

## Diaphragm Function Parameters in Patients with Severe COVID-19

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## Показатели функции диафрагмы у пациентов с COVID-19 тяжелого течения

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### Summary

The aim of the study was to investigate the feasibility of predicting the need for mechanical ventilation in patients with severe COVID-19 disease using ultrasound assessment of diaphragm function.

**Material and methods.** An open prospective pilot study included 60 patients diagnosed with the novel coronavirus infection, who, at the time of admission to the intensive care unit (NEWS score > 6), underwent ultrasound assessment of diaphragm excursion, thickness and the diaphragm thickening fraction. Group 1 ( $n=30$ ) included patients who did not require mechanical ventilation, and group 2 ( $n=30$ ) consisted of patients who were subsequently transferred to mechanical ventilation.

**Results.** Patients in group 2 had significantly lower diaphragm function parameters (left excursion value ( $P<0.001$ ), right excursion value ( $P<0.001$ ), diaphragm thickness on inspiration ( $P=0.043$ ), and thickening fraction ( $P<0.001$ ) than patients in group 1.

**Conclusion.** Decreased diaphragm excursion of less than 17.1 mm on the right side is a predictor of initiation of mechanical ventilation in patients with the COVID-19 infection (sensitivity 93.3%, specificity 76.7%). Morphological examination in deceased patients of group 2 revealed pericellular and perivascular edema, venular thrombosis, endoneurial edema, and sludge in the lumen of arterioles.

**Keywords:** novel coronavirus infection; COVID-19; complications; diaphragm

**Conflict of interest.** The authors declare no conflict of interest.

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### Introduction

ACE2 receptors of alveolar cells of type II are the «entrance gate» of the novel coronavirus infection (COVID-19) into the lungs, which causes lung damage of varying severity and prevalence in all patients who died of COVID-19 [1, 2]. Symptoms of viral infection in moderate, severe and critical dis-

ease include reduced oxygen saturation, dyspnea, low oxygenation index, i.e., represent hypoxia [3]. The volume of pulmonary involvement according to CT scan does not always correlate with the severity of respiratory failure, which warrants the search for additional drivers of respiratory failure in patients with COVID-19 [4–6]. One of these factors could be the functional status of the diaphragm,

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which is suggested by the presence of ACE2 receptors in the human diaphragm and SARS-CoV-2 viral infiltration of the diaphragm in patients with severe COVID-19 [7–9].

The diaphragm is known to be the main inspiratory respiratory muscle and plays a leading role in spontaneous ventilation. Unilateral phrenic nerve blockade leads to a decrease in pulmonary ventilation down to 30% of the baseline [10–12]. In COVID-19, impaired function and/or structure of the diaphragm may be due to a comorbidity (diabetic polyneuropathy), individual characteristics, direct neurotoxic effect of the virus, of respiratory neuropathy of critical illness [13–15].

The aim of the study was to evaluate the feasibility of predicting mechanical ventilation in patients with severe novel coronavirus infection using ultrasound assessment of diaphragmatic function.

### Material and Methods

This open, prospective pilot study included 60 patients diagnosed with the novel coronavirus infection at the moment of their admission to the intensive care unit, who had progressive respiratory failure by days 6–7 from the onset of the disease.

All patients had clinical manifestations of viral pneumonia, confirmed by a positive RT-PCR test for SARS-CoV-2 RNA on admission and a characteristic radiological presentation on chest CT (CT grade 2–4 according to the semi-quantitative visual assessment scale).

The patients were assigned to two groups: group 1 ( $n=30$ ) included patients who did not require invasive ventilation, and group 2 ( $n=30$ ) comprised patients who were put on mechanical ventilation within the first 6–12 hours of admission to the ICU.

The patients placed on the ventilator not due to the progression of coronavirus infection, but for other reasons identified during differential diagnosis (acute cerebrovascular event, pulmonary embolism, etc.) were excluded from the study.

