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Original Article

Predicting severe acute radiation pneumonitis in patients with non-small cell lung cancer receiving postoperative radiotherapy: Development and internal validation of a nomogram based on the clinical and dose–volume histogram parameters

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ABSTRACT

Background and purpose: Postoperative radiotherapy (PORT) can potentially lead to radiation pneumonitis. We aim to develop a nomogram predicting the severe acute radiation pneumonitis (SARP, grade ≥3) in patients with non-small cell lung cancer (NSCLC) receiving PORT.

Materials and methods: Clinical and dose–volume histogram (DVH) factors were collected from 109 patients between 2006 and 2017. The endpoint was the development of SARP within 3 months after PORT. Logistic regression was used to evaluate the prognostic value of each factor in predicting SARP. Nomogram was generated based on multivariate regression coefficients. Area under the ROC curve (AUC), calibration curves, and decision curve analyses (DCA) were conducted to validate the model.

Results: Univariate and multivariate analysis indicated that total lung mean dose (tlMD) (OR: 1.003, 95% CI: 1.001–1.006, $p = 0.013$), percentage of ipsilateral lung volume receiving ≥5 Gy (ilV_5) (OR: 1.084, 95% CI: 1.020–1.151, $p = 0.009$), and concurrent chemoradiotherapy (CCRT) (OR: 4.091, 95%CI: 1.331–12.572, $p = 0.014$) were independent prognosticators of SARP and were included in the nomogram. ROC curves revealed the AUC of the nomogram was 0.842, which was much higher than any factor alone (tlMD: 0.769; ilV_5: 0.744; CCRT: 0.661). Calibration curves showed favorable consistency between the predicted SARP and the actual observation. DCA showed satisfactory positive net benefits of the model among most of the threshold probabilities, indicating great clinical effect.

Conclusion: We identified that the tlMD (>10.8 Gy), ilV_5 (>64.9%), and CCRT could predict SARP among patients with NSCLC receiving PORT. Combining clinical and DVH parameters, a nomogram was first built and validated, showing its potential value in practice.

Lung cancer is the leading cause of cancer-related mortality worldwide [1]. For patients with non-small cell lung cancer (NSCLC) after surgery, postoperative radiotherapy (PORT) is recommended by NCCN panels when there are positive section margins or upstaging of lymph node status to N2 to reduce the risk of local regional recurrence [2].

However, radiotherapy of the thorax is commonly accompanied by radiation pneumonitis (RP), which can lead to chronic respiratory insufficiency and affect a patient's quality of life. For some patients, severe acute radiation pneumonitis (SARP) might occur during the three months after radiotherapy, consequently leading to a poor prognosis and even death [3].

Numerous studies have investigated predictive factors for RP, including clinical and dosimetric factors. The performance status, pulmonary function, tumor location, smoking history, pulmonary emphysema, interstitial lung disease, concurrent chemotherapy had been reported correlating with RP incidence [4–9]. Among the dosimetric factors, mean lung dose (MLD), gross tumor volume (GTV), $V_{5/10/13/20/30}$ (percentage of the lung volume receiving ≥5, 10, 13, 20, 30 Gy) and heart dosimetric variables [5,6,10–12] were reported to be associated with the occurrence of RP. However, most of these studies focused on patients without surgery. As Jain et al. stated, recent researches paid more attention to the understanding of mechanism of RP and using more information about lung ventilation or biomarkers for reducing the incidence of

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RP [13]. So far, only a few studies had evaluated the possible relationship between the incidence of RP and the dose–volume histogram (DVH) parameters among patients with NSCLC receiving PORT [14–17].

In our previous work, we observed that DVH parameters might have some effect on the occurrence of SARP in patients with NSCLC receiving PORT [18]. In the present study, we collected data of the clinical factors, dosimetric parameters, and the occurrence of SARP in these specific patients, attempting to build and validate a combined nomogram predicting SARP.

Materials and methods

Patients

Between June 2006 and October 2017, we retrospectively analyzed 177 patients with NSCLC receiving surgery and sequentially (or concurrently) PORT at West China Hospital, Sichuan University. The inclusion criteria were predefined: receiving lobectomy; treated with postoperative intensity modulated radiation therapy (IMRT) or 3D-conformal RT (3D-CRT) following lobectomy; Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1; RP occurring during the 3 months after the completion of RT. The exclusion criteria included receiving chemotherapy or radiotherapy before surgery, treatment with pneumonectomy or wedge resection, or a total radiation dose less than 50 Gy. Finally, 109 patients were eligible. This study was approved by the West China Hospital Research Ethics Board.

