DOI: https://doi.org/10.30841/2786-720X.2.2025.331930
UDC 616.37-002.2-036.82:615.844

Clinical and pathogenetic relationships of the chronic pancreatitis and osteoarthritis combined course parameters

L. S. Babinets, I. M. Halabitska, B. O. Migenko, N. Ye. Botsyuk, I. V. Makhnitska, O. S. Zemlyak
Ivan Horbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine

Moderate-grade inflammation plays a critical role in the pathophysiology of comorbid conditions such as chronic pancreatitis (CP) and osteoarthritis (OA) and causes changes of other clinical and pathogenic parameters.
The objective: **to investigate the relationships between clinical and pathogenetic parameters, including pain and physical impairment (assessed by the WOMAC, Lequesne, and VAS scores, fecal elastase-1 level, and antioxidant concentrations (retinol and tocopherol)), and their impact on C-reactive protein (CRP) level in patients with comorbid CP and OA.**
Materials and methods**. A predictor model that included the following variables was developed: the Lequesne Algofunctional Index, VAS joint pain score, fecal elastase-1 level, PEI-Q score, and tocopherol level.**
Results**. The developed model demonstrated a high correspondence with the R-squared value, indicating that a significant proportion of CRP variability is explained by the included variables. Analysis of variance (ANOVA) allowed to create an analytical model of relationships of significant clinical and pathogenetic parameters of CP and AO. Significance testing indicated that the Lequesne Algofunctional Index, VAS joint pain score, fecal elastase-1 level, PEI-Q score, and tocopherol level have a significant effect on CRP level, with different degrees of statistical significance.**
Conclusions**. The results of the study indicate the need to take into account the inflammatory process of moderate intensity when developing a treatment strategy for OA and CP. They also allow us to identify factors which are associated with an increased CRP level in this population of patients, based on a linear regression model and analysis of variance (ANOVA) of the relationships between clinical and pathogenetic parameters. The findings emphasize the importance of individualized therapeutic approaches to reduce the impact of chronic inflammation.**
Keywords: *chronic pancreatitis, osteoarthritis, C-reactive protein, linear regression model, Lequesne Algofunctional Index, VAS joint pain, fecal elastase-1, PEI-Q.*

Клініко-патогенетичний зв'язок параметрів комбінованого перебігу хронічного панкреатиту та остеоартриту

Л. С. Бабінець, І. М. Галабіцька, Б. О. Мігенько, Н. Є. Боцюк, І. В. Махніцька, О. С. Земляк

Запалення помірної інтенсивності відіграє ключову роль у патофізіології супутніх захворювань, зокрема хронічного панкреатиту (ХП) та остеоартриту (ОА), спричиняючи зміни клінічних і патогенетичних параметрів.
Мета дослідження**:** вивчення взаємозв'язків між клінічними та патогенетичними параметрами, включно з болем та фізичними порушеннями (оціненими за шкалами WOMAC, Лекена та VAS, рівнем фекальної еластази-1 та концентраціями антиоксидантів (ретинолу та токоферолу)), а також їхнього впливу на рівень С-реактивного білка (СРБ) у пацієнтів із коморбідним ХП та ОА.
Матеріали та методи**.** У дослідженні було створено прогностичну модель, що включала такі змінні: альгофункціональний індекс Лекена, оцінку болю в суглобах за шкалою VAS, рівень фекальної еластази-1, оцінку PEI-Q, рівень токоферолу.
Результати**.** Розроблена модель продемонструвала високу відповідність зі значенням R-квадрат, вказуючи на те, що значна частка варіабельності рівня СРБ пояснюється включеними змінними. Дисперсійний аналіз (ANOVA) дозволив створити аналітичну модель взаємозв'язків між значущими клініко-патогенетичними параметрами ХП та ОА. Тестування значущості показало, що альгофункціональний індекс Лекена, оцінка болю в суглобах за шкалою VAS, рівень фекальної еластази-1, оцінка PEI-Q і рівень токоферолу чинять значний вплив на рівень СРБ з різним ступенем статистичної значущості.
Висновки**.** Результати дослідження вказують на необхідність врахування запального процесу помірної інтенсивності під час розробки стратегії лікування ОА та ХП. Вони також дозволяють визначити фактори, що пов'язані з підвищенням рівня СРБ у цій популяції пацієнтів, на основі моделі лінійної регресії та дисперсійного аналізу (ANOVA) взаємозв'язків клінічних і патогенетичних параметрів. Отримані дані підкреслюють важливість індивідуалізованих терапевтичних підходів для зменшення впливу хронічного запалення.
Ключові слова: *хронічний панкреатит, остеоартрит, С-реактивний білок, лінійна регресійна модель, альгофункціональний індекс Лекена, біль у суглобах за шкалою VAS, фекальна еластаза-1, PEI-Q.*

