ORIGINAL RESEARCH

Development and Validation of Nomograms for Predicting Pneumonia in Patients with COVID-19 and Lung Cancer

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Background: COVID-19 has spread worldwide, becoming a global threat to public health and can lead to complications, especially pneumonia, which can be life-threatening. However, in lung cancer patients, the prediction of pneumonia and severe pneumonia has not been studied. We aimed to develop effective models to assess pneumonia after SARS-CoV-2 infection in lung cancer patients to guide COVID-19 management.

Methods: We retrospectively recruited 621 lung cancer patients diagnosed with COVID-19 via SARS-CoV-2 RT-PCR analysis in two medical centers and divided into training and validation group, respectively. Univariate and multivariate logistic regression analysis were used to identify independent risk factors of all-grade pneumonia and $\geq$ grade 2 pneumonia in the training group. Nomograms were established based on independent predictors and verified in the validation group. C-index, ROC curves, calibration curve, and DCA were used to evaluate the nomograms. Subgroup analyses in immunotherapy or thoracic radiotherapy patients were then conducted.

Results: Among 621 lung cancer patients infected with SARS-CoV-2, 203 (32.7%) developed pneumonia, and 66 (10.6%) were $\geq$ grade 2. Multivariate logistic regression analysis showed that diabetes, thoracic radiotherapy, low platelet and low albumin at diagnosis of COVID-19 were significantly associated with all-grade pneumonia. The C-indices of the prediction nomograms in the training group and validation group were 0.702 and 0.673, respectively. Independent predictors of $\geq$ grade 2 pneumonia were age, KPS, thoracic radiotherapy, platelet and albumin at COVID 19 diagnosis, with C-indices of 0.811 and 0.799 in the training and validation groups. In the thoracic radiotherapy subgroup, 40.8% and 11% patients developed all-grade and $\geq$grade 2 pneumonia, respectively. The rates in the immunotherapy subgroup were 31.3% and 6.6%, respectively.

Conclusion: We developed nomograms predicting the probability of pneumonia in lung cancer patients infected with SARS-CoV-2. The models showed good performance and can be used in the clinical management of COVID-19 in lung cancer patients. Higher-risk patients should be managed with enhanced protective measures and appropriate intervention.

Keywords: COVID-19, pneumonia, lung cancer, risk factor, nomogram

Introduction

In December 2019, the novel Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) spread rapidly throughout the world,[1] causing a global public health problem.[2] As the pandemic progressed and vaccination advanced, herd immunity enhanced and the proportion of severe cases and mortality gradually decreased over time, and the majority of infected individuals had relatively mild disease without signs of pneumonia. However, patients with underlying disease are still at elevated risk of complications, especially pneumonia.[3]

According to the updated global cancer report, lung cancer is ranked the second place in terms of incidence and first in cancer-related mortality rate.[4] Based on the characteristics of pulmonary neoplasms and treatment-related toxicity, it is therefore highly important to focus on advancing the management of COVID-19 pneumonia in lung cancer patients, especially those who received immunotherapy or thoracic radiotherapy (TRT). Immunotherapy represented by immune checkpoint inhibitors (ICIs) impacts the risk of developing pneumonia due to its regulation of immune cells and pro-inflammatory factors,[5,6] immunotherapy against lung cancer decrease COVID-19 severity and incidence of pneumonia to some extent.[7] Radiation may injure normal lung tissue and radiotherapy enhances the rate of pneumonia after SARS-CoV -2 infection.[8,9] At present, there is still a lack of safe and effective therapeutic drugs for COVID-19 in the clinic. Once lung cancer patients develop COVID-19 pneumonia, the poor response to conventional therapy will make condition difficult to control and threaten patients' life. Thus, it is urgently needed to identify the risk factors that aid in predicting COVID-19 pneumonia, provide better protection and strict surveillance to high-risk patients to decrease pneumonia occurrence, avoid delay in anti-neoplastic treatment, and reduce mortality. Building a reliable prediction model is currently important for clinical management of lung cancer patients with COVID-19.

The present studies found that lung cancer patients infected with SARS-CoV-2 have higher rates of severe disease and death than the general population.[10] The comparison of lung cancer patients' performance status before and after COVID-19 period showed a statistically significant worse score in the COVID-19 period.[11] Increased age, comorbidities, and advanced disease were associated with increased risk of death in lung cancer patients, while race and pathologic type were unrelated.[12–14] Studies in the overall population have found that hematological parameters such as lactate dehydrogenase, platelets, and albumin were reported as independent risk factors of severe COVID-19.[15] In solid tumor patients, age and anti-tumor therapy were predictors for COVID-19 death.[16] However, there are no studies predicting of COVID-19 pneumonia in patients with lung cancer.

A nomogram is a user-friendly graphical prediction model that can quantify an individual's risk by integrating multiple risk factors.[17] In this study, we aimed to develop easy-to-use and effective models to assess the risk of pneumonia and moderate-severe pneumonia after SARS-CoV-2 infection in lung cancer patients to stratify patients. These models can be used to assist clinicians in identifying high-risk patients and selecting appropriate treatment strategies.