Definition of clinical and DVH factors

The following factors were collected: age, gender, ECOG performance status, pathological diagnosis, tumor sites, smoking status, pulmonary function, laterality, surgical margin, TNM stage, sequence of chemotherapy and radiotherapy, radiotherapy technique and DVH factors. Pulmonary dysfunction was defined based on the recommendations from American Thoracic Society (ATS) and European Respiratory Society (ERS) [19]. The lung volume was defined as the volume of total/ipsilateral/contralateral lung minus the GTV, respectively [20,21]. V_x was defined as the percentage of lung/heart volume receiving $\geq$x Gy. $D_{2\%}$ was defined as the minimum dose of the 2% volume of total/ipsilateral/contralateral lung, respectively. The following dosimetric parameters were generated from the DVH of lung-GTV, including total/ipsilateral/contralateral lung $V_{5/10/20/30}$, mean dose (MD), $D_{2\%}$, $V_{10/20/30/40/50}$ of heart, radiation dose, planning target volume (PTV) and total lung volume (TLV). All DVH parameters were extracted and calculated from planned dose distribution based on the Convolution/Superposition algorithm.

Radiotherapy

PORT was delivered by 3D-CRT or IMRT with a total dose of 50–66 Gy, at 1.8–2 Gy per fraction, 5 days per week. There is no gross tumor volume (GTV) for patients with negative margins (R0 resection). For patients with microscopic positive margins (R1 resection) or macroscopic positive margins (R2 resection), the GTV enclosed the site of the bronchial positive margin (2 cm around the bronchial stump) or the residual tumor/lymph nodes which had a diameter $\geq$1 cm. The clinical target volume (CTV) includes the GTV plus an 8-mm margin. For patients with R0 resection and positive nodal disease at multiple stations (pN2), the CTV comprised the bronchial stump and high-risk draining lymph node stations as mentioned by Kelsey et al. [22]. The planning target volume (PTV) was defined as the CTV plus 10-mm margins to account for setup uncertainty and respiratory motion. The dose–volume constraints for normal tissues were set as follows: to the spinal cord, <45 Gy; to the esophagus, $V_{50} < 30\%$; to the heart, $V_{40} < 40\%$, and to the whole lung, $V_{20} < 25\%$, $V_{30} < 20\%$ and MLD < 15 Gy. All plans were generated in our treatment plan system (TPS, Philips Pinnacle[3], Milpitas, USA), and delivered by the 6-MV photon beam.

Chemotherapy

All the patients received chemotherapy after surgery. Of these, 28 (25.7%) were confirmed with R1 or R2, and 81 (74.3%) were confirmed with R0 (pN2); they were treated with concurrent and sequential chemotherapy, respectively. The chemotherapy regimens were administered every 21 days for a median cycle of 3 (range, 2–4). The sequential chemotherapy regimens consisted of vinorelbine, paclitaxel, gemcitabine, pemetrexed combined with cisplatin or carboplatin. The concurrent chemotherapy regimens included etoposide, paclitaxel, pemetrexed combined with cisplatin or carboplatin. All the doses and adjustments of the chemotherapy regimen followed the NCCN guidelines [2].

End point definitions

The endpoint was SARP, grade $\geq$3 occurring within 3 months of the completion of PORT. Grade 3 RP was defined as symptomatic disease interfering with the activities of daily living and requiring oxygen support or hospitalization, according to the Common Terminology Criteria for Adverse Events, version 4.03 [23]. The diagnosis of SARP was confirmed by at least two experienced radiation oncologists based on clinical symptoms and changes in CT images.

Statistical methods

The predictive model was built as follows: firstly, univariate logistic regression model was conducted evaluating each factor's ability in predicting SARP. Secondly, factors with $p < 0.05$ in univariate analyses were assessed in multivariate analysis. Finally, factors with significant predictive value in multivariate analysis were used to build the nomogram. Before multivariate analysis, the Spearman rank correlation analyses were performed to avoid multicollinearity between factors.

