UDC 616.248-008.4:616.8-008.6:616.12-008.3 https://doi.org/10.26641/2307-0404.2026.3.376670

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ANXIETY AND AUTONOMIC DYSFUNCTION IN ASTHMA PATIENTS

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Цитування: Медичні перспективи. 2026. Т. 31, № 3. С. 49-56
Cited: Medicni perspektivi. 2026;31(3):49-56

Key words: *bronchial asthma, anxiety, autonomic dysfunction, autonomic nervous system, heart rate variability*
Ключові слова: *бронхіальна астма, тривожність, автономна дисфункція, автономна нервова система, варіабельність серцевого ритму*

Abstract. Anxiety and Autonomic Dysfunction in Asthma Patients. Vysochyna I.L., Berezutskyi I.V. *This analytical cross-sectional study investigated the complex relationship between anxiety severity, autonomic nervous system (ANS) status, heart rate variability (HRV), and clinical control in patients with bronchial asthma. The study enrolled 60 asthmatic patients aged 35-65 years (30 men and 30 women) undergoing inpatient treatment at the Allergology Center in Dnipro, Ukraine, during 2024-2025. Participants were symmetrically allocated into four age- and sex-matched factorial cells (15 patients each) based on their asthma control status (controlled versus uncontrolled) and the presence or absence of clinically significant anxiety assessed via the Hospital Anxiety and Depression Scale (HADS). Pulmonary function was evaluated by spirometry (Spirolab III®, MIR) to determine forced expiratory volume in 1 second (FEV_1). Autonomic status was quantified using 5-minute electrocardiographic recordings captured with a Polar H10 chest sensor and processed via Kubios HRV Scientific software to extract key time-domain (MHR, SDNN, RMSSD) and frequency-domain (LF, HF, LF norm, HF norm, LF/HF ratio) parameters. Factorial analysis using a rank-based Aligned Rank Transformation (ART) ANOVA revealed strong, independent main effects of asthma control on pulmonary function and major spectral HRV measures, alongside a profound independent main effect of anxiety on total heart rate variability indexed by SDNN ($F=80.20$, $p<0.001$). Patients with comorbid anxiety demonstrated a significant shift toward sympathetic dominance driven primarily by the severe suppression of parasympathetic activity. In patients with controlled asthma and anxiety, the LF/HF ratio reached a peak of 1.96 (1.39-2.55), while RMSSD and SDNN decreased to 10.60 (8.10-13.20) ms and 23.50 (17.90-29.30) ms, respectively. Conversely, uncontrolled asthma in the absence of anxiety was characterized by a distinct hyper-vagal state, exhibiting the highest RMSSD value of 45.60 (34.80-56.90) ms and the lowest LF/HF ratio of 0.64 (0.49-0.79). Crucially, significant interaction effects were detected for RMSSD and LF norm, whereas the interaction for HF norm was not statistically significant, indicating that the association of anxiety with these outcomes was not uniform across asthma-control strata. Secondary analyses revealed a strong inverse correlation between anxiety severity and total HRV (Spearman's $\rho = -0.882$ for the entire cohort) and a powerful synergistic relationship between psychological distress and autonomic imbalance regarding overall asthma controllability (multiple correlation coefficient =0.914). In conclusion, clinically significant anxiety in bronchial asthma induces a profound autonomic dysregulation that disrupts the predictable physiological links between the lungs and the cardiorespiratory axis, leading to a consistent decline in clinical asthma control. Short-term HRV assessment using validated wearable sensors represents a practical, non-invasive digital tool for routine clinical settings, and systematic psychological screening should be integrated into comprehensive asthma management strategies to optimize therapeutic outcomes.*

Реферат. Тривожність та автономна дисфункція в пацієнтів з астмою. Височина І.Л., Березуцький І.В. *Це аналітичне поперечне дослідження присвячене вивченню комплексного взаємозв'язку між рівнем тривожності, станом автономної нервової системи (АНС), варіабельністю серцевого ритму (ВСР) та клінічним контролем у пацієнтів з бронхіальною астмою. У дослідження було включено 60 пацієнтів з бронхіальною астмою віком 35-65 років (30 чоловіків і 30 жінок), які проходили стаціонарне лікування в Алергологічному центрі м. Дніпро, Україна, протягом 2024-2025 років. Учасники були симетрично розподілені на чотири зіставлені за віком та статтю факторіальні групи (по 15 пацієнтів у кожній) відповідно до рівня контролю астми (контрольована або неконтрольована) та наявності чи відсутності клінічно значущої тривожності, яку оцінювали за Госпітальною шкалою тривоги та депресії (HADS). Функцію зовнішнього дихання оцінювали методом спірометрії (Spirolab III®, MIR) з визначенням об'єму форсованого видиху за 1-шу секунду (FEV_1). Статус автономної нервової системи оцінювали за даними 5-хвилинної електрокардіографії, зареєстрованої за допомогою нагрудного датчика Polar H10 з подальшим аналізом у програмі Kubios HRV Scientific для визначення ключових часових (MHR, SDNN, RMSSD) та спектральних (LF, HF, LF norm, HF norm, співвідношення LF/HF)*