Severity assessment at the moment of admission to ICU was performed using the National Early Warning Score (NEWS) [16]. General characteristics of patients are shown in Table 1.

As seen from Table 1, patients in both groups did not differ significantly in age, sex, body mass index, volume of lung tissue involvement on CT scan, as well as in severity of disease and comorbidities.

The diaphragm was examined using a General Electric Ligiq e R8 ultrasound scanner (General Electric, USA). The function of the diaphragm was assessed by determining its right and left excursion and thickening during breathing [17, 18].

Assessment of right and left diaphragm excursion was performed in supine position using low-frequency probes (convex or phased array transducers). The probe was placed between the midclavicular and anterior axillary lines with the scanning beam oriented medially in the dorsocranial direction, i. e., the ultrasound beam crossed the diaphragm at right angles. In M-mode, the amplitude of motion of posterior third of diaphragm during normal breathing was measured.

Assessment of diaphragm thickening was performed in the supine position using a high-frequency linear transducer. The study was performed in B-mode. The transducer was placed in the coronary plane along the midaxillary line at the level of the costophrenic sinus. The diaphragm was visualized at its interface with the chest wall with assessment of its maximal thickness on inhalation and minimal thickness on exhalation.

Based on the diaphragm thickness measurement, the thickening fraction was calculated as the ratio of diaphragm thickness on inspiration to diaphragm thickness on expiration.

In the clinical case below, a specimen of the diaphragm of a patient who died of COVID-19 is demonstrated. The sample was taken from the lumbar portion corresponding to the area of ultrasound examination. For microscopic examination of preparations stained with hematoxylin and

**Table 1. General characteristics of patients.**

Parameters	Value in groups		P
	Group 1	Group 2	
Number of patients, <i>n</i>	30	30	
Age, ( <i>M±σ</i> )	74.4±17.28	70.23±18.12	0.482
Males, <i>n</i> (%)	18 (60)	14 (47)	0.438
Females, <i>n</i> (%)	12 (40)	16 (53)	0.565
Body mass index, kg/m <sup>2</sup> ( <i>M±σ</i> )	28.22±3.16	28.21±3.15	0.894
Severity on the NEWS scale on admission to ICU, points, ( <i>M±σ</i> )	6.4±1.9	6.0±2.0	0.585
Oxygen therapy, <i>n</i> (%)	8 (26,7)	6 (20)	
High flow rate oxygenation, <i>n</i> (%)	12 (40)	12 (40)	
Noninvasive lung ventilation, <i>n</i> (%)	10 (33,3)	12 (40)	
Volume of lung involvement ( <i>M±σ</i> ), %	42.7±27.0	55.23±27.15	0.096
<b>Comorbidities</b>			
Diabetes mellitus, <i>n</i>	30	27	
Hypertension, <i>n</i>	26	24	

**Table 2. Parameters of diaphragmatic function in patients with the novel coronavirus infection ( $M \pm \sigma$ ,  $Me$  [0,25; 0,75]).**

Parameters	Values in groups		P-value
	1	2	
Left hemidiaphragm excursion, cm	1.92±0.39	1.29±0.21	<0.001
Right hemidiaphragm excursion, cm	2.21±0.68	1.46±0.2	<0.001
<i>P-value</i>	0,02	0,039	
Diaphragm thickness on expiration, cm	0.21±0.07	0.26±0.18	0,3
Diaphragm thickness on inspiration, cm	0.37±0.13	0.32±0.19	0.043
<i>P-value</i>	0,004	<0,001	
Thickness fraction	1.72 [1.16; 2.32]	0.93 [0.81; 1.02]	<0.001

eosin, a medical transmitted light microscope mVizo-101 (LOMO, Russia) was used. Examination and microphotography were performed using Planamat 5/0.10 objective with XT0028 video attachment, the linear magnification of the microscope was 63–240.