The validation of the nomogram was conducted using the area under the receiver operating characteristic (ROC) curve (AUC), calibration curve (1000 bootstrap resamples) and decision curve analysis (DCA). The ROC curves were used to estimate the discrimination ability of the nomogram and each predictor alone. Also, the optimal cut-off point of the continuous predictors was determined by the ROC curves. Calibration curve was used to compare the predicted probability with the observed probability of SARP. DCA was performed to illustrate the clinical usefulness of the nomogram by quantifying the net benefits at different threshold probabilities.

Data analyses were performed using R software (version 3.4.3) and SPSS (version 22.0). All tests were two-sided. A value of $p < 0.05$ was considered significant.

Results

Patient characteristics

Baseline characteristics of the studied population are summarized in Table 1. In total, 26 (23.9%) patients were diagnosed with SARP (18 [16.5%], 6 [5.5%], and 2 [1.8%] developed grade 3, grade 4, and grade 5 RP, respectively). The median interval from the completion of RT to the occurrence of SARP was 61 days (25–86 days).

Table 1
Baseline characteristics of all patients (n = 109).

Baseline characteristics	Number of patients (%)
Age (years), Median (IQR)	52 (34–68)
Sex	
Male	82 (75.2)
Female	27 (24.8)
ECOG performance status	
0	78 (71.6)
1	31 (28.4)
Pathological diagnosis	
Squamous cell carcinoma	52 (47.7)
Adenocarcinoma	55 (50.5)
Large cell carcinoma	2 (1.8)
Tumor sites	
Upper lobe	67 (61.5)
Middle/lower lobe	42 (38.5)
Laterality	
Left	40 (36.7)
Right	69 (63.3)
Smoking status	
Yes	51 (46.8)
No	58 (53.2)
PF before RT	
Mild dysfunction	94 (86.2)
Moderate dysfunction	15 (13.8)
T stage	
T1/T2/T3/T4	2 (1.8)/32 (29.4)/46 (42.2)/29 (26.6)
N stage	
N0/N1/N2/N3	31 (28.4)/26 (23.9)/48 (44.0)/4 (3.7)
Tumor stage	
IIA/IIB/IIIA/IIIB	4 (3.7)/16 (14.7)/81 (74.3)/8 (7.3)
Surgical margin	
Positive (R1/ R2)	28 (25.7)
Negative (R0)	81 (74.3)
Radiotherapy techniques	
3D-CRT	11 (10.1)
IMRT	98 (89.9)
Radiation dose (Gy), Median (IQR)	60.0 (50.0–62.0)
PTV (cm^3), Median (IQR)	211.2 (150.6–307.2)
TLV (cm^3), Median (IQR)	2498.3 (2276.2–3296.3)
Chemoradiotherapy	
Concurrent	28 (25.7)
Sequential	81 (74.3)

IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; PF, pulmonary function; RT, radiation therapy; 3D-CRT, 3D-conformal radiation therapy; IMRT, intensity modulated radiation therapy; PTV, planning target volume; TLV, total lung volume.

Univariate and multivariate analyses

Univariate analysis indicated that total lung V_{20} (tlV_{20}), total lung MD (tlMD), ipsilateral lung V_5 (ilV_5), ipsilateral lung MD (ilMD), and CCRT were statistically associated with a higher incidence of SARP (Table 2). Spearman's analyses indicated a relatively strong correlation between tlMD and tlV_{20} ($r = 0.845$, $p < 0.001$) and very weak correlations among other factors (Table 3). To avoid multicollinearity, tlMD and tlV_{20} were not included in the multivariate analysis simultaneously. Given that tlMD was more significantly correlated with SARP than tlV_{20} (p value: 0.001 vs. 0.017, Table 2), tlMD instead of tlV20 was included in the multivariate analysis. Thus, the multivariate logistic regression was conducted on factors including tlMD, ilV_5, ilMD and CCRT. In multivariate analysis, tlMD (OR: 1.003, 95%CI: 1.001–1.006, $p = 0.013$), ilV_5 (OR: 1.084, 95%CI: 1.020–1.151, $p = 0.009$), and CCRT (OR: 4.091, 95%CI: 1.331–12.572, $p = 0.014$) were independent prognosticators of SARP (Table 4). These factors were then utilized in the nomogram building. Since a great many patients in our cohort received sequential chemoradiotherapy (SCRT), a subgroup multivariate analysis for this group of patients was also conducted. The result indicated that, for patients with SCRT, tlMD (OR: 1.007, 95%CI: 1.001–1.014, $p = 0.026$) and ilV_5 (OR: 1.085, 95%CI: 1.005–1.171, $p = 0.037$) were still the predictors of SARP, which was in accordance with the result in the total cohort.

