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Prediction of violations of primary and secondary hemostasis in patients with chronic obstructive pulmonary disease

key words: *chronic obstructive pulmonary disease, haemostatic disorders, systemic inflammation, diagnosis, prognosis.*

Chronic obstructive pulmonary disease (COPD) is known to be associated with the development of multiple comorbidities and extrapulmonary systemic effects such as osteoporosis, metabolic syndrome, depression as well as atherosclerosis, thrombosis, pulmonary embolism, etc. that can make the disease much worse in some patients [3, 6–9, 11, 13, 14, 20]. The incidence and intensity of extrapulmonary pathologies, including haemostasis disorders, are also increased with the progression of clinical signs and severity of COPD [10, 12, 18, 21].

It is noteworthy that in a stable phase some COPD patients can develop both hyperaggregation/hypercoagulation disorders (the common changes occurring in COPD patients) and hypoaggregation/hypocoagulation changes. Ukrainian researchers have shown that nearly a quarter of patients have lower aggregation properties of platelets than apparently healthy subjects [4]. Similar results were obtained by foreign researchers who found that aggregation properties of platelets were significantly lower than that of apparently healthy subjects based upon findings of adenosine diphosphate (ADP) and collagen-induced platelet aggregometry [16].

However, the chronic persistent inflammation caused by COPD increases the levels of systemic inflammatory markers, in particular C-reactive protein (CRP) which both activates the production of cytokines and the complement system and enhances formed elements (white blood cells, neutrophils, etc.) adhesion to the vascular endothelium [1, 17, 19]. These processes associated with arterial hypoxia caused by bronchial obstruction contribute to the activation of blood components involved in both primary and secondary haemostasis, which eventually destabilizes the whole haemostatic system [4, 15, 16]. Therefore, increased CRP levels can be considered as an adverse prognostic factor for both the course of COPD and the development of cardiovascular events [15].

The recent studies indicate that haemostasis disorders occurring in COPD patients play an important role in the progression, complications development and prognosis of the disease. Having their burdensome nature in mind, correlating these disorders with severity of the disease and intensity of systemic inflammation, and finding an individual prognostic indicator for the potential of their aggregation and occurrence of coagulation disorders can be a basis for differentiated, pathogenetically grounded programmes to improve the treatment of COPD patients [2, 6].

There is no currently agreement of opinion regarding the informative value or reproducibility of comprehensive haemostatic disorder assessment methodology. There is no clear understanding of the criteria for laboratory assessment of haemostasis disorders in COPD patients, particularly at the primary haemostasis level. A clinician/COPD patient-friendly method of haemostatic disorders prognosis is not yet available which could help prescribe preventive measures, including drug treatment, on a timely basis to prevent adverse complications that can eventually threaten a patient's health and life.

Therefore, the **purpose of our study** was to assess haemostasis in COPD patients in terms of severity of the disease and intensity of systemic inflammation and

to identify the best prognostic indicators of the primary and secondary haemostasis disorders in this population.

Research materials and methods

We have examined 81 COPD patients with stage I–IV ventilation disorders without clinically significant cardiovascular or other pathologies that cause quite distinct haemostatic changes. These patients were in the main study group (mean age – 61.2 ± 8.4 years, males – 69 (85.1%), females – 12 (14.9%), forced expiratory volume in first second (FEV_1) – 51.5 [38.4–62.5]% of predicted value). Pursuant to Decree No 555 issued by the Ministry of Health of Ukraine on 27 June 2013, all patients were assigned to clinical groups (A, B, C or D) according to adverse events in progression of their disease [10].

Based upon the purpose of the study the main group of patients was divided into two subgroups depending on severity of the clinical course of the disease. Subgroup 1 consisted of 22 patients with mild COPD (mean age – (59.8 ± 8.2) years, males – 18 (81.8%), females – 4 (18.2%), FEV1–74.2 [68,2–81,9]% of predicted value); all of them had GOLD stage I or II ventilation disorders (post-bronchodilator FEV1 ≥ 50% of predicted value) and were in clinical group A and B. Subgroup 2 included 59 patients with stage III or IV COPD with severe ventilation disorders (post-bronchodilator FEV1 < 50% of predicted value) who were in clinical group C and D (mean age – (62.1 ± 9.2) years, males – 50 (84.7%), females – 9 (15.3%), FEV1–45.1 [34.7–51.5]% of predicted value). All patients received adequate drug treatment of their disease.