Low-grade inflammation plays a critical role in the pathophysiology of comorbid conditions such as chronic pancreatitis (CP) and osteoarthritis (OA) [1–8]. OA, a prevalent degenerative joint disease, is characterized by chronic inflammation within the joints, which contributes to cartilage degradation and progressive joint pain [9–13]. Similarly, CP is marked by ongoing pancreatic inflammation that can lead to pancreatic tissue damage and impaired function [14–19]. The presence of low-grade inflammation in both conditions can exacerbate

symptoms, lead to disease progression, and impact overall patient quality of life [20–23].

Understanding the interplay between low-grade inflammation in these comorbid conditions is essential for effective management and treatment [24–28]. Elevated biomarkers such as C-reactive protein (CRP) serve as indicators of systemic inflammation and can provide insights into the inflammatory burden experienced by patients with OA and CP [29–34]. Investigating various factors and their influence on CRP levels in this patients population, clinicians can better tailor therapeutic approaches, potentially improving patient outcomes and reducing the impact of chronic inflammation on disease progression. WOMAC, Lequesne Index, and VAS scores measure pain and physical impairment, both of which are influenced by systemic inflammation that may be intensified by pancreatic inflammation in CP. Fecal elastase-1 serves as a marker of pancreatic exocrine function, which insufficiency can promote systemic inflammation and negatively impact joint health. Retinol and tocopherol, as key antioxidants, are often deficient in cases of pancreatic insufficiency, which increases oxidative stress and inflammatory responses, thereby exacerbating OA symptoms. Collectively, these indicators emphasize the link between nutritional deficiencies, increased inflammation, and the severity of symptoms in comorbid OA and CP patients [30–34].

Moreover, lifestyle factors such as obesity, diet, and physical activity significantly influence the level of systemic inflammation, including CRP, in patients with OA and CP [35]. Obesity, in particular, is associated with higher levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), contributing to both the onset and worsening of low-grade inflammation [36]. This inflammatory state accelerates the deterioration of joint tissue in OA and exacerbates pancreatic damage in CP [37]. Lifestyle modifications like weight management, anti-inflammatory diet, and regular low-impact exercise have been shown to lower inflammatory activity and improve joint and pancreatic function [38]. Therefore, addressing these modifiable risk factors can play a crucial role in reducing inflammation and slowing disease progression in patients with these comorbid conditions.

The objective: to investigate the relationships between clinical and pathogenetic parameters, including pain and physical impairment measured by the WOMAC, Lequesne, and VAS scores, fecal elastase-1 levels, and antioxidant concentrations (retinol and tocopherol), and their impact on CRP level in comorbid CP and OA patients.