Development and validation of the nomogram

Based on the multivariate logistic regression coefficients, a predictive model was visually presented as a nomogram (Fig. 1). The ROC curves of tlMD, ilV_5, CCRT, and the nomogram are shown in Fig. 2a. The predictive model showed an excellent AUC of 0.842 (95%CI: 0.759–0.904) by ROC, which was much higher than each parameter alone (tlMD: 0.769, 95%CI: 0.679–0.845; ilV_5: 0.744, 95%CI: 0.651–0.822; CCRT: 0.661, 95%CI: 0.564–0.749). The optimal threshold values (dose–volume constraints) of tlMD and ilV_5 were >10.8 Gy and >64.9%, respectively (Table 4). The nomogram showed great prediction efficiency (sensitivity: 73.1%, specificity: 83.1%). Also, a calibration curve showed favorable consistency between the predicted SARP and the actual observation (Fig. 2b), and DCA showed satisfactory positive net benefits of the nomogram among most of the threshold probabilities, indicating favorable potential clinical effect of the model (Fig. 2c).

Discussion

Several studies have demonstrated that PORT is associated with improved survival for postoperative patients with NSCLC with positive section margins or upstaging to N2 [24,25]. In the present study, our data indicated that tlMD, ilV_5, and CCRT were the independent prognosticators of SARP among patients with NSCLC receiving PORT. To the best of our knowledge, for the first time, we have developed a nomogram predicting the occurrence of SARP. The internal validation of the nomogram demonstrated its superiority compared with any single dosimetric or clinical factor alone.

For patients with locally advanced NSCLC treated with definitive chemo-radiotherapy, the NCCN recommended lung dose–volume constraints for conventionally fractionated radiation therapy: $V_{20} \leq 35\%$, $V_5 \leq 65\%$, and MLD $\leq$20 Gy [2]. However, there is still no principle or recommendation for evidence-based medicine for the dose limits of PORT. In present study, tlMD (>10.8 Gy) and ilV_5 (>64.9%) showed significant associations with SARP incidence in this cohort. One previous study also indicated that V_5 and MLD were independent predictors for grade $\geq$3 RP [26]. Although only 25.4% and 28.4% patients in that study had prior thoracic surgery and chemotherapy; the predictive values of these two dosimetric factors were in accordance with our findings. Notably, lung V_5 was also found as a predicator of radiation induced lung damage in extensive stage small cell lung cancer patients [27]. In addition, in mediastinal lymphoma and esophageal cancer patients treated with RT, lung V_5 still showed its value in predicting RP [28–30]. These findings hinted that V_5 might play a critical role in the development of RP.

In our study, total/ipsilateral/contralateral lung $D_{2\%}$ and the dosimetric parameters of heart (V_{10-50}) were not significant predictors of SARP. A possible explanation of the results was that, unlike those studies among loco-advanced NSCLC patients or mediastinal tumors [11,12,21,28], there was no bulky GTV embedded by normal lung or near the heart in our population.

Our results indicated that patients with CCRT were more likely to develop RP than those receiving SCRT. This finding was consistent with the results of other studies comparing CCRT vs SCRT in patients with unresected NSCLC [31,32]. We suggest that for patients treated with CCRT, the therapeutic schedule should be given with more comprehensive care to reduce or avoid treatment toxicities.

Recently, Boonyawan et al. published a study with the largest sample size to date (199 cases) predicting the occurrence of grade

Table 2
Univariate analysis of the DVH parameters and clinical factors in predicting SARP.

