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The influence of the criterion of abnormal DLco value on the prediction of impaired lung diffusion capacity after SARS-CoV-2 infection

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ABSTRACT

Aim. To predict impaired lung diffusion capacity after SARS-CoV-2 infection depending on the criteria of pathological deviation of DLco value (carbon monoxide transfer factor).

Materials and methods The retrospective study included 341 patients (median age was 48 years, 76.8% of the participants were men) after SARS-CoV-2-associated lung injury. The median volume of lung injury during the acute phase of COVID-19 was 50%. All patients underwent a diffusion test. Descriptive statistics, logistic regression analysis were applied, taking into account the previously obtained model for prognosis of abnormal DLco (<80% of the predicted value (%pred.)) [11]. In the present study on the same sample of patients, the prognosis of abnormal DLco was studied depending on the *criterion 1*: DLco < 80%pred. or *criterion 2*: DLco < predicted – 1.645SD (SD – standard deviation). ROC analysis was used to assess the quality of the binary classifier models.

Results. The coefficients of the logistic regression equations were obtained on the training sample with regard to the chosen criterion of pathological deviation of DLco. The ROC analysis procedure showed that, when applying *criterion 1*, area under curve (AUC) was 0.776, $p < 0.001$ (0.707–0.824 95% confidence interval (CI)), sensitivity and specificity of the training model were 81 and 66%, respectively. When applying *criterion 2*, AUC was 0.759, $p < 0.001$ (0.701–0.817 95% CI), sensitivity and specificity of the training model were 83.4 and 59%, respectively.

Conclusion. The criterion for determining the lower limit of normal DLco (LLN_{DLco}) does not significantly affect the quality of the model for impaired lung diffusion capacity prognosis after SARS-CoV-2-associated lung injury. It is advisable to give preference to a method that is easier to apply in practice.

Keywords: criteria for abnormal DLco, binary classifier model, SARS-CoV-2 infection

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Влияние критерия патологического отклонения показателя DLco на прогнозирование нарушения диффузионной способности легких после перенесенной инфекции SARS-CoV-2

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РЕЗЮМЕ

Цель. Прогнозирование нарушения диффузионной способности легких после перенесенной инфекции SARS-CoV-2 в зависимости от выбранного критерия патологического отклонения показателя DLco (трансфер-фактора монооксида углерода).

Материалы и методы. В ретроспективное исследование включен 341 пациент (медиана возраста 48 лет, 76,8% мужчин) после перенесенного SARS-CoV-2-ассоциированного поражения легких. Медиана объема поражения легочной ткани в острый период заболевания составила 50%. Всем пациентам был выполнен диффузионный тест. Анализ DLco проведен с помощью описательной статистики и логистического регрессионного анализа с учетом полученной ранее модели прогнозирования снижения DLco [11], в которой за нижнюю границу нормы DLco было принято фиксированное значение 80% от должного значения (%долж.). В настоящем исследовании на той же выборке пациентов проведен сравнительный анализ качества моделей прогнозирования снижения DLco в зависимости от критериев его патологического отклонения (критерий 1: DLco < 80%долж.; критерий 2: DLco < должное – 1,645SD, SD – стандартное квадратичное отклонение от среднего). Для оценки качества моделей бинарного классификатора использовался ROC-анализ.

Результаты. На обучающей выборке получены коэффициенты уравнений логистической регрессии с учетом выбранных критериев патологического отклонения DLco. Процедура ROC-анализа показала, что при применении критерия 1 значение AUC (площадь под кривой) составило 0,776; $p < 0,001$ (95%-й доверительный интервал (ДИ) 0,707–0,824), чувствительность и специфичность обучающей модели – 81 и 66% соответственно, при применении критерия 2 значение AUC составило 0,759; $p < 0,001$ (95%-й ДИ 0,701–0,817), чувствительность и специфичность обучающей модели – 83,4 и 59% соответственно.

Заключение. Выбор критерия определения нижней границы нормы показателя DLco не оказывает существенного влияния на качество модели прогнозирования нарушения диффузионной способности легких после перенесенного SARS-CoV-2-ассоциированного поражения легких. Целесообразно отдавать предпочтение методу, который проще применять на практике.

Ключевые слова: критерии патологического отклонения DLco, модель бинарного классификатора, инфекция SARS-CoV-2

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

Источник финансирования. Исследование выполнено без участия спонсоров.