MATERIALS AND METHODS

This study analyzed data from 52 patients diagnosed with OA and CP, with an average age of (52.54 ± 7.78) years. Patients were included based on OA diagnosis, specifically affecting the knee and hip joints. The mean functional status score of joints was (2.11 ± 0.43). The diagnosis of OA was based on clinical evaluation, including patient-reported symptoms of joint pain, stiffness, and functional impairment, along with radiographic evidence of joint space narrowing, osteophyte formation, and subchondral sclerosis. Criteria from the American College of Rheumatology (ACR) were utilized to confirm the diagnosis. The diagnosis of CP was established through evaluation of combination of clinical symptoms, including persistent abdominal pain and signs of malabsorption, alongside with imaging studies such as ultrasound examination, which revealed pancreas structural changes, such as calcifications, ductal dilatation, or gland atrophy. Additionally, pancreatic exocrine insufficiency was confirmed by low fecal elastase-1 level.

Patients were excluded if they had other inflammatory or autoimmune joint diseases, severe comorbidities such as advanced heart failure or cancer, or if they had experienced a recent exacerbation of CP. Metabolic disorders, diabetes, dyslipidemia, and other comorbidities were used as exclusion criteria for the study group. Additional exclusion criteria included chronic use of corticosteroids or immunosuppressive drugs, alcohol abuse or active substance use disorder, participation in other clinical trials within the past three months, and inability to provide informed consent. All participants signed informed consent for the study.

The control group consisted of 30 rather healthy individuals without signs of OA or CP and other chronic diseases, were compatible by age and gender distribution with comorbid patients group.

CRP levels were measured using a high-sensitivity enzyme-linked immunosorbent assay (ELISA), with serum samples obtained from patients. Normal CRP level: less than 10 mg/L. WOMAC Total Score was assessed using a 24-item questionnaire measuring pain, stiffness, and physical function, with higher scores indicating greater impairment. Lequesne Algofunctional Index was used to evaluate OA severity through questions about pain and functional limitations, with higher scores reflecting worse symptoms. VAS Joint Pain was measured using a 10 cm visual analog scale, where patients marked their pain intensity from 0 (no pain) to 10 (worst possible pain). Fecal elastase-1 was determined by a stool test, with enzyme levels used to assess pancreatic exocrine function, where low levels indicated insufficiency. Normal range: 200 to 500 μg/g of stool. Levels below 200 μg/g indicate pancreatic insufficiency. PEI-Q was administered as a questionnaire assessing the impact of pancreatic exocrine insufficiency on gastrointestinal symptoms and quality of life. Tocopherol and retinol were determined using the High-Performance Liquid Chromatography (HPLC) method. Normal tocopherol level: 9.9–39.6 μg/L. Normal retinol level: 30 to 220 μg/L.

The data were expressed as mean ± standard deviation, and the normality of sample distributions was assessed using the Shapiro–Wilk test. The Mann–Whitney U test was employed to compare the indicators. A linear regression model was developed and evaluated to assess the relationship between the variables under investigation. The model's performance was assessed using various statistical techniques. Goodness-of-fit was evaluated with the R-squared value, which measures the proportion of variance in CRP levels explained by the predictors. An analysis of variance (ANOVA) was conducted to determine the overall significance of the regression model, employing F-statistics and p-values to assess whether the model significantly improved the fit compared to a model without predictors. To address multicollinearity, Variance Inflation Factors (VIF) were computed for each predic-

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ISSN 2786-7218 (Online) | ISSN 2786-720X (Print)
№2 (112)/2025

Table 1

Comparison of clinical and biochemical indicators between control group and patients with OA and CP

Indicator	Control group (n = 30)	Patient with OA and CP (n = 52)	p-value
CRP, mg/L	2.47 ± 0.78	4.87 ± 0.49	< 0.05
WOMAC total score, point	2.08 ± 0.54	39.78 ± 2.87	< 0.001
Lequesne Algofunctional Index, point	0.87 ± 0.19	5.78 ± 0.73	< 0.001
VAS joint pain, point	2.78 ± 0.98	51.43 ± 1.84	< 0.001
Fecal elastase-1, μg/g	278.46 ± 15.79	115.98 ± 19.85	< 0.001
PEI-Q, point	0.12 ± 0.08	0.71 ± 0.15	< 0.05
Retinol, μg/L	210.56 ± 17.56	100.87 ± 19.76	< 0.001
Tocopherol, μg/L	15.76 ± 2.85	9.21 ± 3.04	< 0.001

