https://doi.org/10.15360/1813-9779-2022-4-4-10

Pneumomediastinum: a New Look at an Old Problem in a COVID-19 Pandemic

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Пневмомедиастинум: новый взгляд на старую проблему в условиях пандемии COVID-19

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For citation: *Olga Y. Chizhova, Irina A. Ruslyakova, Igor G. Bakulin, Natalia A. Prokofieva, Anastasia G. Sushilova, Galina M. Glazunova, Konstantin M. Lebedinsky.* Pneumomediastinum: a New Look at an Old Problem in a COVID-19 Pandemic. *Obshchaya Reanimatologiya = General Reanimatology.* 2022; 18 (4): 4–10. https://doi.org/10.15360/1813-9779-2022-4-4-10 [In Russ. and Engl.]

Summary

The aim of the study was to identify the risk factors of spontaneous pneumomediastinum and to determine its management strategy in patients with the novel coronavirus infection.

Material and methods. Eighteen patients with spontaneous pneumomediastinum (SPM) hospitalized in the Center for Novel Coronavirus Infection of the Mechnikov Northwestern State Medical University from 2020 to 2021 were examined. The control group consisted of 18 persons selected using matched sampling. We analyzed symptoms, medical and life history, comorbidities, physical examination results, laboratory and instrumental data, and disease management of patients in both groups

Results. The groups were comparable by age and sex. Among all patients hospitalized with the novel coronavirus infection, spontaneous pneumomediastinum was registered in 1.3% (n=18). Analysis of symptoms, medical and life history, comorbidities, physical examination results, laboratory and instrumental data and disease management did not reveal significant differences between the groups. At the same time, the proportion of obese patients in the main group was lower than in the control group. Estimation of HR showed that the risk of spontaneous pneumomediastinum development was significantly lower in obesity (HR=0.14; 95% CI: 0.033–0.63, P=0.010).

Conclusion. The risk of spontaneous pneumomediastinum is significantly lower in obese patients.

Keywords: COVID-19; novel coronavirus infection; spontaneous pneumomediastinum; mediastinal emphysema; obesity

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

The full text version of the paper is available at www.reanimatology.com

Introduction

Since May 2020, the Peter the Great Clinic of the I. I. Mechnikov Northwestern State Medical University has been reassigned to the Covid Center to treat patients with the novel coronavirus infection. During this time, 1,366 patients were hospitalized, including 287 in the ICU. Mortality in the clinic was 9.3%, while in the ICU it reached 44.6%, which indicates the high relevance of identifying predictors of adverse outcomes.

During analysis of fatal outcomes, spontaneous pneumomediastinum (SPM), an uncommon manifestation of spontaneous lung barotrauma in clinical practice, came to our attention.

Pneumomediastinum, or mediastinal emphysema, is a condition in which air is present in the mediastinal tissue [1]. Previously, spontaneous mediastinal emphysema was considered to be a rare stand-alone disease characterized by a benign course and occurring without any particular cause, mainly in young men [2–5]. The first description of SPM was made by Rene Laennec in 1819 in his treatise «De l'auscultation médiate» [6]. Louis Hamman was the first to report SPM as a separate enti-

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ty [7–11], which was later named Hamman syndrome. The first case report of SPM in COVID-19 appeared as early as in the first half of 2020 [12–16]. Most authors identified McLean's phenomenon (increased intrathoracic pressure due to persistent cough combined with decreased pressure in the perialveolar interstitial space) as an essential element of SPM pathogenesis [17]. However, in the last year, more and more frequent clinical case observations of SPM developing in COVID-19 can be found in the literature, where the risk factors included exacerbation of bronchial asthma and chronic obstructive pulmonary disease (COPD) and the use of steroids, which can promote pulmonary interstitial damage, leading to alveolar gas leakage [18]. All authors emphasize the severe course of COVID-19 associated with SPM and accompanied by higher rates of tracheal intubation and mortality [19, 20].

However, whether SPM should be considered a spontaneous or secondary to COVID-19 complication is still unclear, as is the management of such patients [21].

Material and Methods

All cases of SPM in patients with novel coronavirus infection hospitalized at the I. I. Mechnikov University Covid Center from 05.05.2020 to 01.06.2020, from 05.11.2020 to 01.02.2021, and from 01.07.2021 to 27.07.2021 were analyzed. A total of 18 cases of SPM were documented in the patients who comprised the main group. The control group also included 18 patients selected by the matching pair technique (matched by sex, age, and severity of lung involvement).

Patients in both groups were comparable by sex, age, and severity of lung involvement (Table 1).

The mean BMI in the main group was 26 [24; 29] kg/m^2, which was significantly lower than in the control group, where it was 33 [28; 37] kg/m^2 (P=0.0028).

All patients underwent chest CT scan on admission to the hospital. The severity (volume, area, extent) of lung involvement was assessed using an empirical visual semiquantitative scale, considering the approximate volume of lesions in both lungs [22]:

— no typical manifestations was considered as CT-0;

— minimal involvement < 25% of lung volume, CT-1;

— moderate involvement of 25–50% of lung volume, CT-2;

— significant involvement of 50–75% of lung volume, CT-3;

— subtotal involvement > 75% of lung volume, CT-4.