Соответствие принципам этики. Все пациенты подписали добровольное информированное согласие на участие в исследовании. Исследование одобрено независимым этическим комитетом ФГБУ «ГВКГ им. Н.Н. Бурденко» Минобороны РФ (протокол № 254 от 20.04.2022).

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INTRODUCTION

Pulmonary function tests (PFTs) reflect the physiological properties of the lungs and are used to diagnose lung diseases, determine the cause of shortness of breath, monitor disease progression and response to treatment. The key aspect of interpreting PFT results that are accurate from a technical perspective is the classification of observed values — understanding whether they are within the normal range in relation to the healthy population. It was previously found that values of lung function parameters depend on the patient's age, height, and gender [1]. Currently, it is also considered important to take into account the patient's race [2, 3]. Taking all these factors into consideration, reference equations were created to calculate the predicted values of lung function parameters in a particular patient. Thus, the evaluation criterion for lung function parameters is to compare the actual obtained value with the predicted value.

Additionally, in a population of healthy subjects, there is a range of normal values, the lower limit of which is defined either as a fixed value equal to 80% of predicted (80%pred.) [2, 4] or as the difference between the predicted value and 1.654 SD (SD — standard deviation) [3, 5]. Initially, it was decided to determine the range of normal values of the lung function parameters within the 95% confidence interval (CI). However, A.O. Navakatikyan [6] took into account the unidirectionality of pathological changes in lung function parameters and recommended using a one-sided criterion for assessing the limits of the norm. Thus, values that deviate from the limits of the norm by more than 1.645 SD were proposed to be considered pathology. This concept was later adopted by other Russian scientists [1].

Regarding the recent COVID-19 pandemic (COronaVIrus Disease 2019 — coronavirus infection 2019) caused by the SARS-CoV-2 virus (Severe Acute Respiratory Syndrome-related COronaVirus 2), assessing lung function in patients with SARS-CoV-2-associated lung injury plays an important role in creating individual medical rehabilitation programs for patients after hospital discharge. Additionally, restoring lung function parameters to normal is one of the criteria for recovery.

Impaired lung diffusion capacity is the most common and long-lasting defect in lung function associated with SARS-CoV-2-related lung injury, as shown in various studies [7–9]. The criterion for impaired lung diffusion capacity is a decreased DLco (carbon monoxide transfer factor) [10].

In a previous study, a multifactorial logistic regression analysis was used to determine a decision rule for predicting decreased DLco using a fixed value of the lower limit of normal equal to 80%pred. [11]. However, no convincing evidence of the advantage of any proposed criteria for assessing pathological changes of DLco has been found in the available literature.

The aim of this study is to compare models for predicting impaired lung diffusion capacity after SARS–CoV-2-associated lung injury depending on the selected criterion for pathological changes of DLco.

MATERIALS AND METHODS

A retrospective study was conducted on 341 patients after COVID-19 with virus-associated lung injury. The maximum volume of lung tissue damage in the acute phase of COVID-19 according to high-resolution computed tomography of the chest (CT_{max}) and DLco were analyzed. The median age of the patients was 48 (41.5–57) years, 76.8% (262/341) were men. The median CT_{max} was 50 (31–75)%.

A diffusion test (evaluation of DLco) was conducted according to international standards [12].

Начать с It is worth noting that (221/341) of patients – underwent diffusion test within 90 days, 23.5% (80/341) of patients between 90 and180 days, and 11.7% (40/341) of patients – within more than 180 days from the onset of COVID-19.

Pathological deviation of DLco (the lower limit of the normal – LLN) was assessed using the following criteria:

Criterion 1: LLN_{DLCO} = 80%pred. (the fixed value of LLN) [2, 4];

Criterion 2: LLN_{DLCO} = predicted – 1.645 SD (SD – standard deviation) (the individual value of LLN) [3, 5].

The predicted value of DLco was determined according to the European Community of Coal and Steel prediction equations (ECCS, 1993) [5].

Statistical analysis was performed via SPSS 21 and MS Excel 2016 programs. The results were analyzed using descriptive statistics and multivariate logistic regression analysis.

Quantitative data with a skewed distribution were described using the median and interquartile range *Me* (Q_1–Q_3), where Q_1 is the lower quartile and Q_3 is the upper quartile. To compare three independent samples, the Kruskal – Wallis test and Mann – Whitney test with Bonferroni correction were used. Differences were considered statistically significant at $p < 0.05$, where p is the significance level.