		With SARP (n = 26)	Without SARP (n = 83)	Univariate analysis	
		Median (IQR)	Median (IQR)	OR (95%CI)	p value
DVH parameters					
Total lungs					
V_5 (%)		43.2 (36.8–49.9)	41.3 (34.3–49.5)	1.001 (0.987–1.014)	0.927
V_{10} (%)		32.3 (23.3–37.7)	28.6 (23.5–36.2)	1.022 (0.981–1.064)	0.291
V_{20} (%)		22.4 (20.6–24.7)	19.5 (16.5–22.1)	1.104 (1.018–1.197)	0.017
V_{30} (%)		12.4 (9.7–15.7)	12.0 (9.1–14.9)	1.034 (0.960–1.115)	0.378
MD (cGy)		1184.1 (1044.4–1381.6)	1027.6 (880.9–1126.5)	1.005 (1.002–1.007)	0.001
$D_{2\%}$ (Gy)		62.3 (58.6–63.4)	62.20 (57.90–64.0)	0.981 (0.863–1.115)	0.768
Contralateral lung					
V_5 (%)		33.6 (21.2–43.8)	28.8 (21.6–40.3)	1.021 (0.994–1.049)	0.124
V_{10} (%)		20.7 (6.1–27.2)	15.8 (6.2–21.5)	1.025 (0.997–1.054)	0.085
V_{20} (%)		5.4 (2.8–16.2)	5.1 (2.9–12.6)	1.030 (0.987–1.075)	0.178
V_{30} (%)		3.7 (2.3–10.9)	3.0 (2.3–7.4)	1.048 (0.957–1.148)	0.308
MD (cGy)		524.7 (345.9–767.3)	488.0 (349.2–643.7)	1.000 (0.998–1.002)	0.733
$D_{2\%}$ (Gy)		43.10 (40.80–45.0)	44.10 (41.10–45.6)	1.032 (0.871–1.222)	0.715
Ipsilateral lung					
V_5 (%)		74.4 (71.0–76.7)	63.2 (50.4–74.0)	1.095 (1.042–1.152)	0.001
V_{10} (%)		51.9 (41.4–62.7)	52.0 (40.4–61.3)	1.008 (0.975–1.042)	0.646
V_{20} (%)		39.5 (33.6–48.4)	38.0 (32.5–44.2)	1.026 (0.985–1.069)	0.220
V_{30} (%)		22.5 (20.5–27.7)	24.0 (18.7–28.8)	1.022 (0.976–1.070)	0.358
MD (cGy)		1722.9 (1560.0–2062.6)	1623.6 (1459.5–1809.5)	1.002 (1.000–1.003)	0.010
$D_{2\%}$ (Gy)		63.00 (59.60–63.7)	63.80 (56.40–64.9)	0.968 (0.851–1.100)	0.618
Heart					
V_{10} (%)		35.80 (33.30–40.9)	35.60 (33.80–43.1)	1.023 (0.935–1.120)	0.621
V_{20} (%)		27.80 (24.00–31.5)	27.50 (24.50–31.4)	0.994 (0.900–1.098)	0.913
V_{30} (%)		22.50 (19.70–25.4)	22.10 (21.10–23.0)	0.944 (0.803–1.109)	0.481
V_{40} (%)		15.40 (13.60–17.6)	15.20 (14.00–16.6)	0.934 (0.769–1.135)	0.495
V_{50} (%)		10.60 (9.30–12.0)	10.70 (9.70–13.3)	1.143 (0.904–1.446)	0.263
Radiation dose (Gy)		60.0 (50.0–62.0)	56.0 (50.0–62.0)	1.013 (0.941–1.092)	0.725
PTV (cm^3)		211.2 (152.7–305.3)	192.2 (148.9–310.5)	1.000 (0.997–1.003)	0.930
TLV (cm^3)		2505.3 (2279.1–3287.2)	2456.4 (2273.4–3332.3)	1.000 (1.000–1.001)	0.689
Clinical factors					
Age (y) (Continuous variable)	N (%)	52.0 (45.0–60.0)	54.5 (47.0–60.0)	1.015 (0.965–1.068)	0.571
34–45	26 (23.8)				
46–55	38 (34.9)				
56–65	39 (35.8)				
66–74	6 (5.5)				
Sex: male vs. female				0.862 (0.316–2.347)	0.771
ECOG: PS 1 vs. 0				0.906 (0.337–2.433)	0.844
Pathological diagnosis:					
Adenocarcinoma vs. non-adenocarcinoma				2.256 (0.770–6.606)	0.138
Tumor site: middle-lower vs. upper lobe				0.641 (0.250–1.641)	0.353
Laterality: left vs. right				2.074 (0.847–5.078)	0.110
Smoking status: yes vs. no				0.640 (0.260–1.574)	0.331
PF before RT: moderate vs. mild				0.449 (0.094–2.134)	0.314
T stage: T3/T4 vs. T1/T2				1.382 (0.571–3.343)	0.473
N stage: N2/ N3 vs. N0/ N1				1.313 (0.397–4.347)	0.655
Tumor stage: IIIA/ IIIB vs. IIA/IIB				0.561 (0.215–1.460)	0.236
Surgical margin: positive (R1/2) vs. negative (R0)				0.987 (0.432–2.253)	0.975
Radiotherapy technique: 3D-CRT vs. IMRT				0.685 (0.138–3.393)	0.643
Concurrent chemoradiotherapy: yes vs. no				3.912 (1.482–10.327)	0.006