Materials and Methods

Study Population

This retrospective study evaluated patients visiting Shandong Cancer Hospital and Shandong University Qilu Hospital between December 2022 and January 2023. The enrolled criteria for patient are list as follows: 1) Patients with histologically or cytologically confirmed lung cancer (tumor stage and pathologic types were not restricted); 2) Confirmed COVID-19 detecting via SARS-COV-2 nucleic acid in nasopharyngeal and oropharyngeal swab; 3) Age > 18 years. The exclusion criteria are as follows: 1) Patients with a history of other primary malignant tumors; 2) Patients with active pneumonia at baseline; 3) It was assessed as non-COVID-19 pneumonia; 4) It was not possible to ascertain the presence of pneumonia. This study was approved by the Ethics Committee of Shandong Cancer Hospital and complies with the Declaration of Helsinki.

Data Collection

Baseline demographic (age, sex, BMI, Karnofsky Performance Scale score, smoking index, and comorbidities), clinico-pathological (histology, stage, anti-cancer therapy, and hematological data) and follow-up data were collected in detail from the electronic medical records according to a unified form. Baseline was defined as 2 to 4 weeks prior to COVID-19. Hematological data (lymphocyte, platelet, white blood cell, red blood cell, hemoglobin, neutrophil, monocyte, albumin, lactate dehydrogenase, and carcinoembryonic antigen) within a week after COVID-19 diagnosis were also collected, and changes in hematological data were calculated (diagnostic value minus baseline value). Pneumonia and moderate-severe pneumonia (≥ grade 2) were diagnosed and distinguished mainly based on computerized tomography (CT) images, chest X-ray, clinical symptoms, medical history, and laboratory tests according to the World Health Organization (WHO) criteria.[18] The CT scan was performed by using 64-slice spiral CT (Siemens Medical Systems, Germany). To minimize sampling bias, two authors collected the data independently and cross-checked the data with medical personnel.

Model Training and Validation

Patients from Shandong Cancer Hospital were regarded as the training group and patients from Shandong University Qilu Hospital as the validation group. Nomograms of pneumonia and moderate-severe (≥ grade 2) pneumonia were established in the training group and verified in the validation group. We also performed subgroup analysis for the subset who had undergone immunotherapy or thoracic radiotherapy.

Statistical Analysis

Continuous variables are expressed as mean and standard deviation (SD), and categorical variables are expressed in frequency and percentage. In statistical analysis, simple deletion method is adopted to deal with missing data. In the training group, univariate logistic regression analysis was used to access potential risk factors, and variables with p-values less than 0.05 were incorporated into multivariate logistic regression analysis after excluding those with a Pearson correlation coefficient more than 0.4. Factors with p-values less than 0.1 were considered to be important predictors of COVID-19 pneumonia and included to establish the nomogram model. The concordance index (C-index), calibration curve, the area under the receiver operation curve (AUC), and decision curve analysis (DCA) were applied to evaluate the discrimination and clinical efficacy of the model. Roc curve and correction curve are used to evaluate nomogram correction graphically. In the validation group, C-index was used to verify the accuracy of the model. All analyses were performed using the STATA/MP 17.0 and R 4.2.1.

Results

The Demographic and Clinicopathological Features of Patients

Visits were routinely test for COVID-19 nucleic acid detection between December 2022 and January 2023. We retrospectively analyzed 716 lung cancer patients who were diagnosed with COVID-19 during this time period. As shown is Figure 1, patients were selected according to strict inclusion and exclusion criteria: 58 patients due to lack of baseline data; 2 due to age younger than 18 years; 2 due to no clear pathological findings; 24 due to other primary tumor; and 9 patients had pneumonia due to other causes. Ultimately, a total of 621 patients were enrolled for analysis, including 556
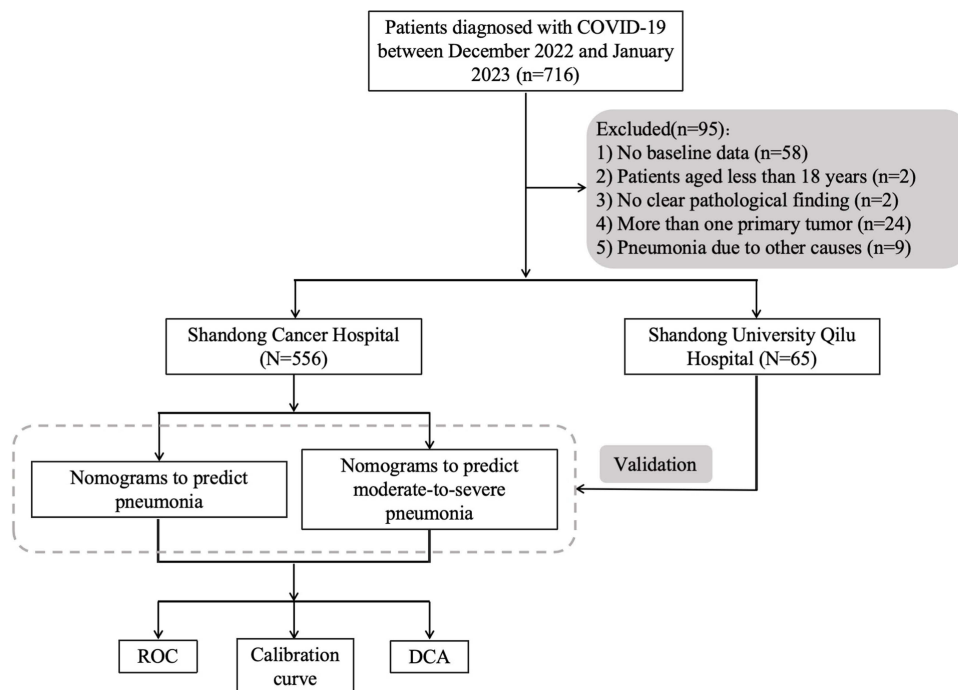

Figure 1 Flow diagram.

patients from Shandong Cancer Hospital, who were divided into the training group, and 65 patients from Shandong University Qilu Hospital, who were divided into the external validation group.

