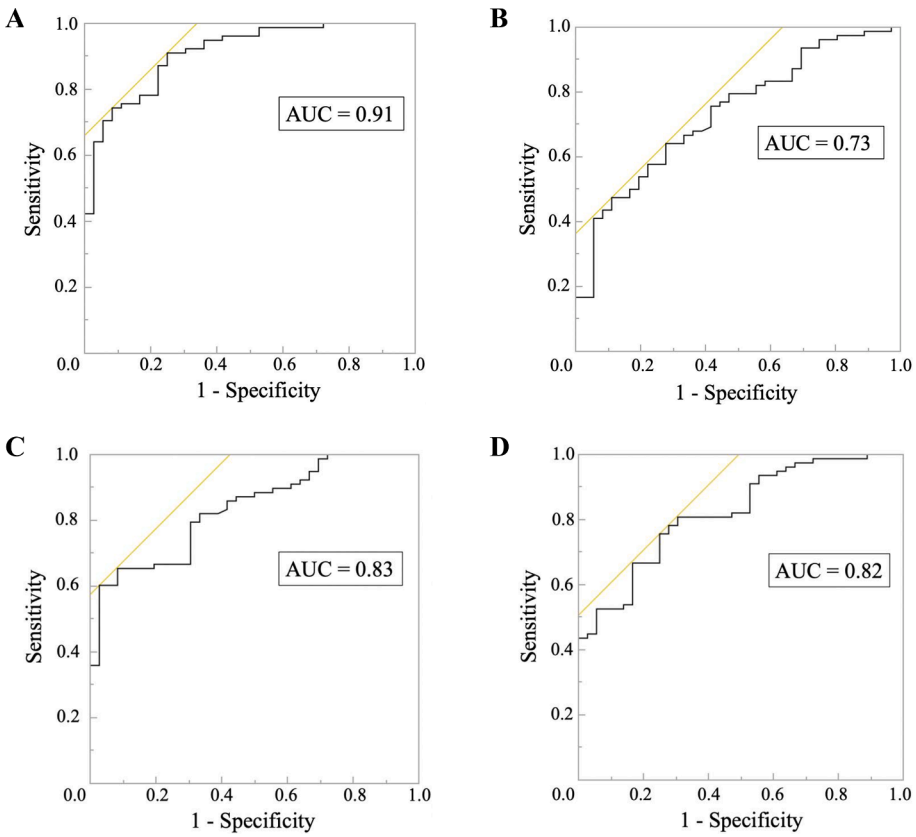


Fig. 2. Receiver operating characteristic curves for multivariable analysis (A), baseline ALC (B), PTV size (C), and kidney V5Gy (D) in predicting the development of severe RIL in the training set.

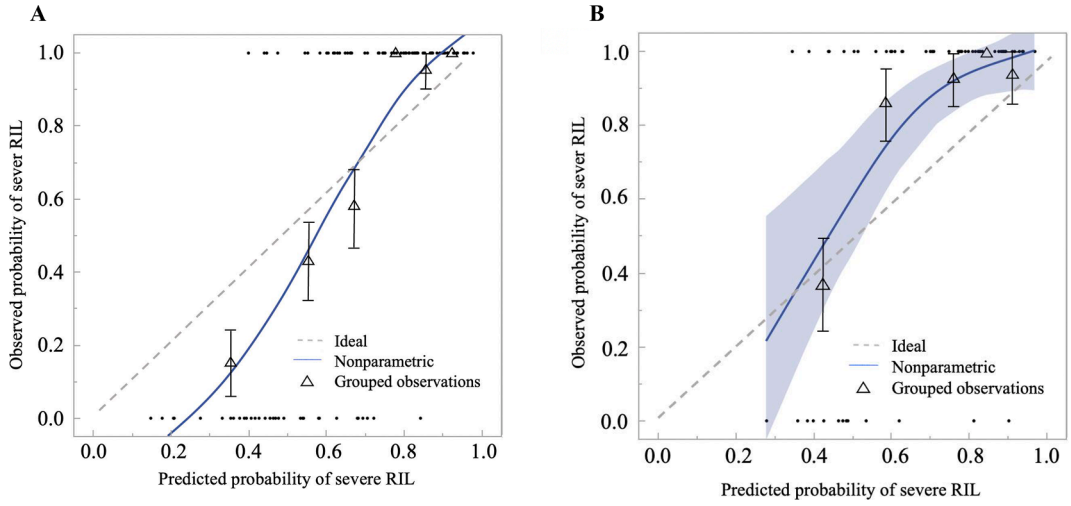


Fig. 3. Calibration plots of the model with training set (A) and external validation set (B). The shaded areas around the curve represent 95 % CI. The actual observed patients are shown as dots. The calibration slope and intercept for training set (A) were −0.81 and 2.37 respectively. The calibration slope and intercept for external validation set (B) were 1.57 and 0.45, respectively.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.phro.2024.100690.

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