In the previous study [11], multivariate logistic regression analysis was used to create a binary classifier model to predict abnormal DLco.

The decision rule for predicting abnormal DLco was built on a training sample. For this purpose, via a random number generator, the total sample was divided into a training and a test (validation) sample in a 3:1 ratio. The coefficients of the logistic regression equation Z were obtained on the training sample.

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

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

where α_0, α_1, $\ldots\alpha_n$ — are model parameters (coefficients), and $x_1 \ldots x_n$ — are predictors.

P — represents the probability of abnormal DLco, where $P = \frac{1}{1 + e^{-z}}$

Logistic regression predicted a decrease in DLco when the Z value was greater than or equal to 0, while DLco was in the normal range if $Z < 0$.

Using the above algorithm, a decision rule was found to predict decreased DLco after SARS-CoV-2-associated lung injury in patients without underlying lung diseases . The logistic regression equation included a single predictor of CT_{max} [11]:

$$Z = \alpha_0 + \alpha_1 \times x_1 \quad (1)$$

where Z is the regression equation, α_0, α_1 – are model parameters (coefficients), and x_1 – is the predictor of CT_{max}.

The decision rule described by equation (1) was used in this study to compare the results of the binary classifier model depending on the selected LLN criterion of DLco.

To assess the quality of the binary classifier model and find the optimal cut-off value for dividing objects into classes, a ROC analysis was performed. The criterion for choosing the cut-off value was the requirement of 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 value of AUC (area under the curve) and the difference between the ROC curve and the diagonal reference line.

RESULTS

The analysis of the Dlco parameter in the study sample is presented in Table 1.

Table 1

DLco parameter at different time intervals (days) from the COVID-19 onset, complicated by virus-associated lung injury, in patients without underlying lung diseases, *Me* (Q_1–Q_3)

Parameter	Total sample n = 341	Sample 1 <90 days (n = 221; 64.8%)	Sample 2 90–180 days (n = 80; 23.5%)	Sample 3 >180 days (n = 40; 11.7%)	p-value: p_{total} / p_{1-2} / p_{1-3} / p_{2-3}
DLco, %pred.	75 (61.7–88.3)	72 (54–84)	81 (67–93.5)	83 (75–95.5)	<0.001[1]/<0.001[2]/ <0.001[2]/0.45[2]

Note. The data are presented as median (lower quartile – upper quartile). p_{total} – significance level between samples 1–3, p_{1-2} – significance level between samples 1 and 2, p_{2-3} – significance level between samples 2 and 3, p_{1-3} – significance level between samples 1 and 3. 1 – Kruskal – Wallis test, 2 – Mann – Whitney test with Bonferroni correction for multiple comparisons.

Table 1 demonstrates that the median DLco in the total sample was decreased. Depending on the time interval between the onset of COVID-19 and the diffusion test, the median DLco tended to increase. Pairwise comparison revealed statistically significant differences between samples 1 and 2, as well as between samples 1 and 3. However, no statistically significant differences in DLco medians were found between samples 2 and 3.

To compare criteria 1 and 2 for determining pathological deviation of DLco, the total sample on which the decision rule was obtained in the previous study [11] was re-divided via a random number generator into a training (n = 262) sample and a validation (n = 79) sample. Further research was conducted in two stages.

Stage 1. Building a binary classifier model if LLN_{DLco} = 80%pred.

Using equation (1), the coefficients of the logistic regression equation were obtained from the training sample:

$$Z = -1.793 + 0.044 \times x_1 \quad (2)$$

The classification results are presented in Table 2.

Table 2

Classification results of DLco in the training sample (CT_{max} is the predictor)

Parameter	$DL_{CO} \geq$ 80%pred. (predicted)	$DL_{CO} <$ 80% pred. (predicted)	Classified correctly, %
$DL_{CO} \geq$ 80%pred., n	66	37	64.1
$DL_{CO} <$ 80%pred., n	27	132	83.0
Overall			75.6

Table 2 demonstrates that the sensitivity, specificity, and accuracy for the training sample using equation 1 were 83, 64.1, and 75.6%, respectively, respectively.

The quality of the model described by equation 2 was verified using the ROC analysis procedure. The ROC curve for the training sample is presented in Fig. 1.

Predicting decreased DLco (<80%pred.), the AUC value was 0.776, $p < 0.001$ (95% CI 0.707–0.824), with sensitivity and specificity (at a cut–off point of 0.165) being 81 and 66%, respectively. Testing the binary classifier model obtained at this stage from a validation sample yielded sensitivity and specificity of 76.6 and 78%, respectively.