A total of 203 (32.7%) patients developed COVID-19 pneumonia. Among them, 140 patients did not have pneumonia at baseline and developed pneumonia after SARS-CoV-2 infection. Sixty-three patients had old lesions in the lungs at baseline, and pneumonia was significantly aggravated after SARS-CoV-2 infection. According to the CT images, chest X-ray, clinical course, and hematological findings, 2 radiologists and clinicians with over 20 years' experience jointly determined that 203 patients developed COVID-19 pneumonia. The World Health Organization's (WHO) grading criteria are used to grade pneumonia. Sixty-six patients were graded as moderate-severe pneumonia.

A 5-month follow-up of 203 patients with pneumonia showed that 99 patients recovered completely and 78 patients had pulmonary sequelae, including pulmonary fibrosis and chronic pneumonia. Thirteen patients died because of pneumonia and 13 patients were lost to follow-up.

Independent Risk Factors for Pneumonia and Moderate-Severe Pneumonia

To investigate factors independently affecting COVID19 pneumonia, multivariate logistic regression analysis was performed on all parameters that were statistically significant on univariate analysis in the training group, as shown in Table 1. The results showed that diabetes (OR = 4.259, p < 0.001), thoracic radiotherapy (OR = 2.799, p < 0.001), platelet at baseline (OR = 0.997, p = 0.055), and albumin (OR = 0.921, p = 0.006) at diagnosis of COVID-19 were independent risk factors for pneumonia.

Table 2 shows the analysis of moderate-severe pneumonia, with age (OR = 1.058, p = 0.034), Karnofsky Performance Scale score (KPS) (KPS ≤ 70 vs ≥90, OR = 8.504, p = 0.002), thoracic radiotherapy (OR = 2.569, p = 0.010), platelet (OR = 0.994, p=0.031) and albumin (OR = 0.892, p = 0.058) at diagnosis of COVID-19 as independent risk factors for moderate-severe pneumonia.

Table 1 Logistic Regression Analysis of Risk Factors for Pneumonia in the Training Group

Parameters	Pneumonia (N=167, %)	Non-Pneumonia (N=389, %)	P value (Univariate Analysis)	P value (Multivariate Analysis)
Age (years)	62.68 ± 9.36	60.41 ± 9.92	0.013	0.635
Sex			0.818	
Male	116 (69)	274 (70)		
Female	51 (31)	115 (30)		
BMI (kg/m²)	24.26 ± 3.33	23.97 ± 3.46	0.361	
KPS				
≧90	78 (46)	206 (53)	reference	
70	8 (5)	17 (4)	0.235	
<70	81 (49)	166 (43)	0.115	
Smoking index				
≤200	9 (12)	37 (20)	0.396	
201–399	4 (5)	7 (4)		
≥400	63 (83)	142 (76)		
Diabetes			0.000	0.000
Yes	29 (17)	24 (6)		
No	138 (83)	365 (94)		
Coronary heart disease			0.234	
Yes	14 (8)	22 (6)		
No	153 (92)	367 (94)		
COPD			0.490	
Yes	2 (1)	8 (2)		
No	165 (99)	381 (98)		

(*Continued*)

Table 1 (Continued).

Parameters	Pneumonia (N=167, %)	Non-Pneumonia (N=389, %)	P value (Univariate Analysis)	P value (Multivariate Analysis)
Emphysema				0.108
Yes	48 (29)	75 (19)	0.014	
No	119 (71)	314 (81)		
Tumor histology				
Adenocarcinoma	75 (45)	203 (52)	reference	
Squamous carcinoma	36 (21)	74 (19)	0.259	
Small cell neuroendocrine carcinoma	46 (27)	88 (22)	0.153	
Large cell neuroendocrine carcinoma	1 (1)	6 (2)	0.901	
Adenosquamous carcinoma	2 (1)	4 (1)	0.729	
Mixed carcinoma	5 (3)	6 (2)	0.190	
Unknown	3 (2)	8 (2)	0.378	
T stage				
0	2 (1)	1 (1)	reference	
1	29 (17)	77 (20)	0.180	
2	44 (27)	126 (32)	0.158	
3	34 (20)	67 (17)	0.270	
4	53 (32)	113 (29)	0.241	
Unknown	5 (3)	5 (1)	-	
N stage				
0	32 (19)	74 (19)	reference	
1	17 (10)	36 (9)	0.808	
2	56 (34)	149 (39)	0.594	
3	60 (36)	126 (32)	0.714	
Unknown	2 (1)	4 (1)	-	
M stage				
0	75 (45)	156 (40)	0.277	
1	92 (55)	233 (60)		
Clinical stage				
I	15 (9)	33 (8)	reference	
II	7 (4)	17 (4)	0.856	
III	52 (31)	102 (27)	0.747	
IV	93 (56)	234 (60)	0.688	
Unknown	0	3 (1)	0.521	
Chemotherapy				
No	22 (13)	59 (15)	0.479	
Yes	145 (87)	330 (85)		
Thoracic radiotherapy				0.000
No	85 (51)	266 (68)	0.000	
Yes	82 (49)	123 (32)		
Concurrent chemoradiotherapy				0.263
No	99 (59)	267 (69)	0.034	
Yes	68 (41)	122 (31)		
Immunotherapy				
No	92 (55)	217 (56)	0.854	
Yes	75 (45)	172 (44)		
TKI				
No	121 (75)	281 (72)	0.976	
Yes	46 (25)	108 (28)		