Verification of pneumomediastinum was performed using CT imaging.

Serila pulse oximetry was performed in all patients, starting from admission. If the signs of acute respiratory failure (ARF) and SpO_2 less than 90% were found, an additional arterial blood gases test with measurement of PaO_2, $PaCO_2$ was performed.

The routine clinical examination included complete blood test, urinalysis, measurement of serum C-reactive protein (CRP), AST, ALT, creatinine, urea, glucose, total protein, ferritin, troponin, D-dimer, as well as coagulation test and ECG.

The efficacy of therapy was evaluated by outcomes (recovery or lethal), as well as by documented adverse events associated with the treatment.

The data were analyzed using the Statistica 12 for Windows software package with the assessment of data distribution normality (Shapiro–Wilk's test), calculation of mean values, mean square deviation, medians, lower and upper quartiles, maximum and minimum values. Pearson's χ^2 test was used to examine correlation between qualitative variables; in case of violation of expected frequencies assumption (presence of at least one value less than 10 in 2×2 tables and more than 25% of such values in multifield tables), Fisher's exact test (FAT) was used. The 95% confidence intervals (95% CI) for qualitative characteristics were calculated by Wilson method. Quantitative indices with a normal distribution were ex-

Table 1. Patient characteristics and laboratory data at the time of hospitalization (*Me* [*Q1*; *Q3*]).

Parameter	Values in groups		*P*-value
	Main	Control	
Age, years	73 [67; 78]	72 [63; 81]	0.94
BMI, kg/m^2	26 [24; 29]	33 [28; 37]	0.0028
CT, day from disease onset	8 [4; 9]	9 [6; 10]	0.31
CT % of right lung involvement	35 [15; 68]	57 [32; 78]	0.056
CT % of left lung involvement	33 [11; 66]	63 [41; 78]	0.025
SpO_2, %	94 [91; 95]	85 [76; 89]	< 0.001
Hospitalization, day from disease onset	7 [5; 9]	9 [6; 10]	0.15
Duration of fever, from disease onset	7 [5; 8]	7 [6; 9]	0.28
Transfer to the ICU, days from disease onset	10 [7; 15]	10 [4; 12]	0.59
Hemoglobin, g/l	125 [105; 142]	129 [118; 143]	0.38
Leucocyte count, ×10^9/l	6.0 [4.7; 7.8]	6.6 [6.1; 8.4]	0.48
Neutrophil count, ×10^9/l	4.7 [3.5; 7.8]	4.9 [2.6; 7.1]	0.70
Lymphocyte count, ×10^9/l	0.8 [0.5; 1.0]	0.8 [0.4; 1.1]	0.76
C-reactive protein, mg/l	54 [29; 97]	124 [46; 159]	0.21
D-dimer, μg/ml	0.53 [0.29; 0.88]	0.53 [0.33; 2.73]	0.75

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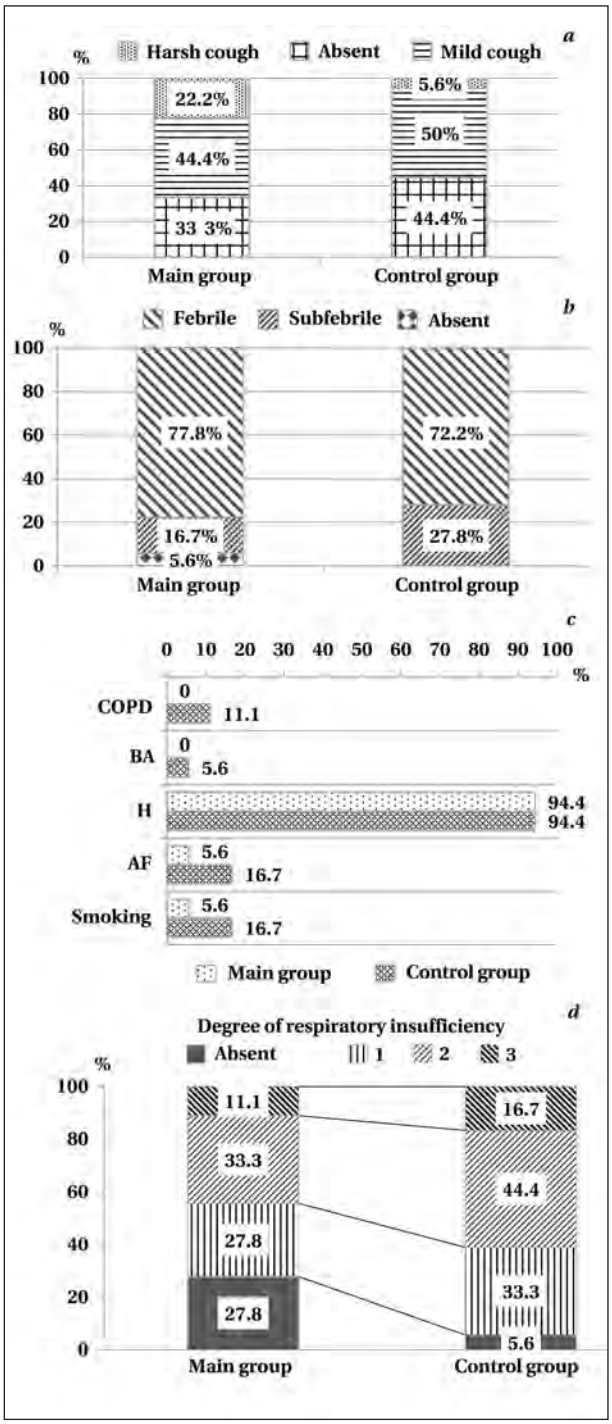

