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A decision rule for identifying patients at high risk for impaired lung diffusion capacity after COVID-19

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ABSTRACT

Aim. To elaborate a decision rule for identifying the main predictors of impaired lung diffusion capacity after COVID-19.

Materials and methods. The retrospective study included 341 patients without underlying lung diseases (median age 48 years) who experienced COVID-19 with bilateral pneumonia. The median extent of parenchymal lesion in the acute phase of COVID-19 (CT_{max}) was 50%. Spirometry, body plethysmography, and lung diffusion capacity for carbon monoxide (DLCO) test were performed. The data were analyzed by descriptive statistics, correlation analysis, one-dimensional logistic regression analysis with an assessment of odds ratios (OR), and multivariate logistic regression analysis. Receiver operating characteristic (ROC) analysis was used to assess the quality of the binary classifier model.

Results. The initial model for predicting reduced DLCO (< 80% of predicted) included the following predictors: CT_{max}, time interval from the COVID-19 onset, gender, age, body mass index. Backward stepwise regression was applied, and a binary classifier model that includes CT_{max} was obtained. The sensitivity and specificity of the model for the training sample were 80 and 67%, respectively, for the test sample – 79 and 70%, respectively. The analysis of OR showed that OR > 1 was observed at CT_{max} > 40%.

Conclusion. The decision rule was obtained for predicting impaired lung diffusion capacity after COVID-19 with virus-associated lung damage in patients without underlying bronchopulmonary diseases. Patients with CT_{max} > 40% require more thorough clinical follow-up with DLCO monitoring after the acute phase of COVID-19.

Keywords: impaired lung diffusion capacity, pulmonary function tests, binary classifier model, COVID-19

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Conformity with the principles of ethics. All study participants signed an informed consent to participate in the study. The study was approved by the Ethics Committee at the Main Military Clinical Hospital named after academician N. N. Burdenko (Protocol No. 04-22 of 20.04.2022).

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Решающее правило для выявления пациентов с высоким риском нарушения диффузионной способности легких после перенесенного COVID-19

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РЕЗЮМЕ

Цель – построение решающего правила для определения наиболее важных предикторов нарушения диффузионной способности легких после перенесенного COVID-19 (Coronavirus disease 2019) с вирус-ассоциированным поражением легких.

Материалы и методы. В ретроспективное исследование включен 341 пациент без бронхолегочной патологии в анамнезе (медиана возраста 48 лет) после перенесенного COVID-19 с вирус-ассоциированным поражением легких. Медиана объема поражения легочной ткани в острый период COVID-19 ($КТ_{макс}$) в общей группе составила 50%. Выполнены спирометрия, бодиплетизмография, диффузионный тест (измерение трансфер-фактора монооксида углерода, DLco). Анализ данных проведен с помощью описательной статистики, корреляционного анализа, одномерного логистического регрессионного анализа с оценкой отношений шансов (ОШ) и многофакторного логистического регрессионного анализа. Для оценки качества модели бинарного классификатора использовался ROC-анализ (receiver operating characteristic analysis).

Результаты. В многофакторный логистический регрессионный анализ снижения DLco (<80% от должного значения) изначально были включены следующие предикторы: $КТ_{макс}$, временной интервал от начала COVID-19, пол, возраст, индекс массы тела. С помощью логистического регрессионного анализа с последовательным исключением наименее значимых предикторов получена модель бинарного классификатора, единственным значимым предиктором в которой стал показатель $КТ_{макс}$. Чувствительность и специфичность полученной модели на обучающей выборке составили 80 и 67% соответственно, на тестовой выборке – 79 и 70% соответственно. Анализ ОШ для полученной модели бинарного классификатора показал, что ОШ > 1 наблюдается при $КТ_{макс}$ > 40%.