(*Continued*)

Table 1 (Continued).

Parameters	Pneumonia (N=167, %)	Non-Pneumonia (N=389, %)	P value (Univariate Analysis)	P value (Multivariate Analysis)
Bevacizumab				
No	145 (87)	319 (82)	0.167	
Yes	22 (13)	70 (28)		
Pre-infection lymphocyte (10^9/L)	1.13 ± 0.60	1.29 ± 0.59	0.005	0.636
Pre-infection monocyte (10^9/L)	0.50 ± 0.29	0.52 ± 0.29	0.499	
Pre-infection lymphocyte/monocyte ratio	3.19 ± 4.45	3.31 ± 3.45	0.836	
Pre-infection platelet (10^9/L)	206.97 ± 77.71	231.25 ± 80.71	0.002	0.055
Pre-infection white blood cell (10^9/L)	5.74 ± 2.85	6.18 ± 3.01	0.126	
Pre-infection red blood cell (10^{12}/L)	4.01 ± 0.71	4.11 ± 0.67	0.138	
Pre-infection hemoglobin (g/L)	123.94 ± 20.37	125.67 ± 19.15	0.364	
Pre-infection neutrophil (10^9/L)	4.00 ± 2.55	4.24 ± 2.78	0.379	
Pre-infection albumin (g/L)	41.49 ± 5.17	41.50 ± 4.99	0.977	
Pre-infection lactate dehydrogenase (U/L)	259.90 ± 250.62	250.46 ± 265.95	0.724	
Pre-infection carcinoembryonic antigen (ng/mL)	25.21 ± 113.81	107.54 ± 762.76	0.155	
Post-infection lymphocyte (10^9/ L)	1.07 ± 0.60	1.20 ± 0.61	0.024	
Post-infection monocyte (10^9/ L)	0.56 ± 0.33	0.57 ± 0.33	0.913	
Post-infection lymphocyte/monocyte ratio	2.62 ± 2.64	2.61 ± 2.00	0.740	
Post-infection platelet (10^9/L)	211.35 ± 86.66	223.81 ± 82.53	0.119	
Post-infection white blood cell (10^9/L)	6.18 ± 3.46	6.29 ± 4.10	0.769	
Post-infection red blood cell (10^{12}/L)	3.95 ± 0.66	4.06 ± 0.65	0.072	
Post-infection hemoglobin (g/L)	121.25 ± 18.58	124.78 ± 18.44	0.046	0.462
Post-infection neutrophil (10^9/L)	4.44 ± 3.13	4.39 ± 3.80	0.890	
Post-infection lactate dehydrogenase (U/L)	284.19 ± 276.48	267.55 ± 504.40	0.705	
Post-infection albumin (g/L)	39.44 ± 5.71	41.24 ± 5.23	0.001	0.006
Post-infection carcinoembryonic antigen (ng/mL)	59.23 ± 299.98	194.07 ± 2894.17	0.633	

Notes: Statistically significant parameters in univariate logistic regression analysis were performed with Pearson correlation test, and those with coefficient more than 0.4 were eliminate. Multivariate logistic regression analysis was performed for the remaining parameters.

Table 2 Logistic Regression Analysis of Risk Factors for Moderate-Severe Pneumonia in the Training Group

Variables	Moderate-severe pneumonia (N=44, %)	Non-moderate-severe pneumonia (N=512,%)	P value (Univariate Analysis)	P value (Multivariate Analysis)
Age (years)	66.68 ± 9.10	60.61 ± 9.72	0.000	0.034
Sex			0.284	
Male	34 (77)	356 (70)		
Female	10 (23)	156 (30)		
BMI (kg/m²)	23.67 ± 3.68	24.09 ± 3.40	0.432	
KPS				
≧90	13 (30)	271 (53)	reference	
70	5 (11)	20 (4)	0.018	0.136
<70	26 (59)	221 (43)	0.000	0.002
Smoking index			0.106	
≤200	2 (9)	44 (18)		
201–399	2 (9)	35 (15)		
≥400	19 (82)	160 (67)		

(Continued)

Table 2 (Continued).