Fig. 1. Patient distribution by presence and severity of cough (*a*) and fever (*b*), by frequency of selected comorbidity signs and history of tobacco smoking (*c*), and by degree of respiratory insufficiency (*d*) on admission.
Note. COPD — chronic obstructive pulmonary disease; BA — bronchial asthma; H — hypertension; AF — atrial fibrillation.

pressed as $M \pm \sigma$, where M is the mean value and σ is the standard deviation. The Student's test was used for their comparison in 2 independent groups. Variables with non-normal distributions were reported as *Me* [*Q1*; *Q3*], where Me was the median, *Q1* and *Q3* were the lower and upper quartiles of the distribution. Mann-Whitney test was used to compare the variables in 2 independent groups. The *P*-value < 0.05 was used as a threshold for significance. Odds ratios (ORs) at 95% confidence interval were used to assess the risk of pneumomediastinum development.

Table 2. Lung tissue involvement in the main group on the day of SPM diagnosis.

Parameter	Patients, *n* (%)	95% CI
CT grade 2	2 (11.1)	3.1–32.8
CT grade 3	5 (27.8)	12.5–50.9
CT grade 4	11 (61.1)	38.6–79.7
Pleural effusion	6 (33.3)	16.3–56.3

Results

When evaluating the symptoms, persistent cough was observed in 4 (22.2%) patients in the main group and in 1 (5.6%) in the control group, the differences between the groups were not significant (Fig. 1, *a*).

The majority of patients in both groups had febrile fever: 14 (77.8%) in the main group, and 13 (72.2%) in the control group, *P*>0.05 (Fig. 1, *b*).

No differences were found between the groups in the timing of hospitalization and duration of fever before admission (Table 1).

There were also no differences in the frequency of selected comorbidity signs and history of tobacco smoking in the groups (Fig. 1, *c*).

History of surgical interventions requiring mechanical ventilation was recorded in 7 patients (38.9%) in the main group and in 3 patients (16.7%) in the control group (*P*=0.14).

No significant differences between the groups were found in severity of respiratory failure (Fig. 1d), but SpO_2 values differed with Me reaching 94 [91; 95] in the main group and 85 [76; 89] in the control group (*P*<0.001).

Comparison of laboratory parameters at the time of admission showed no significant differences between the groups (Table 1).

During hospitalization, all patients were started on a treatment in accordance with the current guidelines of the Russian Ministry of Health, including oxygen therapy through nasal cannulas with a flow rate of up to 10 l/min.

Later, with increasing severity of the condition, the patients underwent control chest CT scan, and 18 of them were found to have SPM (Table 2).

The severity of their disease required transfer to ICU and initiation of different types of respiratory support. There was no significant association between the day of initiation of respiratory support, its duration and the occurrence of SPM (Table 3). However, the obtained data indicate a tendency to a more severe disease in patients of the control group.

The types and parameters of respiratory support in the SPM group are shown in Table 4.

Table 3. Timing of initiation and duration of respiratory support from the moment of hospitalization ($M\pm\sigma$).

Parameter	Values in groups		*P*-value
	Main	Control	
High-flow oxygenation, days from the disease onset	13±7	11±3	0.51
Duration of high-flow oxygenation, days	6±4	3±2	0.16
Noninvasive lung ventilation, days from disease onset	19±11	14±5	0.095
Duration of noninvasive ventilation, days	3±3	4±3	0.72
Mechanical ventilation, days from disease onset	22±9	17±6	0.083

Table 4. Respiratory support in the SPM group.

Variable	Value	
Type	**Patients, *n* (%)**	**95% CI**
Nasal cannula oxygenation	4 (22.2)	9.0-45.2
High-flow oxygenation	1 (5.6)	1.0-25.8
Noninvasive lung ventilation	4 (22.2)	9.0-45.2
Mechanical ventilation PCV	4 (22.2)	9.0-45.2
Mechanical ventilation PCV+	5 (27.8)	12.5-50.9
Parameter	$M\pm\sigma$	
PIP, mbar	16±3	
PEEP, mbar	10±2	
FiO_2, %	86±21	
P/F, mm Hg	110±74	
C_{stat}, ml/mbar	33±12	
Flow, l/min	20±2	
SpO_2, %	92±10	
PO_2, mm Hg	82±61	
PCO_2, mm Hg	40±17	

Table 5. Laboratory values of patients at the time of development of SPM.