Заключение. Получено решающее правило для прогнозирования снижения показателя DLco после перенесенного COVID-19 с вирус-ассоциированным поражением легких у пациентов без бронхолегочной патологии в анамнезе. Показано, что пациентам с $КТ_{макс}$ > 40% требуется более тщательное клиническое наблюдение с обязательным контролем показателя DLco после окончания острой фазы COVID-19.

Ключевые слова: нарушение диффузионной способности легких, легочные функциональные методы исследования, модель бинарного классификатора, COVID-19

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

Соответствие принципам этики. Все участники исследования подписали информированное согласие. Протокол исследования одобрен независимым этическим комитетом ГВКГ им. акад. Н.Н. Бурденко (протокол № 04-22 от 20.04.2022).

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INTRODUCTION

The problem of functional disorders caused by novel coronavirus infection remains relevant in the present time. The results of previous studies showed that the most common functional disorder of the bronchopulmonary system is impaired lung diffusion capacity [1–5] following diffuse alveolar damage and pulmonary embolism [6–8]. Follow-up of COVID-19 survivors has shown that it is relevant to identify patients at high risk for imparted lung diffusion capacity in the post-COVID phase, especially with account of current restrictions on performing lung function tests during the COVID-19 pandemic [9].

The aim of the study was to elaborate a decision rule for identifying the main predictors of impaired lung diffusion capacity after COVID-19 with virus-associated lung damage.

MATERIALS AND METHODS

A retrospective study included 341 patients who experienced COVID-19 with bilateral pneumonia. We analyzed demographic data, the maximum extent of parenchymal lesion in the acute phase of COVID-19 according to high-resolution computed tomography of the chest (CT_{max}), and the time interval from the COVID-19 onset (Table 1). Lung function tests included spirometry, body plethysmography, and lung diffusion capacity for carbon monoxide (DLCO) test. The analyzed pulmonary parameters included forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), slow vital capacity (VC), the FEV_1 / VC ratio, total lung capacity (TLC), and lung diffusion capacity for carbon monoxide adjusted for the hemoglobin level (DLCO) (Table 2). Lung function tests were performed in 64.8% (221/341) of patients within 90 days, in 23.5% (80/341) of patients within 90–180 days, and in 11.7% (40/341) of patients within more than 180 days from the COVID-19 onset.

Table 1

Characteristics of the study group, *n* = 341

Parameter	Value
Gender (men), *n* (%)	262 (76.8)
Age, years, *Me* (Q_1–Q_3)	48 (41.5–57)
BMI, kg / m^2, *Me* (Q_1–Q_3)	29.9 (27–32.5)
Smoking index, pack / years, *Me* (Q_1–Q_3)	0 (0–5.13)
CT_{max}, %, *Me* (Q_1–Q_3)	50 (31–75)
Time interval from the COVID-19 onset:	
<90 days, *n* (%)	221 (64.8)
90–180 days, *n* (%)	80 (23.5)
>180 days, *n* (%)	40 (11.7)

All studies were conducted according to the national and international guidelines [10–12]. The results were expressed as the percentage of predicted values (%pred) calculated according to the European Coal and Steel Society equations (ECCS 1993) [13, 14]. The fixed values of 80%pred were taken as the lower limit of normal (LLN).

Table 2

Lung function and lung diffusion capacity parameters in COVID-19 survivors, *n* = 341

Parameter	Value
VC, %pred., *Me* (Q_1–Q_3)	102 (87–111)
VC< LLN, *n* (%)	63 (18.5)
FVC, %pred., *Me* (Q_1–Q_3)	103 (88–114.2)
FEV_1, %pred., *Me* (Q_1–Q_3)	101 (89–113)
FEV_1< LLN, *n* (%)	58 (17)
FEV_1 / VC, %, *Me* (Q_1–Q_3)	80.3 (76.4–84.3)
FEV_1 / VC < 70%, *n* (%)	25 (7.3)
TLC, %pred., *Me* (Q_1–Q_3)	98 (83.2–108)
TLC < LLN, *n* (%)	68 (19.9)
DLCO, %pred., *Me* (Q_1–Q_3)	75 (61.7–88.3)
DLCO < LLN, *n* (%)	206 (60.4)