Table 2

Parameter estimates of the regression model with corresponding standard errors and 95% confidence intervals

Parameter estimates	Variable	Estimate	Standard error	95% confidence interval
β0	Intercept	4.024	0.7347	2.544 to 5.505
β1	WOMAC total score	0.01376	0.008773	–0.003919 to 0.03144
β2	Lequesne Algofunctional Index	–0.04125	0.009116	–0.05963 to –0.02288
β3	VAS joint pain	0.01737	0.006268	0.004738 to 0.03000
β4	Fecal elastase-1	–0.001189	0.0005766	–0.002351 to –2.715e-005
β5	PEI-Q	0.2647	0.05605	0.1517 to 0.3776
β6	Retinol	–0.8836	0.5535	–1.999 to 0.2318
β7	Tocopherol	–0.2690	0.06087	–0.3917 to –0.1463

tor variable, which helps identify whether predictors are highly correlated with each other, potentially affecting coefficient stability. The significance of each predictor was assessed through t-tests, with p-values used to evaluate the statistical significance of the coefficients. This rigorous statistical analysis aimed to ensure a robust understanding of the factors influencing CRP levels in patients with the specified comorbid conditions.

RESULTS AND DISCUSSION

The Table 1 presents a comparison of clinical and biochemical indicators between the control group and patients with OA and CP. Patients with OA and CP showed a substantial increase in inflammation and pain markers compared to controls, with CRP levels nearly two times ($p < 0.05$) and joint pain (VAS) and functional impairment scores (WOMAC, Lequesne Index) were approximately 18.5 ($p < 0.001$), 6.5 ($p < 0.001$), and 18.6 times higher ($p < 0.001$), in a group of patients with CP and OA compared to a control group. Pancreatic exocrine function, measured by fecal elastase-1, was reduced by 58.3% ($p < 0.001$). PEI-Q scores, indicating pancreatic insufficiency, were nearly 5.9 times higher in patients with CP and OA compared to a control group ($p < 0.001$). Additionally, levels of retinol and tocopherol were reduced by 52.1% and 41.6% in patients with CP and OA compared to a control group ($p < 0.001$).

Given the statistically significant changes in all examined indicators in the patient group compared to the control, an investigation was undertaken to explore the interconnections among these indicators and their role in developing a low-intensity inflammatory process.

The Table 2 presents parameter estimates for a regression model, including the estimated coefficients, their standard errors, and the 95% confidence intervals for each predictor variable. The intercept has a positive estimate, indicating the baseline value of the dependent variable when all predictors are zero. The WOMAC total score has a small positive estimate, though its confidence interval includes zero, suggesting that its relationship with the outcome may not be statistically significant. In contrast, the Lequesne Algofunctional Index shows a significant negative association with the CRP, as its confidence interval lies entirely below zero. VAS joint pain is positively associated with the CRP, and its confidence interval suggests this relationship is statistically significant. Fecal elastase-1 has a very small negative coefficient with a confidence interval just below zero, indicating a potential but weak negative effect.

The PEI-Q has a substantial positive coefficient, with a confidence interval significantly above zero, highlighting a strong and significant positive association. Retinol shows a negative estimate, but its confidence interval crosses zero, indicating that its effect may not be significant. Finally, tocopherol has a negative estimate with a confidence interval that does not include zero, suggesting a significant negative association with the CRP.