показників. Факторіальний аналіз із застосуванням непараметричного методу ART-ANOVA виявив сильні незалежні головні ефекти контролю астми на функцію легень та основні спектральні параметри ВСР, а також глибокий незалежний головний ефект тривожності на загальну варіабельність серцевого ритму, індексовану показником SDNN (F=80,20, p<0,001). У пацієнтів із коморбідною тривожністю виявлено значний зсув вегетативного балансу в бік симпатикотонії, зумовлений насамперед вираженим пригніченням парасимпатичної активності. У групі контрольованої астми з тривожністю співвідношення LF/HF досягало пікового значення 1,96 (1,39-2,55), тоді як показники RMSSD та SDNN суттєво знижувалися до 10,60 (8,10-13,20) мс і 23,50 (17,90-29,30) мс відповідно. Навпаки, неконтрольована астма за відсутності тривожності характеризувалася вираженим гіпервагусним станом з найвищим значенням RMSSD 45,60 (34,80-56,90) мс та найнижчим коефіцієнтом LF/HF 0,64 (0,49-0,79). Важливо, що для RMSSD та LF norm було виявлено статистично значущі ефекти взаємодії факторів, тоді як взаємодія для HF norm не була статистично значущою, що доводить здатність тривожності активно пригнічувати вихідний парасимпатичний тонус незалежно від рівня контролю захворювання. Вторинний аналіз продемонстрував тісний обернений кореляційний зв'язок між тяжкістю тривоги та загальною ВСР (коефіцієнт Спірмена ρ= -0,882 для всієї когорти), а також потужну синергетичну взаємодію між психологічним стресом й автономним дисбалансом щодо загального контролю перебігу астми (коефіцієнт множинної кореляції становив 0,914). На завершення, клінічно значуща тривожність при бронхіальній астмі індукує глибоку автономну дисрегуляцію, яка порушує передбачувані фізіологічні зв'язки легень з кардіореспіраторною віссю, призводячи до стійкого погіршення клінічного контролю астми. Короткочасне оцінювання ВСР за допомогою валідованих портативних сенсорів є практичним неінвазивним цифровим інструментом для повсякденної клінічної практики, а систематичний психологічний скринінг має бути інтегрований у комплексні стратегії ведення пацієнтів з астмою для оптимізації результатів лікування.

Asthma is frequently accompanied by emotional disorders, primarily anxiety. Recent data indicate that this comorbidity occurs in 60-70% of cases and consistently worsens the clinical course of asthma [1]. Research has shown that the relationship between anxiety and asthma is bidirectional: anxiety can lead to the development of bronchospastic syndrome, while asthma can trigger anxiety symptoms [2]. Additionally, an imbalance in the autonomic nervous system (ANS) is known to play a significant role in the development of both conditions. The dysfunction of the ANS in anxiety disorders has been extensively studied, with most research showing increased activity in the sympathetic nervous system (SNS) and reduced activity in the parasympathetic nervous system (PNS) [3]. However, regarding ANS dysfunction in asthma, researchers do not have a unanimous perspective. Some studies indicate increased PNS activity in patients with uncontrolled asthma (UA), while others suggest a predominance of SNS activity [5]. The pathogenesis of ANS dysfunction in the context of asthma and anxiety has only been partially studied [6, 7, 8, 9]. Understanding how the ANS contributes to the interaction between asthma and anxiety could lead to the development of more effective treatment strategies for these patients.

The aim of this study is to investigate the ANS status in patients with asthma and anxiety.

MATERIALS AND METHODS OF RESEARCH

This study utilized an analytical cross-sectional design and was conducted at Dnipro State Medical University, Ukraine. We selected 60 asthmatic patients aged between 35 and 65 years, 30 men and 30 women, undergoing inpatient treatment in the allergological center in Dnipro. Participants were stratified according to asthma control and clinically significant anxiety status, resulting in a balanced allocation across four factorial cells of 15 patients each. All 60 patients received the same treatment regimen, which included a combination of inhaled corticosteroids (ICS) and long-acting beta-agonists (LABAs). The four factorial cells were clinically defined as follows: the first group included patients with CA who were at risk for clinical stress and anxiety (CASA); the second group consisted of patients with controlled asthma without risk of clinical stress and anxiety (CA); the third group was made up of patients with UA at risk for clinical stress and anxiety (UASA); and the fourth group comprised patients with UA who did not have risk factors for clinical stress and anxiety (UA) [10].

The HADS (Hospital Anxiety and Depression Scale) questionnaire was given individually to each patient. This allowed for the assessment of anxiety using the following criteria: 0-7 points – normal; 8-10 points – subclinical anxiety (mild impairment); 11 points and above – clinically significant anxiety [11]. Lung function was assessed using a computerized spirograph (Spirolab III® MIR). Forced Expiratory Volume in 1 second (FEV_1) was determined.