Parameter	Me [Q1; Q3]
Hemoglobin, g/l	109 [91; 133]
Hematocrit	0.330 [0.280; 0.402]
Leucocyte count, $\times10^9$/l	11.3 [9.5; 13.0]
Neutrophil count, $\times10^9$/l	10.0 [7.4; 12.0]
Lymphocyte count, $\times10^9$/l	0.5 [0.3; 1.1]
Platelet count, $\times10^9$/l	226 [162; 282]
Total protein, g/l	54 [50; 63]
Serum albumin, g/l	29 [26; 32]
LDH, U/L	543 [468; 772]
ALT, U/L	33 [25; 53]
AST, U/L	33 [19; 42]
Total bilirubin, mmol/l	10 [8; 15]
C-reactive protein, mg/l	77 [10; 182]
Ferritin, µg/l	994 [299; 1 803]
Procalcitonin, ng/ml	0.399 [0.124; 1.840]
D-dimer, µg/l	1.79 [0.79; 7.50]
IL-6, pg/ml	534 [160; 769]

Laboratory values of patients at the time of SPM development are summarized in Table 5.

No significant association was found between the occurrence of SPM and duration of systemic steroid use or timing of administration of such drugs as JAK1/JAK2 inhibitors or anti-IL-6 monoclonal antibodies (Table 6).

When analyzing the clinical variants of spontaneous lung barotrauma, we found that subcutaneous emphysema was present in 5 (27.8%) patients, whereas in 1 (5.6%) patient it was associated with a pneumothorax and in another 1 (5.6%) with a tension pneumothorax. Isolated SMP was revealed in 10 (55.5%) patients. All patients with SPM underwent diagnostic bronchoscopy, which revealed no visible defects of trachea and bronchi (Fig. 2).

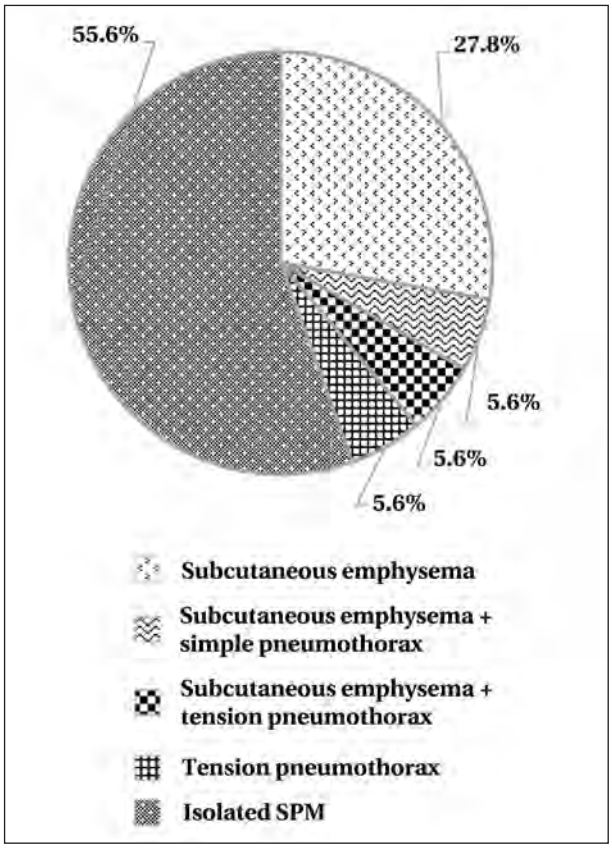

Fig. 2. Types of spontaneous pulmonary barotrauma.

Lethal outcome in the SPM group occurred in 16 (88.9%) patients, on average on day 26±10 of hospitalization (Table 7).

When determining the risks of SPM development, obese patients were found to have a signifi-

Table 6. Analysis of relationship between SPM development and timing and duration of pathogenetic therapy (*Me* [*Q1*; *Q3*]).

Parameter	Values in groups		*P*-value
	Main	Control	
Duration of steroid use, days	10 [5; 12]	8 [6; 10]	0.38
Baricitinib, day from disease onset	8 [6; 10]	13	
Tocilizumab, day from disease onset	11 [10; 15]	11 [10; 15]	0.44

Table 7. Timing of outcomes among patie (*M*±*σ*).

Parameter	Values in groups		*P*-value
	Main	Control	
Lethal outcome, day of disease	20±7	26±10	0.074
Discharge, day of disease	25±1	32±11	0.48

Table 8: Risk assessment of SPM development in patients with/without obesity.

Parameter	Odds ratio [95% CI]	*P*-value
No obesity (reference)	1	
Obesity	0.14 (0.033–0.63)	0.010

cantly lower likelihood of SPM development (OR=0.14; 95% CI: 0.033–0.63, *P*=0.01) versus the patients with normal body weight.

Discussion

Thus, the issue of factors influencing the occurrence of SPM is relevant and still controversial, which requires more detailed studying. The scope of studies in this area is still limited, which is due to the low incidence of SPM in patients with the novel coronavirus infection. In our study, it was 1.3%, with a mortality rate of 88.9%, which is comparable with the available data [23].

Interestingly, the proportion of obese patients in the main group was lower, while the subsequent estimation of OR showed that in obesity the risk of developing SPM was statistically significantly lower. According to Rodriguez-Arciniega T. G. et al. [24], the mean BMI value was slightly lower in SPM group (28 versus 29.5 kg/m^2), but no significant differences compared to the control group were observed. It is worth noting that the authors found SPM only in 9 out of 271 patients.