Statistical analysis of the results was performed using the IBM SPSS Statistics (Version 25) software package. All data were checked for normality of distribution using Shapiro–Wilk test. To compare qualitative variables in unrelated samples we used Fisher exact test, to compare quantitative parameters with non-normal distribution in unrelated samples we used Mann–Whitney *U*-test, in related samples the Wilcoxon *T*-test was employed. To analyze correlation, we used Spearman's rank correlation *R* coefficient. Logistic regression with regression model was used for probability prediction. Using binary logistic regression (forward LR method), we investigated the dependence of the dichotomous variable (starting the mechanical ventilation) on the independent variables (diaphragm excursion, diaphragm thickening fraction). ROC analysis was used to assess the quality of binary classification, and the Youden index (maximization of the sum of sensitivity and specificity) was applied to select the optimal cut-off point. The null hypothesis of lack of significant differences was rejected at  $P \leq 0.05$ .

## Results and discussion

The results of ultrasound examination of the diaphragm in the patients are presented in Table 2. The parameters of diaphragm function (left excursion, right excursion, diaphragm thickness on inhalation, and thickening fraction) differed significantly between patients in groups 1 and 2. No significant differences were observed only for diaphragm thickness on exhalation.

In addition, the right and left hemidiaphragm excursion values differed between the groups. Interestingly, Boussuges A. et al. in their study found no differences in right and left hemidiaphragm excursion in healthy patients [19]. We attribute our findings to such specific features of ultrasound imaging of the left hemidiaphragm as poor acoustic window (gastric bubble on the left side). Based on the sci-

entific literature data, we deem it appropriate to assess the excursion in the area with the best acoustic window, i. e., on the right side [20].

Analysis of the correlation between the left hemidiaphragm excursion and ventilation support requirement revealed a significant ( $P < 0.001$ ) strong correlation with the Spearman *r* value of -0.731. At the same time, higher values of hemidiaphragm excursion were more commonly found in the group of patients who were not placed on respiratory support.

Analysis of relationship between the right hemidiaphragm excursion and mechanical ventilation requirement revealed a significant ( $P < 0.001$ ) moderate correlation (Spearman *r*, -0.576). At the same time, higher hemidiaphragm excursion was more commonly seen in the patients who did not require mechanical ventilation.

Analysis of the correlation between diaphragm thickening fraction and ventilation requirement revealed a significant ( $P < 0.001$ ) strong correlation (Spearman *r*, -0.477). At the same time, higher values of the diaphragm thickening fraction were more commonly seen in patients from group 1.

Despite significant intergroup differences in diaphragm thickness on inspiration, correlation analysis of this variable was not performed due to its secondary character.

To predict the probability of ventilator support initiation based on the parameters of diaphragm function, we developed a logistic regression model. At that, the left hemidiaphragm excursion values lost their statistical significance ( $P = 0.108$ ). Hence,

$$p = 1 / (1 + e^{-z})$$

where *P* is the probability of ventilator support initiation,  $e = 2,718...$  represents the base of natural logarithms;  $z = a + (B1 \times X1) + (B2 \times X2)$ ; *A* (regression equation constant) = 27.479 ( $P = 0.001$ ); *B1* = -11.365 ( $P = 0.003$ ); *X1* is diaphragm thickness fraction; *B2* = -7.097 ( $P = 0.006$ ); *X2* is right hemidiaphragm excursion; Thus,  $z = 27,479 - 11,365 \times X1 - 7,097 \times X2$ .

If the calculated probability was greater than 0.5, the patient was assigned to group 2 (patients on mechanical ventilation).

The percentage of correct predictions in the studied patient sample was 91.7%; the Nagelkerke

R-squared was 0.848. Therefore, the predictive model can be considered adequate in general. The Hosmer–Lemeshow goodness-of-fit test showed agreement between the model and the real data ( $P=0.510$ ).

Based on the predicted values, an ROC curve was plotted to assess the prognostic significance of the regression model (Fig. 1).