The Table 3 presents the results of significance testing for the parameter estimates in a regression model, including the absolute t-values, p-values, and a summary of the statistical significance. The intercept shows a highly significant difference from zero, with a p-value well below the conventional threshold for significance. The WOMAC total score, however, does not reach statistical signifi-

Table 3

Statistical significance of parameter estimates in the regression model

Parameter estimates	Variable	t-value	p-value	p-value summary
β0	Intercept	5.478	< 0.0001	****
β1	WOMAC total score	1.569	0.1239	ns
β2	Lequesne Algofunctional Index	4.525	< 0.0001	****
β3	VAS joint pain	2.771	0.0082	**
β4	Fecal elastase-1	2.062	0.0451	*
β5	PEI-Q	4.722	< 0.0001	****
β6	Retinol	1.596	0.1175	ns
β7	Tocopherol	4.419	< 0.0001	****

Table 4

Parameter estimates and confidence intervals for predictors in the regression model

Parameter estimates	Variable	Estimate	Standard error	95% confidence interval
β0	Intercept	5.298	0.3831	4.527 to 6.069
β1	Lequesne Algofunctional Index	–0.03547	0.009510	–0.05461 to –0.01633
β2	VAS joint pain	0.01606	0.006670	0.002630 to 0.02948
β3	Fecal elastase-1	–0.001510	0.0006030	–0.002724 to –0.0002966
β4	PEI-Q	0.2591	0.05920	0.1399 to 0.3783
β5	Tocopherol	–0.4294	0.02440	–0.4785 to –0.3803

Table 5

Significance testing of regression model parameters

Parameter estimates	Variable	t-value	p-value	p-value summary
β0	Intercept	13.83	< 0.0001	****
β1	Lequesne Algofunctional Index	3.730	0.0005	***
β2	VAS joint pain	2.407	0.0201	*
β3	Fecal elastase-1	2.505	0.0159	*
β4	PEI-Q	4.376	< 0.0001	****
β5	Tocopherol	17.60	< 0.0001	****

cance, as indicated by a p-value above the standard cutoff. The Lequesne Algofunctional Index, VAS joint pain, fecal elastase-1, PEI-Q, and tocopherol all show significant differences from zero, with varying levels of significance, as denoted by their respective p-value summaries. In contrast, Retinol, similar to the WOMAC score, does not exhibit a statistically significant difference from zero.

Indicators that were statistically nonsignificant were removed from the study, and the analysis was repeated. The Table 4 provides parameter estimates for a regression model, detailing the estimated coefficients, their standard errors, and the 95% confidence intervals for each predictor variable. The intercept has a positive estimate, indicating the baseline value of the dependent variable, with a confidence interval that suggests this estimate is precise. The Lequesne Algofunctional Index has a negative coefficient, indicating a significant inverse relationship with CRP, as reflected by its confidence interval, which does not include zero. Similarly, VAS joint pain shows a positive association with the outcome, with its confidence interval also excluding zero, suggesting a significant effect. Fecal elastase-1 has a small negative coefficient, indicating a weak inverse relationship with the CRP, with the confidence interval showing statistical significance. The PEI-Q variable has a positive coefficient, suggesting a strong positive association with CRP, supported by a confidence interval entirely above zero. Lastly, tocopherol has a significant negative coefficient, indicating a strong inverse relationship with the CRP, with a narrow confidence interval that further confirms this effect.

The Lequesne Algofunctional Index also demonstrates a significant negative effect on the outcome, with a p-value indicating strong evidence against the null hypothesis. Both VAS joint pain and fecal elastase-1 show statistically significant positive and negative relationships with the CRP, respectively, though their p-values indicate a lower level of significance compared to other variables. The PEI-Q variable shows a highly significant positive association with the CRP, reflected in a strong t-value and a p-value well below the conventional significance level. Tocopherol has an exceptionally strong negative association with the CRP, with a very high t-value and a p-value far below the significance threshold, indicating a highly significant effect. These results suggest that all variables except the intercept are significantly different from zero, with varying degrees of statistical significance (Table 5).