The control group consisted of 25 apparently healthy subjects comparable by age and gender with patients in the main group (mean age – 54.0 ± 4.0 years, males – 20 (80.0%) ($p > 0.05$), females – 5 (20.0%) ($p > 0.05$)).

For assessment of primary haemostasis platelet adhesion assay (PAA) and induced optical aggregometry (by the optical method with AP 2110 aggregometer (Solar, Belarus) set at weak (ADP concentration 2.0 μM) and strong (collagen concentration 2.0 μM) aggregation inducers) were performed for all subjects.

In order to assess secondary haemostasis photometric (turbodensitometric) coagulogram was performed by the use of semi-automatic 2-channel optical coagulation analyser COA 2 (LabiTec, Germany).

The immunoturbidimetric test on automatic analyser Cobas E411 (RocheDiagnostics GmbH, Germany) was used to measure the severity of systemic inflammation by serum CRP.

The ROC (receiver operating characteristic) analysis was performed to assess the prognostic potential of the indicators; the result is presented as the area under the ROC curve (AUC) built by the use of the sensitivity (Se) and specificity (Sp) values of the diagnostic test with 95% confidence interval (95% CI AUC). The standard error for AUC was calculated by the methodology offered by DeLong et al. (1988).

The results of the ROC analysis were considered statistically significant at AUC > 0.5. The AUC in the range between 0.9 and 1.0 meant that the indicator had excellent diagnostic accuracy; 'very good' in the range between 0.8 and 0.9; 'good' when it was between 0.7 and 0.8;'average' when it was between 0.6 and 0.7; 'unsatisfactory' when it was between 0.5 and 0.6; and there was 'lack' of diagnostic accuracy when the value was < 0.5.

The threshold prognostic values of the diagnostic tests were calculated by the optimal ROC cut-off points with the use of the Youden index. The ROC analysis was performed and the ROC curves were built with MedCalc Statistical Software free trial version 17.4 available on the developer's official website.

The difference between the compared values was considered statistically significant at $p < 0.05$.

Statistical analysis of the study results was performed by the use of EXCEL-2007® and STATISTICA 6.1 software. (Stat Softline, serial number AGAK909E415822FA).

Results and discussion

The analysis of primary haemostasis showed that PAA levels in the main group were significantly higher than those in the control group (42.0 [31.0–49.0]% and 27.0 [22.0–31.0]%, respectively) ($p < 0.05$). In subgroups 1 and 2 PAA levels were substantially the same (42.0 [25.0–46.0]% and 37.0 [25.0–48.0]%, respectively) ($p > 0.05$) and higher than in healthy subjects ($p < 0.05$).

The distribution of subjects by ADP-induced platelet aggregation types (normal aggregation, hypoaggregation, hyperaggregation) has demonstrated the presence of blood platelet aggregation disorders in all subgroups of COPD patients (Table 1). There was significant difference between the subgroups and the control group in terms of the number of cases of primary haemostasis disorders. In particular, a third of patients in subgroup 1 had normal platelet aggregation activity, nearly a half had hyperaggregation while hypoaggregation was observed in a fifth of patients. In subgroup 2, only a fifth of patients had hyperaggregation of platelets and a tenth of patients showed the signs of hypoaggregation.

Evidence suggests that a long–term use of inhaled glucocorticosteroids (IGCC) blocks the synthesis of thromboxane A2, which is directly involved in the release of granules by platelets, while reducing platelet aggregation activity thereby normalising platelet aggregation in patients with severe COPD vs. those with a mild form of the disease.