The data analysis was performed using descriptive statistics and multivariate logistic regression analysis using the SPSS 21 and MS Excel 2016 software packages. Quantitative data with non-normal distribution were presented as the median and the

interquartile range (*Me* (Q_1–Q_3)). The Mann – Whitney test was used to compare two independent samples. Qualitative variables were presented as a percentage (%); the differences were assessed using the χ^2 test with the Yates correction or the Fisher's exact test. The relationship between the traits was studied using partial correlations. The differences were considered statistically significant at $p < 0.05$. To assess the risks of abnormal parameters, the one-dimensional logistic regression analysis with the assessment of odds ratios (OR) was applied.

To construct a binary classifier model for predicting abnormal DLCO, the multivariate logistic regression analysis was used. The decision rule for predicting abnormal DLCO was obtained in a training sample. For this purpose, the total sample was split into a training and a test (validation) sample by random selection with a 3:1 split ratio. The logistic regression coefficients were obtained in the training sample.

Z is the regression equation, which has the form of:

$$Z = \alpha_0 + \alpha_1 x_1 + \ldots + \alpha_n x_n,$$

α_0, α_1, $\ldots\alpha_n$ – model parameters (coefficients), $x_1 \ldots . x_n$ – predictors.

$P = \frac{1}{1+e^{-z}}$ is the probability of abnormal DLCO, where

The logistic regression model predicted a decrease in DLCO at $Z \geq 0$ and normal DLCO values at $Z < 0$.

To assess the quality of the binary classifier model and find the optimal cut-off value for dividing objects into subsets, the ROC analysis was performed. The criterion for choosing the cut-off value was the requirement to the maximum sum of sensitivity and specificity. The ability of the created model to recognize the presence or absence of abnormal DLCO was assessed by the area under the curve (AUC) and by the correspondence of the ROC curve to the diagonal reference line.

RESULTS

In previous studies, a moderate inverse correlation was revealed between CT_{max} and DLCO [3, 15]. Besides, the bigger the time interval between the onset of COVID-19 and the DLCO test was, the less frequently abnormal DLCO was observed [4, 5]. Considering the results obtained, we divided the general sample into two subgroups: group 1 included 39.6% (135/341) of patients with normal DLCO, group 2 encompassed 60.4% (206/341) of patients with reduced DLCO. After that, we analyzed DLCO depending on CT_{max}, the time interval from the COVID-19 onset (T), gender, age, and BMI (Table 3).

Table 3 shows that, depending on DLCO (normal or reduced), the groups differed in the time interval from the onset of COVID-19 (it was shorter in group 2) and in CT_{max} (it was greater in group 2). No differences in gender, age, and BMI were identified between the groups.

The partial correlation coefficient demonstrated a significant inverse correlation between DLCO and CT_{max} ($r = –0.601$; $p < 0.01$) at fixed values of the time interval from the COVID-19 onset, gender, age, and BMI (Fig. 1).

Table 3

Characteristics of patients depending on the DL_{CO} value, *Me* (Q_1–Q_3)

Parameter	Group 1 DLCO ≥ 80%pred. *n* = 135/341 (39.6%)	Group 2 DLCO < 80%pred. *n* = 206/341 (60.4%)	*p*
Gender (men / women), *n* (%)	107 (79.3) / 28 (20.7)	155 (75.2) / 51 (24.8)	0.467[1]
Age, years	47 (40–58)	49 (43–57)	0.539[2]
BMI, kg / m^2	29.7 (26.9–32.3)	30 (27–33)	0.579[2]
T, days	81 (42–145)	39.5 (27–93)	<0.001[2]
$CT_{max,}$ %	35 (25–52)	70 (48–80)	<0.001[2]

Note. T – time interval from the onset of COVID-19 to the DLCO test; *p* – level of significance (half bold font marks *p* values for statistically significant differences).
[1] the χ^2 test with the Yates correction; [2] the Mann – Whitney test.