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ISSN 2786-7218 (Online) | ISSN 2786-720X (Print)
№2 (112)/2025

Table 6

Goodness-of-fit statistics for the regression model

Goodness-of-fit	
DF	46
R-squared	0.9863

The Table 6 displays the goodness-of-fit metrics for the regression model. It provides the degrees of freedom (DF), which reflect the number of independent pieces of information used in parameter estimation. The R-squared value indicates the proportion of variance in the dependent variable explained by the model. A high R-squared value suggests that the model provides an excellent fit to the data, accounting for a substantial amount of the variability in the outcome variable.

The Table 7 provides the analysis of variance (ANOVA) for the regression model. It includes the sum of squares (SS), DF, mean square (MS), F-statistic, and p-value. The regression sum of squares reflects the variation explained by the model, while the residual sum of squares represents the variation not explained by the model. The MS for regression and residual are calculated by dividing the respective sum of squares by their DF. The F-statistic, with its associated DF, assesses the overall significance of the model. The p-value indicates whether the model explains a statistically significant amount of variance in the dependent variable.

The Table 8 presents multicollinearity diagnostics for the regression model, including the Variance Inflation Factor (VIF) and the R-squared value with other variables for each predictor. The VIF measures how much the variance of the estimated regression coefficient is inflated due to multicollinearity with other predictors. The R-squared value with other variables indicates the proportion of variance in a given predictor that is explained by the other predictors in the model. Higher VIF values suggest greater multicollinearity, which may affect the stability of the coefficient estimates. The Lequesne Algofunctional Index and fecal elastase-1 have moderate VIF values, indicating relatively low multicollinearity. VAS joint pain and PEI-Q also show moderate VIF values, while tocopherol has a higher VIF, suggesting that it may be more influenced by multicollinearity with other predictors.

The result of the analysis is the development of a robust linear regression model. This model effectively incorporates various predictor variables, as evidenced by the high goodness-of-fit statistics and significant parameter estimates. The comprehensive evaluation, including multicollinearity diagnostics and analysis of variance, demonstrates the model's strong explanatory power and its capacity to account for the variance in the dependent variable:

$$y = 5.298 - 0.03547x_1 + 0.01606x_2 - 0.001510x_3 + 0.2591x_4 - 0.4294x_5$$

In this regression model:
y represents the CRP level;
x_1 is the Lequesne Algofunctional Index;
x_2 is the VAS joint pain score;
x_3 is the fecal elastase-1 level;
x_4 is the PEI-Q score;
x_5 is the tocopherol level.

In our study, we observed significant associations between key inflammatory marker (CRP), and clinical parameters like the Lequesne Algofunctional Index and VAS joint pain score. Our findings show that both these indices were significantly associated with CRP levels, suggesting a clear link between clinical manifestations of pain and joint dysfunction with systemic inflammation. These results align with other studies that emphasize the importance of CRP as a biomarker of inflammation and disease severity in OA and CP, our findings regarding the negative association of tocopherol (vitamin E) with CRP are consistent with previous reports on the anti-inflammatory effects of antioxidants in chronic diseases [39–42]. Studies have shown that tocopherol has protective properties, potentially reducing oxidative stress and inflammation in patients with CP and OA [43, 44]. Similarly, the fecal elastase-1 as a marker of pancreatic exocrine insufficiency is well documented, and its inverse relationship with CRP in our model underscores the link between pancreatic function and systemic inflammation [45–49]. However, some studies suggest that the effect size of tocopherol and fecal elastase-1 may vary based

Table 7

Analysis of variance for the regression model

Analysis of variance	SS	DF	MS	F (DFn, DFd)	p-value
Regression	2.515	5	0.5029	F (5, 46) = 663.2	< 0.0001
Residual	0.03488	46	0.0007583		
Total	2.549	51			

Table 8

Multicollinearity diagnostics for predictor variables

Multicollinearity	Variable	VIF	R2 with other variables
β0	Intercept		
β1	Lequesne Algofunctional Index	2.007	0.5017
β2	VAS joint pain	5.319	0.8120
β3	Fecal elastase-1	2.811	0.6443
β4	PEI-Q	2.568	0.6106
β5	Tocopherol	7.099	0.8591

on disease stage, highlighting the need for further research to assess their long-term impact on inflammation [50–52]. Overall, our results contribute to the growing body of evidence highlighting the multifaceted role of inflammation in CP and OA and emphasize the need for individualized approaches to managing inflammation in these conditions.