In an attempt to explain the results obtained, obesity was considered to be an unfavorable predictor for any respiratory complications [25, 26], but on the other hand, the fact that low nutritional status is critical in COPD, especially its emphysema phenotype, shoul not be underestimated. The emphysema phenotype is well known to be associated with a decreased nutritional status [25, 27, 28]. In addition, there is evidence of an inverse relationship between adipose tissue mass and the emphysema progression [29–31]. These data could partially explain the results of our study and can serve as a basis for further research to identify risk factors of SPM in patients with the novel coronavirus infection involving larger number of participants.

Conclusion

The risk of spontaneous pneumomediastinum is significantly lower in obese patients.

References

1. *Платов И. И., Моисеев В. С.* Спонтанный пневмомедиастинум. *Проблемы туберкулеза*. 1998; 5: 61–62. [*Platov I. I., Moiseev V. S.* Spontaneous pneumomediastinum. *Tuberculosis problems / Probl Tuberk*. 1998; 5: 61–62. (in Russ.)]. PMID: 9866405.
2. *Caceres M., Ali, S. Z., Braud R., Weiman, D., Garrett H. E Jr.* Spontaneous pneumomediastinum: a comparative study and review of the literature. *Ann Thorac Surg*. 2008; 86 (3): 962–966. DOI: 10.1016/j.athoracsur.2008.04.067. PMID: 18721592.
3. *Jougon J. B., Ballester M., Delcambre F., Mac Bride T., Dromer C. E.H., Velly J.- F.* Assessment of spontaneous pneumomediastinum: experience with 12 patients. *Ann Thorac Surg*. 2003; 75 (6): 1711–1714. DOI: 10.1016/s0003-4975 (03)00027-4. PMID: 12822604.
4. *Koullias G. J., Korkolis D. P., Wang X. J., Hammond G. L.* Current assessment and management of spontaneous pneumomediastinum: experience in 24 adult patients. *Eur J Cardiothorac Surg*. 2004; 25 (5): 852–855. DOI: 10.1016/j.ejcts.2004.01.042. PMID: 15082293.
5. *Yellin A., Gapany-Gapanavicius M., Lieberman Y.* Spontaneous pneumomediastinum: is it a rare cause of chest pain? *Thorax*. 1983; 38 (5): 383–385. DOI: 10.1136/thx.38.5.383. PMID: 6879488.
6. *Laennec R. T.* De l'auscultation médiate: ou traité du diagnostic des maladies des poumons et du coeur. *Brosson et Chaudé*. (in French).1819; 2.
7. *Халев Ю. В.* Медиастинальная эмфизема. *Кардиология*. 1982; 22 (4): 111–113. [*Khalev Iu. V.* Mediastinal emphysema. *Kardiologija*. 1982; 22 (4): 111–113. (in Russ).] PMID: 7077917.
8. *Campillo-Soto A., Coll-Salinas A., Soria-Aledo V., Blanco-Barrio A., Flores-Pastor B., Candel-Arenas M., Aguayo-Albasini J. L.* Spontaneous pneumomediastinum: descriptive study of our experience with 36 cases. *Arch Bronconeumol*. 2005; 41 (9): 528–531. (in Spanish). DOI: 10.1016/s1579-2129 (06)60274-7. PMID: 16194517.
9. *Jougon J.B., Ballester M., Delcambre F., Mac Bride T., Dromer C.E.H., Velly J.F.* Assessment of spontaneous pneumomediastinum: experience with 12 patients. *Ann Thorac Surg*. 2003; 75 (6): 1711–1714. DOI: 10.1016/s0003-4975 (03)00027-4. PMID: 12822604.