DVH, dose–volume histogram; SARP, severe acute radiation pneumonitis; IQR, interquartile range; OR, odds ratio; 95% CI, 95% confidence interval; V_x, the percentage of the lung volume that received more than x Gy, respectively; MD, mean dose; $D_{2\%}$, the minimum dose of the 2% volume of lung; PTV, planning target volume; TLV, total lung volume; PF, pulmonary function; ECOG PS, Eastern Cooperative Oncology Group performance status; 3D-CRT: 3D-conformal radiation therapy; IMRT: intensity modulated radiation therapy.

Table 3
Spearman's rank correlation analyses among these factors with $p < 0.05$ in univariate logistic regression.

	tlMD	tlV_{20}	ilMD	ilV_5	CCRT
tlMD	1.000	0.845	0.358	0.257	0.116
tlV_{20}	0.845	1.000	0.324	0.224	0.064
ilMD	0.358	0.324	1.000	0.378	−0.065
ilV_5	0.257	0.224	0.378	1.000	0.084
CCRT	0.116	0.064	-0.065	0.084	1.000

tlV_{20}: total lung V_{20}; tlMD: total lung mean dose; ilV_5: ipsilateral lung V_5; ilMD: ipsilateral lung mean dose; CCRT: concurrent chemoradiotherapy.

Table 4
Multivariate and ROC analysis of the DVH parameters, clinical factor and nomogram model in predicting SARP.

	Multivariate analysis			ROC curve				
	Regression coefficient	OR (95%CI)	*p* value	AUC (95%CI)	Cutoff point	*p* value	Sensitivity	Specificity
DVH parameters								
Total lung MD (Gy)	0.003	1.003 (1.001–1.006)	0.013	0.769 (0.679–0.845)	10.8 Gy	<0.001	73.1	73.5
Ipsilateral lung V_5 (%)	0.081	1.084 (1.020–1.151)	0.009	0.744 (0.651–0.822)	64.9%	<0.001	96.2	51.8
Clinical factors								
CCRT: yes vs. no	1.409	4.091 (1.331–12.572)	0.014	0.661 (0.564–0.749)	–	0.002	73.1	59.0
*Nomogram**		–	–	0.842 (0.759–0.904)		<0.001	73.1	83.1

ROC curve: receiver operating characteristic curve; DVH: dose–volume histogram; SARP: severe acute radiation pneumonitis; OR: odds ratio; 95% CI: 95% confidence interval; AUC: the area under the curve; MD: mean dose; V_5: the percentage of lung volume that received more than 5 Gy; CCRT: concurrent chemoradiotherapy.
*The constant in the logistic regression equation is −11.123.
The logistic regression equation is: logit(p) = −11.123 + 0.003 × Total lung MLD (Gy) + 0.081 × Ipsilateral lung V_5 (%) + 1.409 × with CCRT.
The probability (P) of a patient to have SARP is $p = \frac{1}{1+\exp[-\text{logit}(p)]}$.