Variables	Moderate-severe pneumonia (N=44, %)	Non-moderate-severe pneumonia (N=512,%)	P value (Univariate Analysis)	P value (Multivariate Analysis)
Diabetes			0.047	0.158
Yes	4 (9)	45 (9)		
No	40 (91)	467 (91)		
Coronary heart disease			0.923	
Yes	3 (7)	33 (6)		
No	41 (93)	479 (94)		
COPD			-	
Yes	0 (0)	10 (2)		
No	44 (100)	502 (98)		
Emphysema			0.632	
Yes	11 (25)	112 (22)		
No	33 (75)	400 (78)		
Tumor histology				
Adenocarcinoma	14 (32)	264 (52)	reference	
Squamous carcinoma	9 (20)	101 (20)	0.241	
Small cell neuroendocrine carcinoma	17 (39)	116 (22)	0.007	
Large cell neuroendocrine carcinoma	0 (0)	5 (1)	-	
Adenosquamous carcinoma	0 (0)	8 (1)	-	
Mixed carcinoma	2 (5)	9 (2)	0.084	
Unknown	1 (2)	9 (2)	0.369	
T stage				
0	1 (2)	3 (1)	reference	
1	5 (11)	101 (20)	0.077	
2	12 (27)	158 (31)	0.135	
3	12 (27)	89 (17)	0.299	
4	11 (25)	155 (30)	0.122	
Unknown	3 (8)	6 (1)	-	
N stage				
0	6 (14)	101 (20)	reference	
1	5 (11)	48 (9)	0.382	
2	18 (40)	187 (36)	0.332	
3	13 (30)	173 (34)	0.659	
Unknown	2 (5)	3 (1)	-	
M stage				
0	19 (43)	212 (41)	0.807	
1	25 (57)	300 (59)		
Clinical stage				
I	1 (2)	45 (9)	reference	
II	2 (5)	21 (4)	0.246	
III	16 (36)	140 (27)	0.105	
IV	25 (57)	302 (59)	0.188	
Unknown	0 (0)	4 (1)	-	
Metastatic sites				
Bone	9 (20)	139 (27)	0.337	
Lung/pleura	10 (23)	99 (19)	0.587	
Brain	9 (20)	118 (23)	0.695	
Liver	3 (7)	53 (10)	0.459	

(*Continued*)

Table 2 (Continued).

Variables	Moderate-severe pneumonia (N=44, %)	Non-moderate-severe pneumonia (N=512,%)	P value (Univariate Analysis)	P value (Multivariate Analysis)
Chemotherapy				
No	7 (16)	74 (14)	0.745	
Yes	37 (84)	438 (86)		
Pemetrexed				
No	36 (82)	320 (62)	0.012	0.235
Yes	8 (18)	192 (38)		
Thoracic radiotherapy				0.010
No	21 (48)	304 (59)	0.032	
Yes	23 (52)	208 (41)		
Concurrent chemoradiotherapy				
No	26 (59)	340 (66)	0.346	
Yes	18 (41)	172 (34)		
Immunotherapy				
No	30 (68)	279 (54)	0.079	
Yes	14 (32)	233 (46)		
TKI				
No	33 (75)	369 (72)	0.666	
Yes	11 (25)	143 (28)		
Bevacizumab				
No	39 (89)	425 (83)	0.334	
Yes	5 (11)	87 (17)		
Pre-infection lymphocyte (10^9/L)	0.86 ± 0.55	1.27 ± 0.59	0.000	0.269
Pre-infection monocyte (10^9/L)	0.48 ± 0.24	0.52 ± 0.29	0.485	
Pre-infection lymphocyte/monocyte ratio	2.16 ± 1.52	3.36 ± 3.85	0.014	0.481
Pre-infection platelet (10^9/L)	186.53 ± 85.84	227.08 ± 79.53	0.004	
Pre-infection white blood cell (10^9/L)	5.04 ± 2.29	6.13 ± 3.01	0.032	
Pre-infection red blood cell (10^{12}/L)	3.79 ± 0.84	4.11 ± 0.67	0.008	
Pre-infection hemoglobin (g/L)	118.72 ± 21.68	125.66 ± 19.29	0.041	
Pre-infection neutrophil (10^9/L)	3.60 ± 2.09	4.21 ± 2.75	0.195	
Pre-infection albumin (g/L)	38.87 ± 4.91	41.71 ± 5.00	0.002	
Pre-infection lactate dehydrogenase (U/L)	361.23 ± 491.13	245.80 ± 236.37	0.069	
Pre-infection carcinoembryonic antigen (ng/mL)	17.79 ± 35.79	88.04 ± 666.73	0.486	
Post-infection white blood cell (10^9/L)	6.71 ± 4.70	6.21 ± 3.82	0.418	
Post-infection red blood cell (10^{12}/L)	3.75 ± 0.87	4.05 ± 0.63	0.003	0.143
Post-infection hemoglobin (g/L)	116.43 ± 22.87	124.31 ± 17.97	0.007	
Post-infection lymphocyte (10^9/ L)	0.86 ± 0.55	1.19 ± 0.61	0.001	
Post-infection monocyte (10^9L)	0.58 ± 0.44	0.56 ± 0.32	0.754	
Post-infection lymphocyte/monocyte ratio	2.17 ± 2.06	2.66 ± 2.22	0.152	
Post-infection platelet (10^9/L)	179.27 ± 94.59	223.88 ± 81.94	0.001	0.031
Post-infection neutrophil (10^9/L)	5.20 ± 4.17	4.33 ± 3.54	0.135	
Post-infection lactate dehydrogenase (U/L)	384.24 ± 485.06	262.78 ± 441.88	0.181	
Post-infection carcinoembryonic antigen (ng/mL)	105.88 ± 501.22	154.87 ± 2482.81	0.914	
Post-infection albumin (g/L)	36.38 ± 6.60	41.16 ± 5.18	0.000	0.058

Construction and Validation of Discrimination Nomograms

Based on the predictors of pneumonia, the C-index of the constructed nomogram was 0.702 (0.648–0.757). The calibration curve showed that the predicted results were in good agreement with the observed results, and the DCA

showed that the model had a good net benefit (Figure 2). The C-index for the validation group was 0.673 (0.532–0.814), demonstrating the stability of the model.