As with ADP-induced aggregation, the distribution of the study patients and the control group subjects by collagen-induced platelet aggregation types (hypoaggregation, normal aggregation, hyperaggregation) has demonstrated the presence of blood platelet aggregation disorders in all subgroups of COPD patients which were significantly different from the values measured in the control group (Table 2). In the mild COPD group,

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hyperaggregation was observed in nearly a half of patients while hypoaggregation was only found in a sixth of patients.

As to severe COPD, in subgroup 2 the distribution of patients was substantially the same (about a third of patients for each type) through there were slightly more persons with hypoaggregation. It is conceivable that the use of medication treatment such as IGCCs in patients with a severe form of the disease can cause hypoaggregation changes in platelet activity due to the second (irreversible) phase of the aggregation cascade.

The PAA index prognostic potential in COPD patients for diagnosis of ADP- and collagen-induced platelet aggregation disorders were measured with the use of the ROC analysis (Fig. 1). The analysis was performed in the main group taking into account the presence of aggregation disorders (hyperaggregation or hypoaggregation) in the subjects.

It was found that the areas under the ROC curves built according to the PAA index for both aggregation inducers in cases of hyperaggregation and hypoaggregation disorders were greater than 0.7 (AUC = 0.779 and 0.943, respectively) and reached a statistically significant level (95% CI AUC = 0.679–0.860 and 0.873–0.981, respectively) ($p \leq 0.001$).

The optimal PAA cut-off points for ADP- and collagen-induced aggregation disorders that can be used as a critical value are: > 41% for diagnosis of hyperaggregation disorders, and ≤ 28% for diagnosis of hypoaggregation disorders (Fig. 2).

It has been found that the operating characteristics (sensitivity, specificity, AUC) in prognosis of hyperaggregation disorders by the PAA index can be assessed as 'excellent' for both aggregation inducers (Se = 93.3%; Sp = 91.1%). This means that a COPD patient should be diagnosed with platelet hyperaggregation at PAA higher than 41.0%.

In prognosis of hypoaggregation disorders in COPD patients, PAA has high specificity (Sp = 88.1%) and low sensitivity (Se = 43.5%). The high specificity of the test suggests that persons with normal aggregation are not likely to be classified as having hypoaggregation.

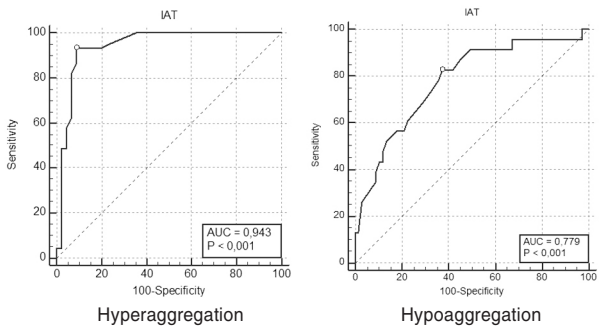

Fig. 1. ROC curves for prognosis of platelet aggregation disorders in COPD patients

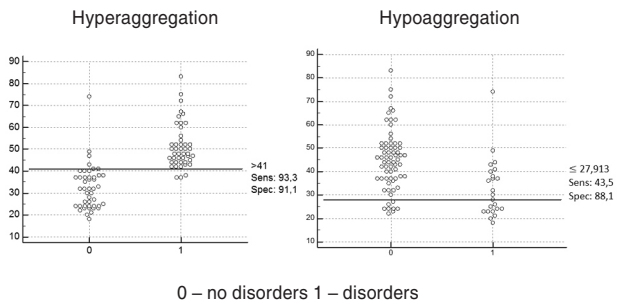

Fig. 2. PAA optimal cut-off point for prognosis of significant ADP – and collagen-induced platelet aggregation disorders in COPD patients

Table 1. Distribution of subjects after ADP-induced platelet aggregometry by type of platelet aggregation activity