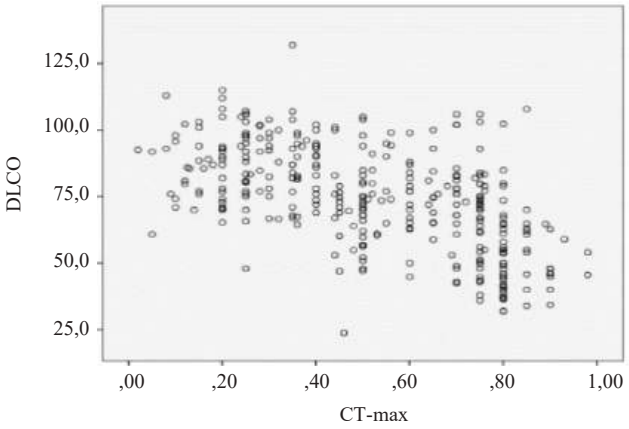

Fig. 1. Correlation analysis of the relationship between DLCO and CT_{max} (partial correlation, $r = –0.601$; $p < 0.01$)

Then we constructed a decision rule to identify patients at high risk for impaired lung diffusion capacity after COVID-19. For this purpose, the general sample was split in a 3:1 ratio into a training (n = 252) and a test (n = 89) subset. Age, gender, BMI, and parameters with a statistically significant association with reduced DLCO (CT_{max} and T) were selected as predictors. Following the conducted analysis, the following logistic regression equation was obtained:

$$Z = –1.279 + 0.05 \times x_1 – 0.004 \times x_2 – 0.046 \times x_3 + \\ + 0.017 \times x_4 + 0.653 \times x_5 \quad (1),$$

where x_1, x_2, x_3, x_4, x_5 are input parameters of the model (predictors): x_1 – CT_{max} (%), x_2 – time interval between the COVID-19 onset and the DLCO test (days); x_3 – BMI (kg/m^2), x_4 – age (years), x_5 – logistic regression coefficient encoding gender: 1 – male, 0 – female. The results of the logistic regression analysis are presented in Table 4.

Table 4 shows that the sensitivity, specificity, and accuracy for the training sample using equation 1 were 82.5, 61.2, and 74.2%, respectively.

Further, the logistic regression analysis was performed with stepwise exclusion of the least significant variables. As a result, predictors, such as gender, age, and BMI, were excluded from the model, and the following logistic regression equation was obtained:

$$Z = –1.564 + 0.046 \times x_1 – 0.003 \times x_2 \quad (2),$$

where x_1 is CT_{max} (%), x_2 is the time interval from the onset of COVID-19 to the DLCO test (days).

The results of the classification obtained at this stage are shown in Table 5.

Table 5 shows that the sensitivity, specificity, and accuracy for the training sample using equation 2 were 82.5, 61.2, and 74.2%, respectively.

The quality of the model described by equation 2 was verified using the ROC analysis (Fig.2): in the training sample, the AUC value was 0.789 (95% confidence interval (CI) 0.733–0.844), the sensitivity and specificity (at the cut–off point of 0.258) were 80 and 67%, respectively.

Table 4

Results of the classification in the training sample (predictors: CT_{max}, time interval between the COVID-19 onset and the DLCO test, age, gender, BMI)

Parameter	DLCO ≥ 80%pred., *n* (predicted)	DLCO < 80%pred., *n* (predicted)	Classified correctly, %
DLCO ≥ 80%pred., *n*	60	38	61.2
DLCO < 80%pred., *n*	27	127	82.5
Total			74.2

Table 5

The results of the classification in the training sample (predictors: CT_{max}, time interval from the onset of COVID-19 to the DLCO test)

Parameter	DLCO ≥ 80%pred., *n* (predicted)	DLCO < 80%pred., *n* (predicted)	Classified correctly, %
DLCO ≥ 80%pred., *n*	60	38	61.2
DLCO < 80%pred., *n*	27	127	82.5
Total			74.2