The area under the curve for the predicted values was 0.977 ( $P<0.001$ ). The area values between 0.946 and 1.000 corresponded to the 95% confidence interval. The regression model predicts initiation of mechanical ventilation based on independent variables (diaphragm excursion, diaphragm thickening fraction) with a sensitivity of 93.3% and specificity of 93.3% (cut-off point 0.529).

A ROC-curve was plotted to assess the sensitivity and specificity of right hemidiaphragm excursion and diaphragm thickening fraction as predictors of critical novel coronavirus infection (COVID-19). The area under the curve for the right hemidiaphragm excursion was 0.832 ( $P<0.001$ ). The area values from 0.719 to 0.946 corresponded to the 95% confidence interval.

The area under the curve for the diaphragm thickening fraction was 0.775 ( $P<0.001$ ). The area values from 0.657 to 0.893 corresponded to the 95% confidence interval.

Curves evaluating the prognostic significance of right hemidiaphragm excursion and diaphragm thickening fraction in ROC analysis are shown in Fig. 1. The cutoff values of right hemidiaphragm excursion as a predictor of extremely severe course of novel coronavirus infection (COVID-19) of 17.1 mm or less had a sensitivity of 93.3% and a specificity of 76.7%. The findings were consistent with those of Boussuges A., who showed that diaphragm excursion in healthy individuals was  $18\pm 3$  mm in men and  $16\pm 3$  mm in women [19]. Consequently, the decrease of this parameter has a prognostic value for possible switching the patient to ventilator support.

The cutoff values of diaphragm thickening fraction for predicting a critical COVID-19) of 1.3 times or less had a sensitivity of 70% and a specificity of 60%.

The severity of respiratory failure may be related to the direct myo- and neurotoxic effects of the virus [8]. To verify the morphology underlying the diaphragmatic dysfunction, we performed a single morphological study of the diaphragm and phrenic nerve of a patient who died from COVID-19. The specimens showed pericellular and perivascular edema, venular thrombosis, endoneurial edema, and sludge in the arteriolar lumen (Fig. 3).

The morphological changes of the phrenic nerve in this case can explain the acute decompensation of respiratory failure with respiratory arrest in patients with COVID-19.

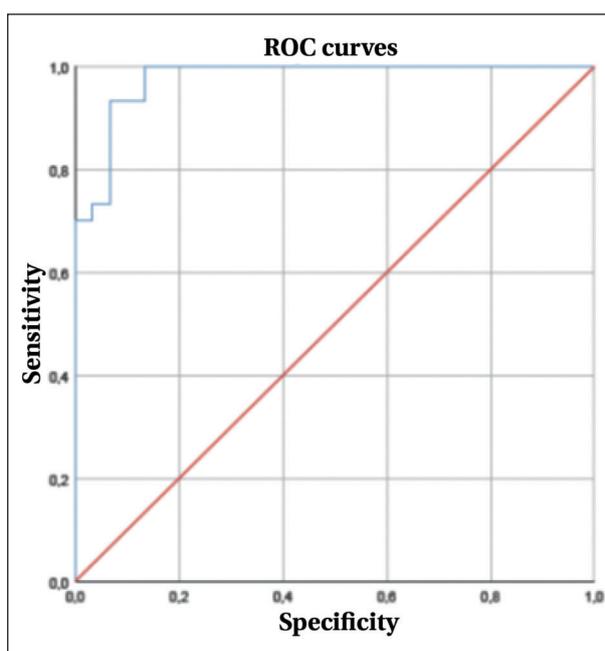


Fig. 1. A curve for assessing the prognostic significance of the regression model.