As shown in Figure 3, a nomogram was also constructed on the basis of independent predictors of moderate-severe pneumonia, and the C-index was 0.811 (0.738–0.884). Calibration curve and DCA show that the nomogram had good discrimination and achieved preferable prediction accuracy than pneumonia. The external verification performance was also satisfactory, with a C-index of 0.799 (0.677–0.921).

Subgroup Analysis

Both thoracic radiotherapy and immunotherapy may affect the occurrence of pneumonia, and thoracic radiotherapy is an independent risk factor for pneumonia. Therefore, subgroup analyses were performed in patients who had previously received thoracic radiotherapy or immunotherapy separately. Among 218 patients who had previously received thoracic radiotherapy, 89 (40.8%) developed pneumonia, and 24 (11.0%) developed moderate-severe pneumonia, which were higher than the general population. Patients with emphysema were more likely to develop all-grade pneumonia (OR = 1.945, p = 0.036). The risk of moderate-severe pneumonia increases with higher single doses (>2Gy vs ≤2Gy, OR =
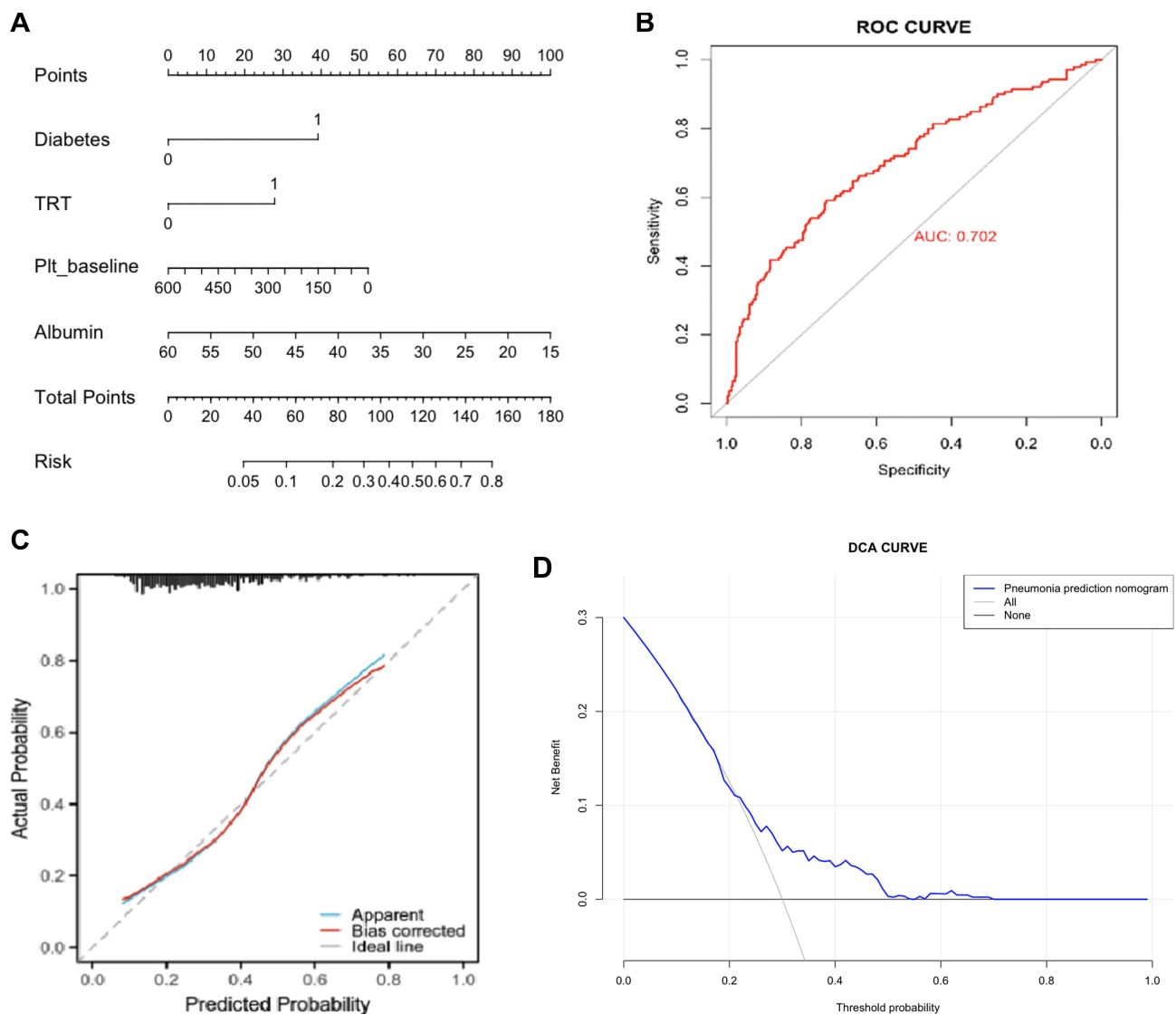