Study groups and subgroups	Type of platelet aggregation activity					
	hypoaggregation		normal		hyperaggregation	
	abs.	P ± m_p,%	abs.	P ± m_p,%	abs.	P ± m_p,%
Main group (n = 81): Subgroup 1 (n = 22) Subgroup 2 (n = 59)	9 5 4	11.1 ± 3.2* 22.7 ± 8.3*# 6.8 ± 4.7*#	51 8 43	63.0 ± 5.1* 36.4 ± 9.6*# 72.9 ± 8.5*#	21 9 12	25.9 ± 4.1* 40.9 ± 10.6*# 20.3 ± 7.2*#
Control group (n = 25)	0	0.0 ± 0.0	25	100.0 ± 0.0	0	0.0 ± 0.0

Notes: * – $p < 0.05$ according to $\chi 2$ vs. the control group; # – $p < 0.05$ according to $\chi 2$ between subgroup 1 and 2.

Table 2. Distribution of subjects after collagen-induced platelet aggregometry by type of platelet aggregation activity

Study groups and subgroups	Type of platelet aggregation activity					
	hypoaggregation		normal		hyperaggregation	
	abs.	P ± m_p,%	abs.	P ± m_p,%	abs.	P ± m_p,%
Main group (n = 81): Subgroup 1 (n = 22) Subgroup 2 (n = 59):	27 4 23	33.3 ± 4.3* 18.2 ± 7.3*# 39.0 ± 8.9*#	26 8 9	32.1 ± 4.6* 36.4 ± 9.6*# 30.5 ± 8.6*#	28 10 9	34.6 ± 5.4* 45.4 ± 10.5*# 30.5 ± 8.6*#
Control group (n = 25)	0	0.0 ± 0.0	25	100.0 ± 0.00	0	0.0 ± 0.0

Note: please see the key under Table 1

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However, the low sensitivity of the test can cause numerous false negative results.

The distribution of the study patients by secondary haemostasis disorder types has demonstrated that nearly a half of patients and the main group in general, and subgroups 1 and 2 had the signs of hypercoagulation disorders. In addition, a tenth of COPD patients both in the main group and subgroups 1 and 2 had hypocoagulation changes in the indicator. Subgroups 1 and 2 were identical by the levels of the indicator (Table 3).

Therefore, disorders in the intrinsic coagulation cascade pathway occur in patients with both mild and severe COPD, tend to be associated with hypercoagulation and do not correlate with the disease severity.

As to the intensity of systemic inflammation, CRP levels in the main group were significantly higher than those in the control group (5.50 [4.47–8.42] and 3.65 [3.50–3.90] mg/L, respectively). In subgroups 1 and 2, the values were also higher than the marker in the control group (4.48 [4.36–5.72] and 5.64 [4.55–8.50] mg/L, respectively) ($p < 0.05$) but did not differ from each other ($p > 0.05$).

The ROC analysis was performed to assess the prognostic potential of CRP in relation to hypercoagulation disorders. Each study patient was classified as having or not having hypercoagulation disorders. The area under the ROC curve for CRP reached a statistically significant level (AUC = 0.638; 95% CI AUC = 0.530–0.736) ($p < 0.05$) which means that CRP levels could be used for prognosis of hypercoagulation disorders of haemostasis in COPD patients (Fig. 3).

The level of its diagnostic accuracy for prognosis of coagulation disorders can be assessed as 'average' as the area under the ROC curve value is in the range between 0.6 and 0.7. The measurement of CRP levels for prognosis of hypercoagulation disorders in the study patients has low specificity (Sp = 53.1%) and rather high sensitivity (Se = 77.6%). The low specificity of the diagnostic test also suggests that based upon its data persons without disorders can be often classified as having coagulation disorders. However, rather high sensitivity of the test will not cause numerous false negative results. Therefore, CRP levels could be used as a marker for prognosis of hypercoagulation disorders in COPD patients.

According to the data of our study, the CRP cut–off point that could be used as a critical value for diagnosis of hypercoagulation disorders was over 4.62 mg/L. This means the CRP levels higher than this value in COPD patients can be the sign of hypercoagulation.