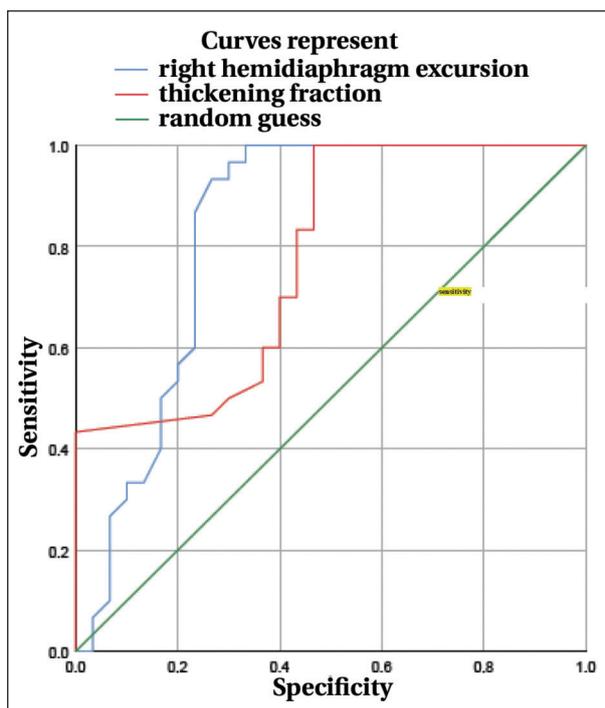
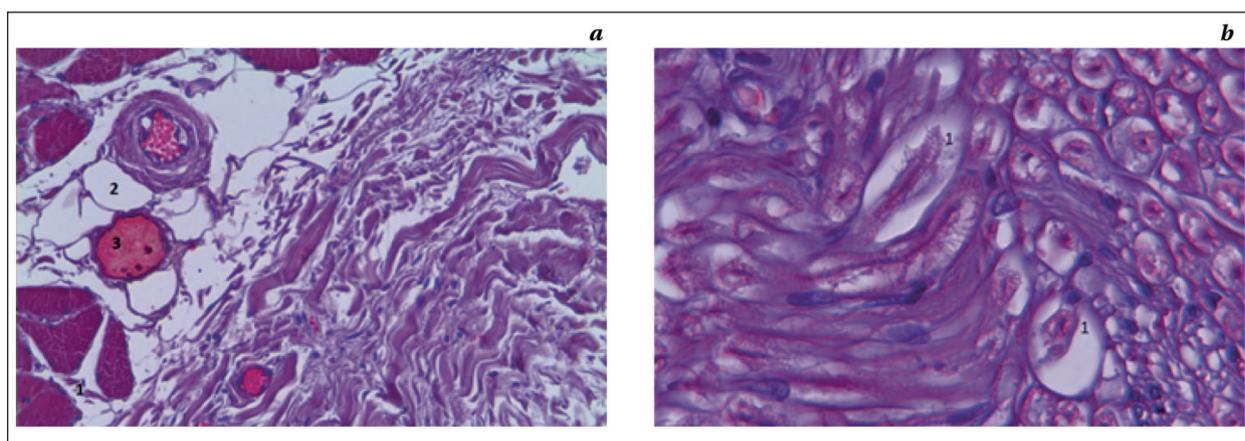


Fig. 2. The curves of prognostic value assessment of the right hemidiaphragm excursion (shown in blue), the diaphragm thickening fraction (in red) in ROC analysis.

The obtained morphological data warrant further investigation of the relationship between diaphragm function and its morphological changes in patients with COVID-19.



**Fig. 3. Specimen of the diaphragm (a) and phrenic nerve (b) of a patient who died of COVID-19.**

**Note.** Hematoxylin and eosin staining. XT0028 video attachment. *a* —  $\times 20$  magnification. Pericellular (1) and perivascular (2) edema, venous thrombosis (3). *b* —  $\times 63$  magnification. Endoneural edema (1).

## Conclusion

Patients with critical novel coronavirus infection who require mechanical ventilation demonstrate diaphragm dysfunction with its reduced motion and abnormal contraction.

Decreased right hemidiaphragm excursion less than 17.1 mm is a predictor of ventilator support in COVID-19 patient with a sensitivity of 93.3% and a specificity of 76.7%.

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