Figure 2 Nomogram (**A**), ROC (**B**), calibration curve (**C**), and DCA (**D**) of training group for pneumonia prediction.
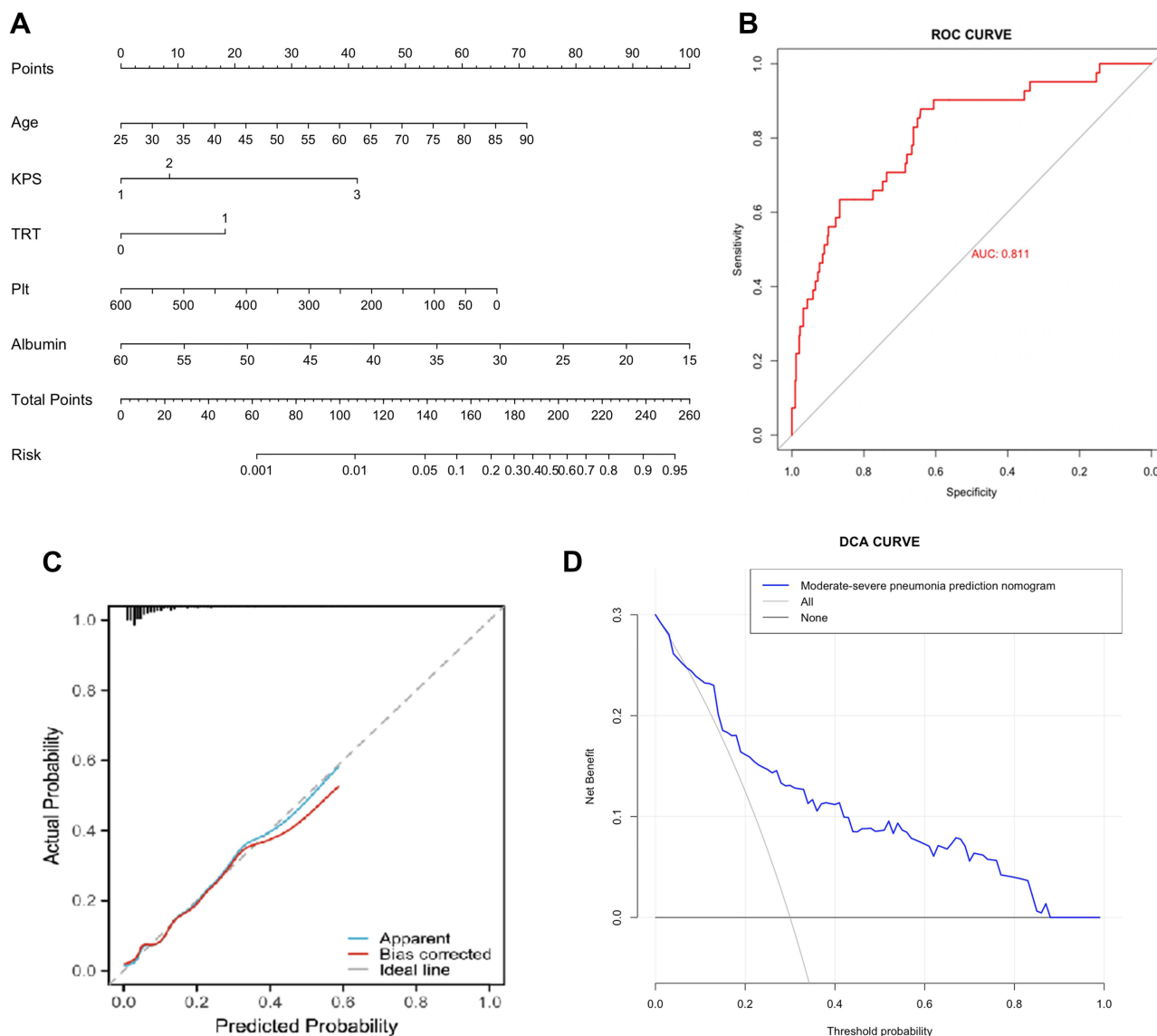
Figure 3 Nomogram (**A**), ROC (**B**), calibration curve (**C**), and DCA (**D**) of training group for moderate-severe pneumonia prediction.

4.575, p = 0.002). Two hundred and seventy-two had received immunotherapy, including programmed cell death 1 (PD-1) and programmed death ligand 1 (PD-L1) inhibitors. Twenty-six patients had received more than one line of immunotherapy. The median number of immunotherapy cycle was 4. Pneumonia occurred in 85 patients (31.3%) and 18 (6.6%) developed moderate-severe pneumonia. Patients who received more immunotherapy cycles had a lower risk of pneumonia (OR = 0.923, p = 0.020). Patients with low lymphocytes (OR = 0.247, p = 0.033) and high neutrophils (OR = 1.167, p = 0.006) at diagnosis of COVID-19 were more likely to develop moderate-severe pneumonia. Patients with a low lymphocyte/monocyte ratio at baseline (OR = 0.546, p = 0.037) or diagnosis of COVID-19 (OR = 0.448, p = 0.015) were more likely to develop moderate-severe pneumonia.