Conclusions

1. Haemostatic disorders occur in more than a half of COPD patients with 67,9% primary haemostasis disorders and 53,1% secondary haemostasis disorders. 34,6% of primary haemostasis disorders are associated with hyperaggregation and 33,3% with hypoaggregation.

2. Patients with mild COPD most commonly (45.4%) develop hyperaggregation primary haemostasis disorders ($p < 0.05$). Patients with severe COPD who receive adequate IGCC therapy are slightly more likely to have hypoaggregation (39.0%) than hyperaggregation (30.5%) primary haemostasis disorders ($p < 0.05$).

3. In most cases (95.3%), coagulation disorders in COPD patients are associated with hypercoagulation. 77.3% of patients with mild COPD and 40.7% of patients with severe COPD develop hypercoagulation disorders which do not correlate with the disease severity.

4. PAA is the best prognostic indicator of primary haemostasis disorders in COPD patients: its level over 41.0% is the sign of hyperaggregation while hypoaggregation is diagnosed when it is lower than 28.0%. CRP is the best prognostic indicator of secondary haemostasis disorders in COPD patients: its level over 4.62 mg/L suggests of haemostasis disorders associated with hypercoagulation.

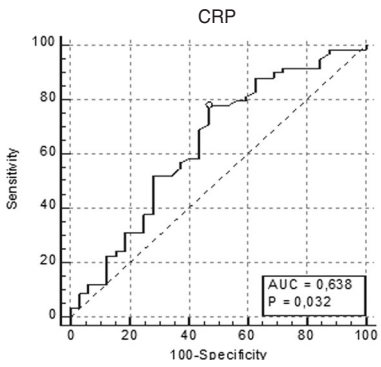

Fig. 3. Operational characteristics for prognosis of secondary haemostasis disorders in COPD patients by CRP levels

Table 3. Distribution of subjects by type of secondary haemostasis disorders

Study groups and subgroups	Type of disorder					
	hypocoagulation		normal		hypercoagulation	
	abs.	P ± m_p,%	abs.	P ± m_p,%	abs.	P ± m_p,%
Main group (n = 81): Subgroup 1 (n = 22) Subgroup 2 (n = 59):	2 0 2	2.5 ± 1.5* 0.0 ± 0.0 3.4 ± 3.2*	38 5 33	46.9 ± 4.6* 22.7 ± 8.3 55.2 ± 9.2*	41 17 22	50.6 ± 4.7* 76.2 ± 9.3 41.4 ± 9.1*
Control group (n = 25)	0	0.0 ± 0.0	25	100.0 ± 0.0	0	0.0 ± 0.0

Note:* – $p < 0.05$ according to $\chi 2$ vs. the control group.