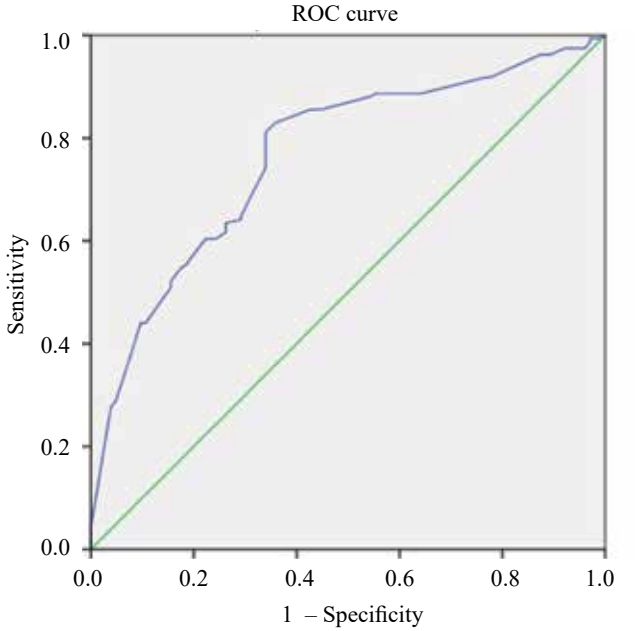

Fig. 1 – the ROC curve of the training sample (CT_{max} is the predictor) to predict abnormal DLco (< 80%pred.), AUC 0.776 (95% CI 0.707–0.824, $p < 0.001$). The cut–off point was 0.165

Stage 2. Building a binary classifier model if LLN_{DLco} = predicted – 1.645 SD.

Similar to *stage 1*, the coefficients of the logistic regression equation were obtained on the training sample using equation (1):

$$Z = -1.997 + 0.043 \times x_1 \quad (3)$$

The classification results are presented in Table 3.

Table 3

Classification results of DLco in the training sample (CT_{max} is the predictor)

Parameter	$DL_{CO} \geq$ LLN, n (predicted)	$DL_{CO} <$ LLN, n (predicted)	Classified correctly, %
$DL_{CO} \geq$ LLN, n	73	44	62.4
$DL_{CO} <$ LLN, n	34	111	76.6
Overall			70.2

Note. LLN is lower limit of normal, equal to predicted – 1.645SD, SD – standard deviation.

Table 3 demonstrates that the sensitivity, specificity, and accuracy for the training sample using equation 1 were 76.6, 62.4, and 70.2%, respectively.

The quality of the model described by equation 3 was verified using the ROC analysis procedure. The ROC curve for the training sample is presented in Fig. 2.

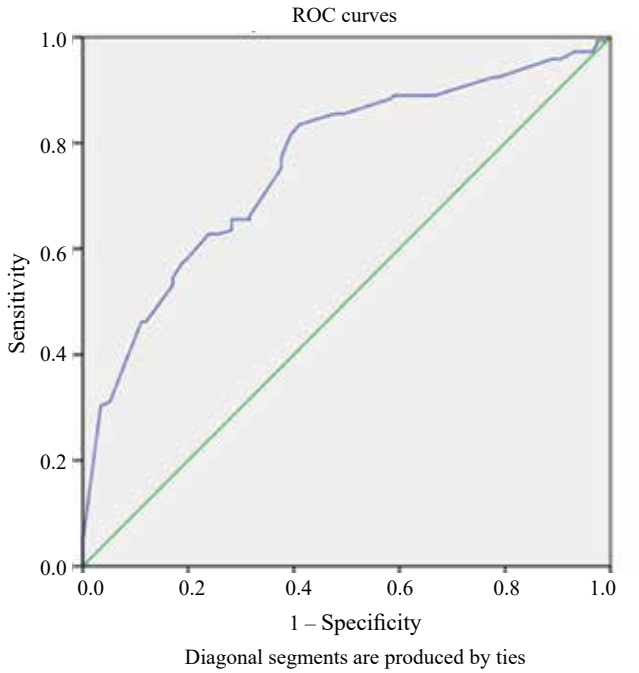

Fig. 2. The ROC curve of the training sample (CT_{max} is the predictor) to predict an abnormal DLco (< predicted – 1.645SD), AUC 0.759 (95% CI 0.701–0.817, $p < 0.001$). The cut–off point was –0.191

Predicting decreased DLco (<predicted – 1.645SD), the AUC value was 0.759, $p < 0.001$ (95% CI 0.701–0.817), with sensitivity and specificity (at a cut–off point of –0.191) being 83.4 and 59%, respectively. Testing the binary classifier model obtained at this stage from a validation sample yielded sensitivity and specificity of 76.2 and 67.6%, respectively.