10. *Macia I., Moya J., Ramos R., Morera R., Escobar I., Saumench J., Perna V., Rivas F.* Spontaneous pneumomediastinum: 41 cases. *Eur J Cardiothorac Surg.* 2007; 31 (6): 1110–1114. DOI: 10.1016/j.ejcts.2007.03.008. PMID: 17420139.
11. *Zhou C., Gao C., Xie Y., Xu M.* COVID-19 with spontaneous pneumomediastinum. *Lancet Infect Dis.* 2020; 20 (4): 510. DOI: 10.1016/S1473-3099(20)30156-0. PMID: 32164830.
12. *Wang W., Gao R., Zheng Y., Jiang L.* COVID-19 with spontaneous pneumothorax, pneumomediastinum and subcutaneous emphysema. *J Travel Med.* 2020; 27 (5): taaa062. DOI: 10.1093/jtm/taaa062. PMID: 32330274.
13. *Kolani S., Houari N., Haloua M., Lamrani Y.A., Boubbou M., Serraj M., Aamara, B., Maaroufi M., Alami B.* Spontaneous pneumomediastinum occurring in the SARS-COV-2 infection. *ID Cases.* 2020; 21: e00806. DOI: 10.1016/j.idcr.2020.e00806. PMID: 32395425.
14. *Wang J., Su X., Zhang T., Zheng C.* Spontaneous pneumomediastinum: a probable unusual complication of coronavirus disease 2019 (COVID-19) pneumonia. *Korean J Radiol.* 2020; 21 (5): 627–628. DOI: 10.3348/kjr.2020.0281. PMID: 32323507.
15. *Mohan V., Tauseen R.A.* Spontaneous pneumomediastinum in COVID-19. *BMJ Case Rep.* 2020; 13 (5): e236519. DOI: 10.1136/bcr-2020-236519. PMID: 32457032.
16. *Janssen J., Kamps M.J.A., Joosten T.M.B., Barten D.G.* Spontaneous pneumomediastinum in a male adult with COVID-19 pneumonia. *Am J Emerg Med.* 2021; 40: 228.e3-228.e5 DOI: 10.1016/j.ajem. 2020.07.066. PMID: 32800430.
17. *Sahni S., Verma S., Grullon J., Esquire A., Patel P., Talwar A.* Spontaneous pneumomediastinum: time for consensus. *N Am J Med Sci.* 2013; 5 (8): 460–464. DOI: 10.4103/1947-2714.117296. PMID: 24083220.
18. *Vega J.M.L., Gordo M.L.P., Tascón A.D., Vélez S.O.* Pneumomediastinum and spontaneous pneumothorax as an extrapulmonary complication of COVID-19 disease. *Emerg Radiol.* 2020; 27 (6): 727–730. DOI: 10.1007/s10140-020-01806-0. PMID: 32524296.
19. *Quincho-Lopez A., Quincho-Lopez D.L., Hurtado-Medina F. D.* Case report: pneumothorax and pneumomediastinum as uncommon complications of COVID-19 pneumonia — literature review. *Am J Trop Med Hyg.* 2020; 103 (3): 1170–1176. DOI: 10.4269/ajtmh.20-0815. PMID: 32705978.
20. *Singh A., Bass J., Lindner D.H.* Rare complication of pneumomediastinum and pneumopericardium in a patient with COVID-19 pneumonia. *Case Rep Pulmonol.* 2020: 8845256. DOI: 10.1155/2020/8845256. PMID: 33204564.
21. *Inui S., Fujikawa A., Jitsu M., Kunishima N., Watanabe S., Suzuki Y., Umeda S., Uwabe Y.* Chest CT findings in cases from the cruise ship diamond princess with Coronavirus disease (COVID-19). *Radiol Cardiothoracic Imaging.* 2020; 2 (2): e200110. DOI: 10.1148/ryct.2020200110. PMID: 33778566.
22. *Shaikh N., Al Ameri G., Shaheen M., Abdaljawad W. I., Al Wraidat M., Al Alawi A.A.S., Ali H.S., Mohamed A.S., Daeri H., Khatib M.Y., Elshafei M.S., Nashwan A.J.* Spontaneous pneumomediastinum and pneumothorax in COVID-19 patients: a tertiary care experience. *Health Sci Rep.* 2021; 4 (3): e339. DOI: 10.1002/hsr2.339. PMID: 34355063.
23. *Rodriguez-Arciniega T.G., Sierra-Diaz E., Flores-Martinez J.A., Alvizo-Perez M.E., Lopez-Leal I.N., Corona-Nakamura A.L., Castellanos-Garcia H.E., Bravo-CuellarA.* Frequency and risk factors for spontaneous pneumomediastinum in COVID-19 patients. *Front Med (Lausanna).* 2021; 8: 662358. DOI: 10.3389/fmed.2021.662358.
24. *Арутюнов, Г. П., Тарловская, Е. И., Арутюнов, А. Г., Беленков, Ю. Н., Конради, А. О., Лопатин, Ю. М., Ребров, А. П., Терещенко, С. Н., Чесникова, А. И., Айрапетян, Г. Г., Бабин, А. П., Бакулин, И. Г., Бакулина, Н. В., Балыкова, Л. А., Благонравова, А. С., Болдина, М. В., Вайсберг, А. Р., Галявич, А. С., Гомонова, В. В., Григорьева, Н. Ю., Губарева, И. В., Демко, И. В., Евзерихина, А. В., Жарков, А. В., Камилова, У. К., Ким, З. Ф., Кузнецова, Т. Ю., Ларева, Н. В., Макарова, Е. В., Мальчикова, С. В., Недогода, С. В., Петрова, М. М., Починка, И. Г., Протасов, К. В., Проценко, Д. Н., Рузанов, Д. Ю., Сайганов, С. А., Сарыбаев, А. Ш., Селезнева, Н. М., Сугралиев, А. Б., Фомин, И. В., Хлынова, О. В., Чижова, О. Ю., Шапошник, И. И., Щукарев, Д. А., Абдрахманова, А. К., Аветисян, С. А., Авоян, О. Г., Азарян, К. К., Аймаханова, Г. Т., Айыпова, Д. А., Акунов, А. Ч., Алиева, М. К., Апаркина, А. В., Арусланова, О. Р., Ашина, Е. Ю., Бадина, О. Ю., Барышева, О. Ю., Батчаева, А. С., Битиева, А. М., Бихтеев, И. У., Бородулина, Н. А., Брагин, М. В., Буду, А. М., Бурыгина, Л. А., Быкова, Г. А., Варламова, Д. Д., Везикова, Н. Н., Вербицкая, Е. А., Вилкова, О. Е., Винникова, Е. А., Вустина, В. В., Галова, Е. А., Генкель, В. В., Горшенина, Е. И., Гостищев, Р. В., Григорьева, Е. В., Губарева, Е. Ю., Дабылова, Г. М., Демченко, А. И., Долгих, О. Ю., Дуванов, И. А., Дуйшобаев, М. Ы., Евдокимов, Д. С., Егорова, К. Е., Ермилова, А. Н., Желдыбаева, А. Е., Заречнова, Н. В., Иванова, С. Ю., Иванченко, Е. Ю., Ильина, М. В., Казаковцева, М. В., Казымова, Е. В., Калинина, Ю. С., Камардина, Н. А., Караченова, А. М., Каретников, И. А., Кароли, Н. А., Карпов, О. В., Карсиев М. Х., Каскаева Д. С., Касымова К. Ф., Керимбекова, Ж. Б., Керимова, А. Ш., Ким, Е. С., Киселева, Н. В., Клименко, Д. А., Климова, А. В., Ковалишена, О. В., Колмакова, Е. В., Колчинская, Т. П., Колядич, М. И., Кондрякова, О. В., Коновал, М. П., Константинов, Д. Ю., Константинова, Е. А., Кордюкова, В. А., Королева, Е. В., Крапошина, А. Ю., Крюкова, Т. В., Кузнецова А. С., Кузьмина Т. Ю., Кузьмичев, К. В., Кулчороева, Ч. К., Куприна, Т. В., Куранова, И. М., Куренкова, Л. В., Курчугина, Н. Ю., Кушубакова, Н. А., Леванкова, В. И., Левин,М. Е., Любавина, Н. А., Магдеева, Н. А., Мазалов, К. В., Майсеенко, В. И., Макарова, А. С., Марипов, А. М., Марусина, А. А., Мельников, Е. С., Моисеенко, Н. Б., Мурадова, Ф. Н., Мурадян, Р. Г., Мусаелян, Ш. Н., Никитина, Н. М., Огурлиева, Б. Б., Одегова, А. А., Омарова, Ю. В., Омурзакова, Н. А., Оспанова, Ш. О., Пахомова, Е. В., Петров, Л. Д., Пластинина, С. С., Погребецкая, В. А., Поляков Д. С., Пономаренко, Е. В., Попова, Л. Л., Прокофьева, Н. А., Пудова, И. А., Раков, Н. А., Рахимов, А. Н., Розанова, Н. А., Серикболкызы, С., Симонов, А. А., Скачкова, В. В., Смирнова, Л. А., Соловьева, Д. В., Соловьева, И. А., Сохова, Ф. М., Субботин, А. К., Сухомлинова, И. М., Сушилова, А. Г., Тагаева, Д. Р., Титойкина, Ю. В., Тихонова, Е. П., Токмин, Д. С., Торгунакова, М. С., Треногина, К. В., Тростянецкая, Н. А., Трофимов, Д. А., Туличев, А. А., Тупицин, Д. И., Турсунова, А. Т., Уланова, Н. Д., Фатенков, О. В., Федоришина, О. В., Филь, Т. С., Фомина, И. Ю., Фоминова, И. С., Фролова, И. А., Цвингер, С. М., Цома, В. В., Чолпонбаева, М. Б., Чудиновских, Т. И., Шахгильдян, Л. Д., Шевченко, О. А., Шешина, Т. В., Шишкина, Е. А., Шишков, К. Ю., Щербаков, С. Ю., Яушева, Е. А.*; Международный регистр «Анализ динамики Коморбидных заболеваний