Discussion

COVID-19 is an acute infectious disease caused by the novel coronavirus (SARS-CoV-2) that spreads rapidly, imposing a significant burden on human health and healthcare systems.[19] Previous studies have reported the hospitalization mortality of 1.4–4.3%.[20] Lung cancer patients infected with SARS-CoV-2 experience more severe conditions, with a mortality rate ranging from 25% to 36%.[13,21,22] Identifying high-risk groups and implementing specific preventive

measures for them holds significant importance.[23,24] To our knowledge, this study is the first to construct a visual predictive model for lung cancer patients progressing to pneumonia, particularly moderate-severe pneumonia, after SARS-CoV-2 infection. The nomograms established in this study can effectively predict the risk of all-grade pneumonia and moderate-severe pneumonia, thereby identifying high-risk individuals for COVID-19 pneumonia, which holds significant clinical application potential.

In our study, diabetes at baseline was identified as an independent risk factor for pneumonia and it is speculated that SARS-CoV-2 infection might lead to severe fluctuations in blood glucose levels among diabetic patients, creating a vicious cycle, possibly associated with the lowered immunity in these individuals. Previous research has indicated higher probabilities of complications and mortality among diabetic patients,[25–27] with some studies considering diabetes as a prognostic risk factor for COVID-19.[28] Keynote-001 clinical trial found that patients with a history of thoracic radiotherapy have a higher overall frequency of treatment-related pulmonary toxicity, possibly linked to radiation-induced damage to normal lung tissues and changes in the immune microenvironment.[29] This study found that patients previously treated with thoracic radiotherapy were more prone to developing COVID-19 pneumonia. Thrombocytopenia emerged as another independent risk factor, likely associated with thrombocytopenia-related critical illnesses, commonly seen in COVID-19 patients with organ dysfunction or compromised physiological functions.[30] Hypoalbuminemia represents poor nutritional status in patients, thus understanding the heightened risk of pneumonia among this subgroup.

Advanced age, low KPS, history of thoracic radiotherapy, platelet and albumin at diagnosis of COVID-19 were identified as independent risk factors for patients developing moderate-severe pneumonia. Advanced age and low KPS both signify poor physical condition. Some studies have found that elderly patients are more prone to complications,[20] and advanced age is an independent risk factor for severe illness.[31]

The incidence of pneumonia increases among patients with a history of thoracic radiotherapy, and the occurrence of moderate-severe pneumonia rises with the increase in the single radiation dose, suggesting clinicians should use high-dose radiotherapy cautiously. While smoking is not a risk factor, patients with emphysema, which is one of the consequences of smoking, were more prone to developing COVID-19 pneumonia after receiving thoracic radiotherapy.[32]

In our study, the incidence of pneumonia in the subgroup undergoing immunotherapy was slightly lower than the general population, with the treatment cycle being a protective factor, potentially linked to enhanced antiviral T-cell immune response. Another study also indicated that immunotherapy did not increase the risk of severe infections or cytokine storms.[7] Patients receiving immunotherapy had a lower mortality rate than the general population.[33,34] Lymphocytes and neutrophils, respectively, act as risk and protective factors. Some studies have shown that lymphocyte count affects the prognosis of COVID-19 patients.[35] The specific mechanism might involve the effect of SARS-CoV-2 on T lymphocytes, where T lymphocyte damage becomes a crucial factor leading to patient deterioration.[36] Analysis of patient lymphocyte spectra showed decreased lymphocytes and increased neutrophils.[37] Neutrophils are important inflammatory cells that often exhibit immune cell response dysregulation and subsequent immune abnormalities in severe viral diseases. Moreover, due to compromised immune function, severely viral infected patients are more prone to concurrent bacterial infections, potentially explaining the elevated neutrophil counts observed in our study. Qin et al found that neutrophil counts might be higher in severe COVID-19 cases.[38]

We acknowledge the limitations of our study. Firstly, the retrospective nature of the analysis might introduce potential biases and confounding factors. Secondly, it did not distinguish the possible differences between variants of SARS-CoV-2. Finally, this study only included clinical parameters and could not analyze specific mechanisms. Further research is needed for a deeper understanding of the pathogenesis of COVID-19 pneumonia.

Conclusion

In this study, visual nomograms were constructed to predict COVID-19 pneumonia with satisfactory discrimination and calibration. It also demonstrated good discriminatory ability in predicting moderate-severe pneumonia. Rigorously validated by external validation groups, the efficacy of nomograms was promising, potentially serving as a convenient, intuitive and individual clinical tool for assessing the risk of pneumonia in lung cancer patients with SARS-CoV-2 infection, aiding in individualized management and treatment adjustments of COVID-19 patients.

Data Sharing Statement

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Ethics Approval and Consent to Participate

This research is conducted according to the World Medical Association Declaration of Helsinki.

Acknowledgment

Informed consent was obtained from all study participants prior to the commencement of the study.

Disclosure

The authors report no conflicts of interest in this work.

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