According to the literature, abnormal lung function can be found in >50% of patients during the follow-up after COVID-19-related hospitalization. Lung diffusion capacity is the most common COVID-19-related complication [13]. M. Bellan et al. revealed that DLco was decreased (<80%pred.) in 51.6% (113/219) of patients and was less than 60%pred. in 15.5% (34/219) of patients after severe COVID-19 [14].

The present study also demonstrated a decrease in DLco within up to 90 days after the onset of COVID-19 and a gradual improvement of lung diffusion capacity as the period of time from the disease onset increases, which is consistent with data obtained in other patient populations [15, 16]. The issue of the lung function parameters dynamics remains important to this day and is being studied both in cases of mild/moderate and severe/extremely severe COVID-19 [17, 18].

In many studies devoted to the lung function after a SARS-CoV-2 infection, LLN of DLco 80%pred. was applied [19–21]. At the same time, in 2022, the American Thoracic Society and European Respiratory Society recommended using the 5th percentile or 1.645SD from the predicted value (Z-score = –1.645) as LLN for all lung function parameters [3]. This is not a new idea, as it was proposed and supported by Russian researchers in the 1960–1980s [1, 6]. However, the lack of appropriate software at that time did not allow this approach to be widely used in clinical practice. In turn, the approach proposed by the American Thoracic Society to use a fixed value of 80%pred. as LLN of the lung function parameters [2] was easy to use and proved itself well in clinical practice.

It should be noted that in a few studies dedicated to the study of the lung function after COVID-19, Z-score = –1.96 was taken as LLN of the lung function parameters [22]. At the same time, no justification was found in the literature for the advantage of any of the proposed criteria for LLN DLco and its effect on the accuracy of diagnosing impaired lung diffusion capacity.

In the present study, via a binary classifier model that includes a single predictor (CTmax), the effect of the pathological DLco deviation criterion on the prediction of lung diffusion capacity was analyzed in an examined group of patients. The study was conducted on a sample of patients without underlying lung diseases who had suffered SARS-CoV-2-associated lung injury. There are no similar studies found in the literature.

In the present study, the analysis of the classification results of the obtained models did not demonstrate significant differences in predicting impaired lung diffusion capacity depending on the criterion for LLN of DLco. Thus, the accuracy of the obtained models was 75.6 and 70.2% for criterion 1 (LLN_{DLco} = 80% pred.) and criterion 2 (LLN_{DLco} = predicted –1.645SD), respectively. The ROC analysis on a

training sample demonstrated that the sensitivity of the model was slightly higher when using criterion 2 in comparison with criterion 1 (83.4 and 81%, respectively).

However, the specificity was higher when using criterion 1 in comparison with criterion 2 (66 and 59%, respectively). In the validation sample, the sensitivity of the models was almost the same (76.6 and 76.2% for criterion 1 and 2, respectively), while the specificity was higher when using criterion 1 (78 and 67.6% for criterion 1 and 2, respectively).

The limitations of this study include the insufficient number of enrolled patients in the period from 6 months to 1 year from COVID-19 onset. Additionally, the ECCS 1993 reference value system was used to determine the predicted value of DLco, while the GLI (Global Lung Function Initiative) system is being widely introduced into clinical practice [3]. However, the effectiveness of the GLI system in clinical practice, its consistency with the ECCS 1993 system, as well as the correspondence of DLco, the predicted value of which is calculated using the GLI system, clinical and X-ray data, has not yet been studied in Russia.

CONCLUSION

For patients without underlying lung diseases, it was shown that the choice of the criterion for assessing LLN of DLco does not significantly affect the sensitivity of the prediction model of DLco decrease after suffering SARS-CoV-2-associated lung injury. However, the specificity of the prediction model was higher when using a fixed value of LLN of DLco (LLN_{DLco} = 80% pred.). In this regard, the authors do not see the advantages of determining LLN of DLco according to any of the criteria considered. In such cases, it is advisable to give preference to a method that is easier to apply in practice.

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

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