CONCLUSIONS

These findings highlight the importance of low-grade inflammation in managing OA and CP and provide insights into the factors that contribute to elevated CRP levels in this patient population according a linear regression model and analysis of variance (ANOVA) of relationships of clinical and pathogenetic parameters. The model's results indicate that CRP is significantly influenced by factors such as the Lequesne Algofunctional Index, VAS joint pain, fecal elastase-1, PEI-Q, and tocopherol levels. The goodness-of-fit statistics demonstrate that the model explains a substantial portion of the variability in CRP levels. Multicollinearity diagnostics suggest that while most predictors have moderate VIF values. Overall, the model effectively captures the relationships between CRP and the predictors, highlighting its strong explanatory power and relevance.

Information about the authors

Babinets Liliia S. – Ivan Horbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine; tel.: (067) 352-07-43. *E-mail: lilyababinets@gmail.com*
ORCID: 0000-0002-0560-1943

Halabitska Iryna M. – Ivan Horbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine; tel.: (097) 798-28-93. *E-mail: halabitska@tdmu.edu.ua*
ORCID: 0000-0002-9028-7230

Migenko Bogdan O. – Ivan Horbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine; tel.: (067) 810-57-20. *E-mail: migenko@tdmu.edu.ua*
ORCID: 0000-0003-2192-7238

Botsyuk Nataliia Ye. – Ivan Horbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine; tel.: (067) 352-18-82. *E-mail: botcyk@tdmu.edu.ua*
ORCID: 0000-0002-2959-1866

Makhnitska Iryna V. – Ivan Horbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine; tel.: (098) 451-51-30. *E-mail: makhnitcka_iv@tdmu.edu.ua*
ORCID: 0000-0003-3847-3586

Zemlyak Olexandr S. – Ivan Horbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine; tel.: (050) 413-56-09. *E-mail: zemliak@tdmu.edu.ua*
ORCID: 0000-0002-6346-0931

Відомості про авторів

Бабінець Лілія Степанівна – Тернопільський національний медичний університет імені І. Я. Горбачевського МОЗ України; тел.: (067) 352-07-43. *E-mail: lilyababinets@gmail.com*
ORCID: 0000-0002-0560-1943

Галабіцька Ірина Михайлівна – Тернопільський національний медичний університет імені І. Я. Горбачевського МОЗ України; тел.: (097) 798-28-93. *E-mail: halabitska@tdmu.edu.ua*
ORCID: 0000-0002-9028-7230

Мігенько Богдан Орестович – Тернопільський національний медичний університет імені І. Я. Горбачевського МОЗ України; тел.: (067) 810-57-20. *E-mail: migenko@tdmu.edu.ua*
ORCID: 0000-0003-2192-7238

Боцюк Наталія Євгенівна – Тернопільський національний медичний університет імені І. Я. Горбачевського МОЗ України; тел.: (067) 352-18-82. *E-mail: botcyk@tdmu.edu.ua*
ORCID: 0000-0002-2959-1866

Махніцька Ірина Володимирівна – Тернопільський національний медичний університет імені І. Я. Горбачевського МОЗ України; тел.: (098) 451-51-30. *E-mail: makhnitcka_iv@tdmu.edu.ua*
ORCID: 0000-0003-3847-3586

Земляк Олександр Степанович – Тернопільський національний медичний університет імені І. Я. Горбачевського МОЗ України; тел.: (050) 413-56-09. *E-mail: zemliak@tdmu.edu.ua*
ORCID: 0000-0002-6346-0931

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Стаття надійшла до редакції 29.10.2024. – Дата першого рішення 01.11.2024. – Стаття подана до друку 05.12.2024