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Список літератури

1. Авдеев С.Н., Баймаканова Г.Е. С-реактивный белок – новый или старый маркер бронхолегочных инфекций. Атмосфера. Пульмонология и аллергология. 2008. № 4. С. 26–32.
2. Добрянський Д.В. Гемореологічні та імунні порушення та їх медикаментозна корекція фенспіридом у хворих на хронічне обструктивне захворювання легень. Астма та алергія. 2011. № 1. С. 28–31.
3. Конопкіна Л.І. Роль розчинної молекули міжклітинної адгезії у формуванні та прогресуванні хронічного обструктивного захворювання легень. Український пульмонологічний журнал. 2008. № 1. С. 29–30.
4. Меренкова Е.А., Моногарова Н.Е. Состояние агрегационной способности тромбоцитов при патологии легких у больных различных нозологических групп. Украинский пульмонологический журнал. 2006. № 1. С. 39–43.
5. Наказ МОЗ України від 27.06.2013 № 555 «Уніфікований клінічний протокол первинної, вторинної (спеціалізованої), третинної (високоспеціалізованої) медичної допомоги та медичної реабілітації. Хронічне обструктивне захворювання легень». Київ: Міністерство охорони здоров'я України, 2013. 92 с.
6. Островський М.М., Герич П.Р. До питання поліморбідності та коморбідності у хворих на ХОЗЛ. Український пульмонологічний журнал. 2011. № 4. С. 19–24.
7. Перцева Т.О., Конопкіна Л.І., Губа Ю.В. Особливості психічного статусу хворих на хронічне обструктивне захворювання легень у різні фази патологічного процесу. Медичні перспективи. 2016. Т. XXI, № 1. С. 19–23.
8. Перцева Т.О., Конопкіна Л.І., Губа Ю.В. Порівняльний аналіз клініко-функціонального та психічного статусу хворих на хронічне обструктивне захворювання легень. Український пульмонологічний журнал. 2016. № 2. С. 9–13.
9. Перцева Т.О., Конопкіна Л.І., Братусь О.В. Роль колонізації нижніх дихальних шляхів бактеріальною флорою у формуванні хронічного системного запалення при хронічному обструктивному захворюванні легень. Медичні перспективи. 2009. Т. 14, № 1. С. 126–131.
10. Перцева Т.О., Конопкіна Л.І., Яковлєва В.Г. Стан тромбоцитарно-судинної та коагуляційної ланок гемостазу у хворих на хронічне обструктивне захворювання легень. Проблеми екології та медицини. 2014. Т. 18, № 5–6. С. 30–37.
11. Хронічне обструктивне захворювання легень: нові відтінки проблеми: Монографія / Ю.І. Фещенко, Ю.Б. Чайковський, М.М. Островський та ін. Івано-Франківськ, СІМИК, 2016. 400 с.
12. Яковлєва В.Г. Особливості порушень коагуляційної ланки гемостазу у хворих на хронічне обструктивне захворювання легень. Медичні перспективи. 2015. Т. XX, № 3. С. 56–60.
13. Agusti A.G.N., Noguera A., Sauleda J. Systemic effects of chronic obstructive pulmonary disease: what we know and what we don't know. European Respiratory Journal. 2003. Vol. 21. P. 347–360.
14. Andreassen H., Vestbo J. Chronic obstructive pulmonary disease as a systemic disease: an epidemiological perspective. European Respiratory Journal. 2003. Vol. 22 (46). P. 2s-4s.
15. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta–analysis / W.Q. Gan, S.F. Man, A. Senthilselvan, D.D. Sin. Thorax. 2004. Vol. 59 (7). P. 574–580.
16. Association of Increased Platelet Volume In Patients of Chronic Obstructive Pulmonary Disease: Clinical Implications / R. Bansal, H.L. Gupta, A. Goel, M. Yadav. Journal Indian Academy of Clinical Medicine. 2002. Vol. 3 (2). P. 169–172.