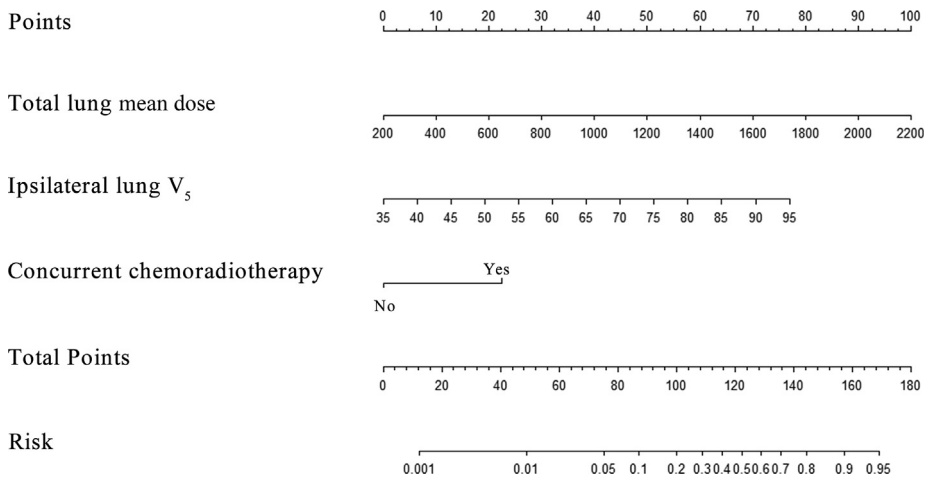

Fig. 1. Nomogram predicting the occurrence of SARP. For each individual patient, three lines are drawn upward to determine the points received from the three variables in the nomogram. The sum of these points is located on the "Total Points" axis, and a line is drawn downward to determine the likelihood of this patient to have SARP.

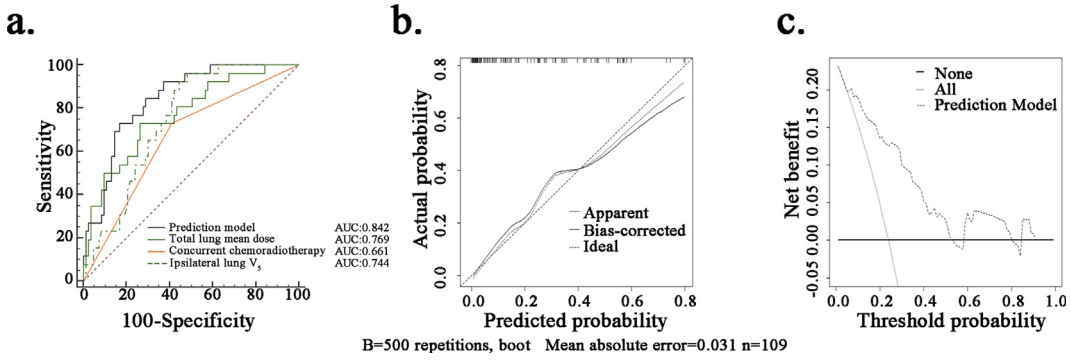

Fig. 2. a. ROC curves of total lung mean dose, ipsilateral lung V_5, CCRT, and the predictive model. b. Calibration curves of the nomogram predicting the occurrence of SARP. The x-axis and y-axis indicate the predicted and actual probabilities of having SARP, respectively. A perfect prediction would correspond to a slope of 1 (diagonal 45-degree broken line). c. Decision curves of the nomogram predicting the occurrence of SARP. The x-axis shows the threshold probabilities. The y-axis measures the net benefit, which is calculated by adding the true positives and subtracting the false positives. The horizontal line along the x-axis assumes that no patient will have SARP whereas the solid gray line assumes that all patients will have SARP at a specific threshold probability. The dashed line represents the net benefit of using the nomogram.

≥2 RP after PORT among patients with NSCLC [17]. In this interesting study, they found that lung V_{10} and V_{20} could predict grade ≥2 RP, while our findings suggested that tlMD and ilV5 were significantly associated with SARP. Several differences existed between these two studies, which might have affected the data interpretation. Firstly, three surgical methods were recorded in their research, including wedge resection (12%), lobectomy (76%), and pneumonectomy (12%), while all cases in our present study received lobectomy. Distinct surgical procedures would lead to different residual lung volumes, which might affect the RP incidence consequently. Secondly, 35 (17%) patients in their study received proton therapy, which might decrease the possibility of RP occurrence. Although Liao and her colleagues reported the similar rates of grade ≥3 RP (6.5% in IMRT and 10.5% in proton therapy group respectively) in a randomized study recently published [33], Chang et al. from the same institution reported an incidence of 1.6% (1/64) grade 2 RP among patients with NSCLC receiving CCRT (proton radiotherapy) [34]. Also, Hoppe et al. [35] and Nguyen