у пациентов, перенесших инфицирование SARS-CoV-2» (АКТИВ SARS-CoV-2): анализ предикторов неблагоприятных исходов острой стадии новой коронавирусной инфекции. *Российский кардиологический журнал*. 2021; 26 (4): 116–131. DOI: 10.15829/1560-4071-2021-4470 [*Arutyunov G.P., Tarlovskaya E.I., Arutyunov A.G., Belenkov Y.N., Konradi A.O., Lopatin Y.M., Rebrov A.P., Tereshchenko S.N., Chesnikova A.I., Hayrapetyan H.G., Babin A.P., Bakulin I.G., Bakulina N.V., Balykova L.A., Blagonravova A.S., Boldina M.V., Vaisberg A.R., Galyavich A.S., Gomonova V.V., Grigorieva N.U., Gubareva I.V., Demko I.V., Evzerikhina A.V., Zharkov A.V., Kamilova U.K., Kim Z.F., Kuznetsova T.Yu., Lareva N.V., Makarova E.V., Malchikova S.V., Nedogoda S.V., Petrova M.M., Pochinka I.G., Protasov K.V., Protsenko D.N., Ruzanov D.Yu., Sayganov S.A., Sarybaev A.S., Selezneva N.M., Sugraliev A.B., Fomin I.V., Khlynova O.V., Chizhova O.Yu., Shaposhnik I.I., Schukarev D.A., Abdrahmanova A.K., Avetisian S.A., Avoyan H.G., Azarian K.K., Aimakhanova G.T., Ayipova D.A., Akunov A.C., Alieva M.K., Aparkina A.V., Aruslanova O.R., Ashina E.Yu., Badina O.Y., Barisheva O.Yu., Batchayeva A.S., Bikhteyev I.U., Borodulina N.A., Bragin M.V., Budu A.M., Burygina L.A., Bykova G.A., Varlamova D.D., Vezikova N.N., Verbitskaya E.A., Vilkova O.E., Vinnikova E.A., Vustina V.V., Galova E.A., Genkel V.V., Gorshenina E.I., Gostishev R.V., Grigorieva E.V., Gubareva E.Yu., Dabylova G.M., Demchenko A.I., Dolgikh O.Yu., Duvanov I.A., Duyshobayev M.Y., Evdokimov D.S., Egorova K.E., Ermilova A.N., Zheldybayeva A.E., Zarechnova N.V., Ivanova S.Yu., Ivanchenko E.Yu., Ilina M.V., Kazakovtseva M.V., Kazymova E.V., Kalinina Yu.S., Kamardina N.A., Karachenova A.M., Karetnikov I.A., Karoli N.A., Karpov O.V., Karsiev M.K., Kaskaeva D.S., Kasymova K.F., Kerimbekova Z.B., Kerimova A.S., Kim E.S., Kiseleva N.V., Klimenko D.A., Klimova A.V., Kovalishena O.V., Kolmakova E.V., Kolchinskaya T.P., Kolyadich M.I., Kondriakova O.V., Konoval M.P., Konstantinov D.Yu., Konstantinova E.A., Kordukova V.A., Koroleva E.V., Kraposhina A.Yu., Kriukova T.V., Kuznetsova A.S., Kuzmina T.Y., Kuzmichev K.V., Kulchoroeva C.K., Kuprina T.V., Kouranova I.V., Kurenkova L.V., Kurchugina N.Yu., Kushubakova N.A., Levankova V.I., Levin M.E., Lyubavina N.A., Magdeyeva N.A., Mazalov K.V., Majseenko V.I., Makarova A.S., Maripov A.M., Marusina A.A., Melnikov E.S., Moiseenko N.B., Muradova F.N., Muradyan R.G., Musaelian S.N., Nikitina N.M., Ogurlieva B.B., Odegova A.A., Omarova Yu.M., Omurzakova N.A., Ospanova S.O., Pahomova E.V., Petrov L.D., Plastinina S.S., Pogrebetskaya V.A., Polyakov D.S., Ponomarenko E.V., Popova L.L., Prokofeva N.A., Pudova I.A., Rakov N.A., Rakhimov A.N., Rozanova N.A., Serikbolkyzy S., Simonov A.A., Skachkova V.V., Smirnova L.A., Soloveva D.V., Soloveva I.A., Sokhova F.M., Subbotin A.K., Sukhomlinova I.M., Sushilova A.G., Tagayeva D.R., Titojkina Yu.V., Tikhonova E.P., Tokmin D.S., Torgunakova M.S., Trenogina K.V., Trostianetckaia N.A., Trofimov D.A., Tulichev A.A., Tupitsin D.I., Tursunova A.T., Ulanova N.D., Fatenkov O.V., Fedorishina O.V., Fil T.S., Fomina I.Yu., Fominova I.S., Frolova I.A., Tsvinger S.M., Tsoma V.V., Cholponbaeva M.B., Chudinovskikh T.I., Shakhgildyan L.D., Shevchenko O.A., Sheshina T.V., Shishkina E.A., Shishkov K.Yu., Sherbakov S.Y., Yausheva E.A.* International register «Dynamics analysis of comorbidities in SARS-CoV-2 survivors» (AKTIV SARS-CoV-2): analysis of predictors of short-term adverse outcomes in COVID-19. *Russian Journal of Cardiology/ Rossiysky Kardiologichesky Zhournal*. 2021; 26 (4): 4470. DOI: 10.15829/1560-4071-2021-4470].