References

1. Avdeev SN, Baymakanova GE. S-reaktivnyy belok – novyy ili staryy marker bronkholegochnykh infektsiy (C-reactive protein - a new or old marker of bronchopulmonary infections). Atmosfera. Pul'monologiya i allergologiya. 2008;4:26–32.
2. Dobryans'kiy DV. Gemoreologichni ta imunni porushennya ta ïkh medikamentozna korektsiya fenspiridom u khvorikh na khronichne obstruktivne zakhvoryuvannya legen' (Hemorheological and immune disorders and their medication correction by using fenspirid in patients with chronic obstructive pulmonary disease). Astma ta alergiya. 2011;1:28–31.
3. Konopkina LI. Rol' rozchinnoï molekuli mizhklitinnoï adgeziï u formuvanni ta progresuvanni khronichnogo obstruktivnogo zakhvoryuvannya legen' (The role of soluble molecule of intercellular adhesion in the formation and progression of chronic obstructive pulmonary disease). Ukraïns'kiy pul'monologichniy zhurnal. 2008;1:29–30.
4. Merenkova EA, Monogarova NE. Sostoyanie agregatsionnoy sposobnosti trombotsitov pri patologii legkikh u bol'nykh razlichnykh nozologicheskikh grupp (The condition of platelet aggregation ability in lung pathology in patients of various nosological groups). Ukrainskiy pul'monologicheskiy zhurnal. 2006;1:39–43.
5. Nakaz MOZ Ukraïni vid 27.06.2013 № 555 «Unifikovaniy klinichniy protokol pervinnoï, vtorinnoï (spetsializovanoï), tretinnoï (visokospetsializovannoï) medichnoï dopomogi ta medichnoï reabilitatsiï. Khronichne obstruktivne zakhvoryuvannya legen'» (Order of the Ministry of Health of Ukraine dated June 27, 2013 №555 «Unified clinical protocol of primary, secondary (specialized), tertiary (highly specialized) medical care and medical rehabilitation. Chronic obstructive pulmonary disease). Kiïv: Ministerstvo okhoroni zdorov'ya Ukraïni, 2013. 92 p.
6. Ostrovs'kiy MM, Gerich PR. Do pitannya polimorbidnosti ta komorbidnosti u khvorikh na KhOZL (To the question of polymorbidity and comorbidity in patients with COPD). Ukraïns'kiy pul'monologichniy zhurnal. 2011;4:19–24.
7. Pertseva TO, Konopkina LI, Guba YuV. Osoblivosti psikhichnogo statusu khvorikh na khronichne obstruktivne zakhvoryuvannya legen' u rizni fazi patologichnogo protsesu (Features of the mental status of patients with chronic obstructive pulmonary disease in different phases of the pathological process). Medichni perspektivi. 2016;XXI(1):19–23.
8. Pertseva TO, Konopkina LI, Guba YuV. Porivnyal'niy analiz kliniko-funktsional'nogo ta psikhichnogo statusu khvorikh na khronichne obstruktivne zakhvoryuvannya legen' (Comparative analysis of clinical-functional and mental status of patients with chronic obstructive pulmonary disease). Ukraïns'kiy pul'monologichniy zhurnal. 2016;2:9–13.
9. Pertseva TO, Konopkina LI, Bratus' OV. Rol' kolonizatsiï nizhnikh dikhal'nikh shlyakhiv bakterial'noyu floroyu u formuvanni khronichnogo sistemnogo zapalennya pri khronichnomu obstruktivnomu zakhvoryuvanni legen' (The role of colonization of the lower respiratory tract by bacterial flora in the formation of chronic systemic inflammation in chronic obstructive pulmonary disease). Medichni perspektivi. 2009;14(1):126–131.
10. Pertseva TO, Konopkina LI, Yakovleva VG. Stan trombotsitarno-sudinnoï ta koagulyatsiynoï lanok gemostazu u khvorikh na khronichne obstruktivne zakhvoryuvannya legen' (State of platelet-vascular and coagulation units of hemostasis in patients with chronic obstructive pulmonary disease). Problemi ekologiï ta meditsini. 2014;18(5–6):30–37.
11. Feshchenko YuI, Chaykovs'kiy YuB, Ostrovs'kiy MM, et al. Khronichne obstruktivne zakhvoryuvannya legen': novi vidtinki problemi (Chronic obstructive pulmonary disease: new shades of the problem): Monografiya. Ivano-Frankivs'k, SIMIK, 2016. 400 p.
12. Yakovleva VG. Osoblivosti porushen' koagulyatsiynoï lanki gemostazu u khvorikh na khronichne obstruktivne zakhvoryuvannya legen' (Features of the coagulation step of hemostasis disorders n patients with chronic obstructive pulmonary disease). Medichni perspektivi. 2015;XX(3):56–60.
13. Agusti AGN, Noguera A, Sauleda J. Systemic effects of chronic obstructive pulmonary disease: what we know and what we don't know. European Respiratory Journal. 2003;21:347–360.
14. Andreassen H, Vestbo J. Chronic obstructive pulmonary disease as a systemic disease: an epidemiological perspective. European Respiratory Journal. 2003;22(46):2s-4s.
15. Gan WQ, Man SF, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. Thorax. 2004;59(7):574–580.
16. Bansal R, Gupta HL, Goel A, Yadav M. Association of Increased Platelet Volume In Patients of Chronic Obstructive Pulmonary Disease: Clinical Implications. Journal Indian Academy of Clinical Medicine. 2002;3(2):169–172.

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