et al. [36] observed no RP and only 1.5% (2/134) grade 3 RP in patients receiving proton therapy and concurrent chemotherapy among the patients with inoperable NSCLC, respectively. However, the incidences of grade 3 or higher RP have been previously reported to be in a range of 9%–12% worldwide in patients with locally advanced NSCLC treated with CCRT (photon therapy) [37]. Thirdly, a quarter of patients in Boonyawan's study had not received chemotherapy, which was reported to be a risk factor of RP [38,39]. From our point of view, all patients in the present cohort received treatment that is more specific and consistent with the current NCCN guidelines (lobectomy and adjuvant treatment procedure) [2].

The study from Uno et al. found that the V_{13}, $V_{20,}$ or MLD might predict RP, but their data come from patients receiving salvage radiotherapy for recurrent NSCLC [14]. We also noticed that data had been published in 2009 [15] and 2012 [16] which found that the ipsilateral $V_{30} > 340\ cm^3$ as well as adjuvant chemotherapy and lung V_{20}–V_{40} were significantly correlated with grade $\geq$2 RP in patients receiving PORT. While, the population they analyzed was similar to the study of Boonyawan et al. [17], and a number of the patients had received pneumonectomy.

Recently, several biological factors have also been investigated and considered as the predictors of the development of RP. Researches showed that the increased TGF-β1 plasma level after RT, IL-6, IL-10, ACE and the single nucleotide polymorphisms (SNPs) in the TGF-β1, were reported to be associated with risk of RP in lung cancer patients [40–43]. From the perspective of precision medicine, a more comprehensive prediction model combining the individual genomic information, dosimetric, and clinical parameters should be developed in the future.

The statistical performance of the internal validation should be mentioned when interpreting the value of the present nomogram. So far, the external validation is the gold standard and should be obtained whenever possible. Unfortunately, even in some famous organizations, researchers had to perform an internal validation among the single-institutional population. Besides the ROC curve analysis, the calibration curve and DCA had been used in present study, which belong to the bootstrap validation methods. According to the opinion of the clinical statistician, in a relative small sample size, the bootstrap validation shows several advantages [44]. In a commentary published recently, the authors also recommend that the bootstrapping analysis was preferred when attempting the internal validation [45]. While in practice, as Balachandran et al. [46] stated, the performance and limitations of these predicting models need to be appreciated before being used in decision making with a rigorous scholarship.

Several limitations should be addressed here. Firstly, selective bias existed in the present study due to its retrospective nature. Secondly, the sample size of this study is relatively small, and more prospective studies are necessary. However, the treatment strategies of patients in the present study were in line with the recommendation of the current NCCN guidelines, and the data could still be helpful for oncologists making treatment decisions and TPS plan evaluation. Thirdly, although the internal validation showed that the present predictive model had a relatively excellent AUC of 0.842, the result would be more convincing if it had been verified by an external validation. To our knowledge, a large international phase 3 trial (Lung Adjuvant Radiotherapy Trial, Lung ART) evaluating PORT in patients with completely resected N2 stage NSCLC, is currently ongoing [47]. Although the outcome has not been reported, we look forward to their reports on clinical benefits, treatment-related toxicities, and other translational work.

In conclusion, the multivariate analysis identified the tlMD (>10.8 Gy), ilV_5 (>64.9%), and CCRT as independent risk factors for acute grade $\geq$3 RP in patients with NSCLC receiving PORT. A predictive nomogram was built and its efficiency confirmed by internal validation. Although needing further verification, our work still has a value for evaluation of treatment plans, and forecasting the presence of SARP among such patients.

Conflict of interest

All authors declare no conflict of interest.

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Authors' contributions

Youling Gong conceived and designed the study. Xin Tang, Yanying Li, Xue Tian and Youling Gong collected the data. Xin Tang and Youling Gong analyzed, interpreted the data and drafted the article. Xiaojuan Zhou, Yongsheng Wang, Meijuan Huang, Li Ren, Lin Zhou, Jianxin Xue, Zhenyu Ding, Jiang Zhu, Yong Xu, Feng Peng, Jin Wang and You Lu revised the paper critically. All authors approved the final version to be submitted.

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