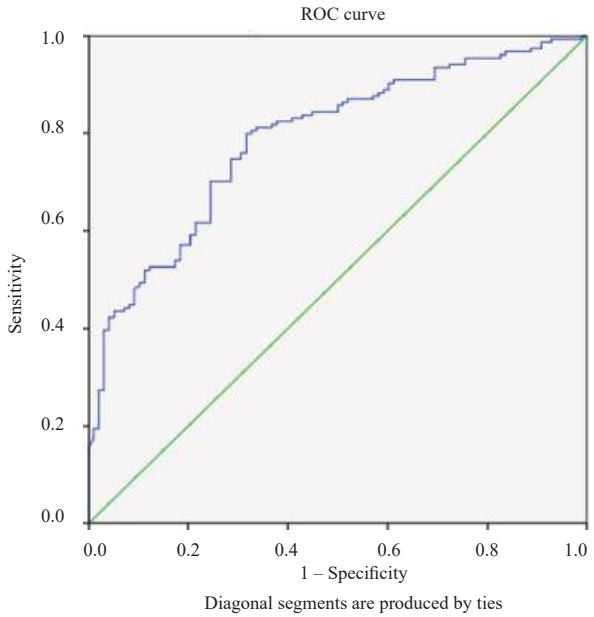

Fig. 2. The ROC analysis for the training sample (predictors: CTmax, time interval from the onset of COVID-19) to predict reduced DL_{CO}

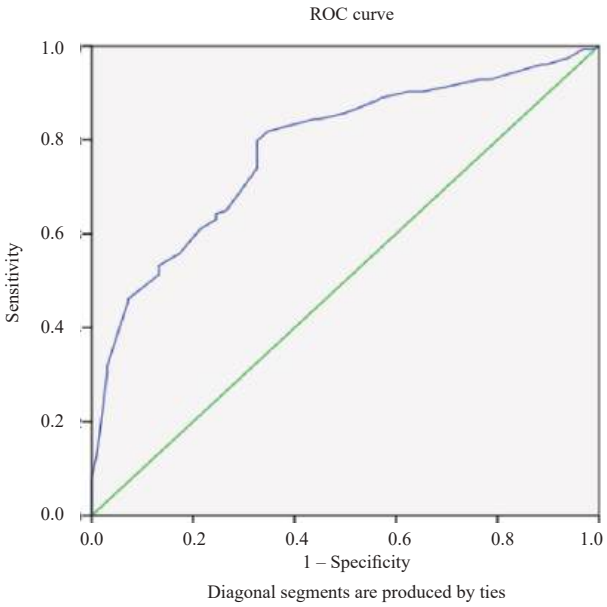

Fig. 3. ROC analysis for the training sample (predictor: CTmax) to predict reduced DL_{CO}

At $Z \geq 0.258$, reduced DLCO was predicted; at $Z < 0.258$, DLCO was within the normal range. When testing the resulting model in the test sample, sensitivity and specificity were 77 and 70%, respectively. The classifier model with a single predictor CT_{max} was also studied and the following logistic regression equation was obtained:

$$Z = -1.564 + 0.046 \times x_1 \quad (3),$$

where x_1 is CT_{max} (%).

The results of the classification obtained at this stage are shown in Table 6.

Table 6

The results of the classification in the training sample (predictors: CT_{max})

Parameter	DLCO ≥ 80%pred., *n* (predicted)	DLCO < 80%pred.., *n* (predicted)	Classified correctly, %
DLCO ≥ 80%pred., *n*	60	38	65.3
DLCO < 80%pred., *n*	27	127	81.8
Total			75.4

Table 6 shows that the sensitivity, specificity, and accuracy for the training sample using equation 3 were 81.8, 65.3, and 75.4%, respectively.