25. *Gu S., Li R., Leader J.K., Zheng B., Bon J., Gur D., Sciurba F, Jin C., Pu J.* Obesity and extent of emphysema depicted at CT. *Clin Radiol*. 2015; 70 (5): e14-e19. DOI: 10.1016/j.crad.2015.01.007. PMID: 25703460.
26. *Guerra S., Sherrill D.L., Bobadilla A., Martinez F.D., Barbee R.A.* The relation of body mass index to asthma, chronic bronchitis, and emphysema. *Chest*. 2002; 122 (4): 1256–1263. DOI: 10.1378/chest. 122.4.1256. PMID: 12377850.
27. *Grace J., Leader J.K., Nouraie S.M., Pu J., Chandra D., Zhang Y., Sciurba F.C., Bon J.* Mediastinal and subcutaneous chest fat are differentially associated with emphysema progression and clinical outcomes in smokers. *Respiration*. 2017; 94 (6): 501–509. DOI: 10.1159/000479886. PMID: 28910816.
28. *Bhatia S., Sood A.* Obesity and obstructive lung disease: An epidemiologic review. *Mechanisms and Manifestations of Obesity in Lung Disease*. 2019; 67–87. DOI: 10.1016/B978-0-12-813553-2.00004-X.
29. *Чижова О.Ю., Павлова Е.Ю., Семенова Е.А.* Системные эффекты двойной бронходилатации в терапии хронической обструктивной болезни легких (клиническое наблюдение). *Практическая пульмонология*. 2017; 3: 115–120. [*Chizhova O.Yu., Pavlova E.Yu., Semenova E.A.* Systemic effects of double bronchodilation in a patient with chronic obstructive pulmonary disease: a clinical case. *Practical pulmonology / Prakticheskaya Pulmonologiya*. 2017; 3: 115–120. (in Russ.).

Received 20.03.2022