The ROC analysis showed (Fig. 3) that when using equation 3 in the training sample, the AUC value was 0.780 (95% CI 0.723–0.837), sensitivity and specificity (at the cut–off point of 0.171) were 80 and 67%, respectively. In the test sample, sensitivity and specificity were 79 and 70%, respectively.

At $Z \geq 0.171$, reduced DLCO was predicted, at $Z < 0.171$, DLCO was within the normal range.

Using equation 3, OR was calculated [16]:

$$OR = e^{-1,564}e^{0,046x}1 \quad (4),$$

where x_1 is CT_{max} (%).

Equation 4 evidences that OR > 1 is observed at $CT_{max} > 40\%$.

DISCUSSION

Predicting the state of medical systems depending on factors affecting them is an important task of statistical analysis. The use of mathematical models solves a lot of tasks, such as assessing the influence of factors on the response rate, changes in the parameter caused by changes in factors affecting the system, predicting the response rate for the given values of factors [17].

The methods for binary classification include both classical discriminant analysis and logistic regression analysis, which are used in various fields of medicine [18–20]. In this study, the created binary classifier model allows to predict reduced DLCO after COVID-19 with virus-associated lung damage.

The correlation analysis, data analysis depending on the DLCO value (normal or reduced), and the created binary classifier models showed that CT_{max} is an important predictor of reduced DLCO after

COVID-19 with virus-associated lung damage in patients without an underlying lung pathology.

Similar studies have been conducted abroad. W. Qin et al. [21] also did not reveal statistically significant differences in age, gender, and BMI between groups with reduced and normal DLCO 3 months after COVID-19. In addition, after exploring a wide range of possible abnormal DLCO predictors (demographic and clinical data, results of laboratory and instrumental research and X-ray, treatment regimens, the presence of acute respiratory distress syndrome) in 81 patients 3 months after COVID-19, the authors concluded that CT_{max} and acute respiratory distress syndrome affected DLCO after the acute phase of COVID-19.

In the present study, using the logistic regression analysis with the stepwise exclusion of the least significant predictors also demonstrated that CT_{max} contributed to a decrease in DLCO. The sensitivity and specificity of the created model were 80 and 67% for the training sample, respectively, and 79 and 70% for the test sample, respectively. The inclusion of additional predictors in the model, such as gender, age, BMI, and the time interval from the onset of COVID-19 to the DLCO test, did not significantly affect the quality of the decision rule. Moreover, it was shown that at $CT_{max} > 40\%$, reduced DLCO can be reliably expected after the end of the acute phase of COVID-19.

LIMITATIONS OF THE STUDY

To create a model for predicting reduced DLCO after COVID-19, we used the results of lung function tests obtained mainly in the first 6 months after the acute phase of the disease. It should be taken into account that CT_{max} reflects the volume, but does not characterize the depth and morphological features of lung tissue damage, which may subsequently affect DLCO. I.E. Tyurin et al. [22] pointed out that the clinical manifestation and prognostic value of radiological signs, such as ground-glass opacities and consolidation, appear to be completely different even for the same lesion volume.

CONCLUSION

A decision rule was obtained for predicting reduced DLCO after COVID-19 with virus-associated lung damage in patients without an underlying lung pathology. The analysis of chest CT scans in the acute phase of COVID-19 is essential for predicting impaired lung diffusion capacity. Patients with $CT_{max} > 40\%$ require more thorough clinical follow-up with obligatory DLCO monitoring after the acute phase of COVID-19.

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Savushkina O.I. – conception and design, selection and examination of patients, analysis and interpretation of the data, critical revision of the manuscript for important intellectual content, drafting of the manuscript. Muraveva E.S. – analysis and statistical processing of the data, drafting of the article. Zhitareva I.V. – analysis and statistical processing of the data, critical revision of the manuscript for important intellectual data. Davydov D.V. – critical revision of the manuscript for important intellectual data. Kryukov E.V. – final approval of the manuscript for publication, critical revision of the manuscript for important intellectual data.

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