ANS status was assessed using Heart Rate Variability (HRV). The ANS supplies nerves to both the heart and lungs. It regulates the heart rate and the force of contraction in the heart, as well as bronchial smooth muscle constriction and mucus hypersecretion in the lungs. There is a connection between these two components. Therefore, HRV is recognized as a reliable method for diagnosing autonomic dysfunction in both the myocardium and respiratory

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systems. Non-invasive assessments of the ANS are conducted using HRV based on established measurement standards, physiological interpretations, and clinical uses outlined in the guidelines from the working group of the European and American Society of Cardiology and Electrophysiology [12]. In 2024, the Psychophysiological Research Societies Committee released an updated report on Heart Rate and Heart Rate Variability. This report provides guidelines for methodology, interpretation, and reporting in HRV research. It supports the use of mobile HRV recording devices and encourages the application of short-term HRV measurements [13]. Recent studies have demonstrated the validity and reliability of short-term heart rate variability (HRV) parameters in assessing the status of ANS [14, 15, 16].

HRV parameters were derived from 5-min electrocardiogram recordings by the Polar H10 sensor chest strap device (Polar Electro Oy, Kempele, Finland) in a seated position after ensuring clean ECG signals, absence of movement artifacts and comfortable breathing. After extraction of the 1-channel ECG data and RR data (exported from the Elite HRV app) import into Kubios HRV Scientific Software version 3.5.0 (Biosignal Analysis and Medical Imaging Group, Department of Physics, University of Kuopio, Finland) was conducted. For the HRV analysis, we used both the time domain and frequency domain methods: heart rate (MHR), the square root of the variance of RR intervals (SDNN), the square root of the mean squared differences of successive RR intervals (RMSSD); very low frequency (VLF), low frequency (LF), high frequency (HF), normalized low frequency (LF Norm), normalized high frequency (HF Norm), and the LF/HF ratio.

The study procedure was explained to the patients. We only included research participants who were willing to provide written Patient Informed Consent for the Study (Code: 22253/2024). The patients were selected based on their clinical history. We excluded patients with other diseases like hypertension, diabetes, thyroid disorders, and ischemic heart disease. Smokers, alcoholics and pregnant women also were excluded from our study. All patients underwent clinical examination and investigations during the period from 09.00 AM to 12.00 PM to avoid confounding effects of circadian rhythm on HRV. On the day of the HRV study, patients did not receive inhalation therapy. Statistical evaluation was performed using the Microsoft Office Excel and IBM SPSS Statistics (version 27.0.1.0) [17].

Continuous variables were summarized as median (Q1-Q3). The two categorical factors were asthma control (controlled vs uncontrolled) and clinically significant anxiety (present vs absent). Because the outcomes were analyzed without assuming normality, a rank-based aligned-rank transformation (ART) procedure was applied to the full 2×2 factorial structure. The ART approach permits separate testing of the main effect of asthma control, the main effect of anxiety, and the asthma-control × anxiety interaction while retaining the factorial design. No Student's t-test was used, because the analysis did not assume normally distributed continuous outcomes.

For each factorial effect, F statistics with 1 and 56 degrees of freedom, two-sided p values, and partial eta-squared (partial η^2) were reported. P values for factorial outcomes were unadjusted for multiplicity and were interpreted at $\alpha=0.05$. Spearman rank correlations were used as secondary analyses to quantify associations involving HADS-A and selected HRV measures. The sign of each coefficient was interpreted according to the direction of the association; negative coefficients indicate inverse relationships and positive coefficients indicate direct relationships.

The study protocol was approved by the Biomedical Ethics Committee of Dnipro State Medical University (Extract from the Minutes No. 33, dated 17 December 2025). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki (World Medical Association, 2013 revision). Written informed consent was obtained from every participant before enrollment. Clinical and imaging data were analysed in anonymised form to protect confidentiality.

RESULTS AND DISCUSSION

A total of 60 patients with bronchial asthma were included in the study. According to asthma control and anxiety status, participants were allocated into four age- and sex-matched factorial cells comprising 15 patients in each factorial cell.

Descriptive characteristics

The four factorial cells were balanced. Table 1 presents the baseline clinical, pulmonary, heart-rate, and HRV variables represented as median and interquartile range (Q1-Q3). HADS-A values were substantially higher in the clinically significant anxiety groups, whereas ACQ-7 and FEV_1 differentiated controlled from uncontrolled asthma as expected from the factorial classification. ACQ-7 and HADS-A are shown descriptively because they were used to define the corresponding experimental factors.

Factorial Analysis

The Aligned Rank Transformation (ART) analysis of the pulmonary and HRV outcomes is shown in Table 2. The principal findings revealed strong main effects of asthma control on pulmonary function and several key HRV measures, together with a strong

main effect of anxiety on SDNN (F=80.20, p<0.001). Significant interactions were detected for RMSSD and LF norm, whereas the interaction for HF norm was not statistically significant, indicating that the association of anxiety with these outcomes was not uniform across asthma-control strata.

Table 1

Clinical, pulmonary, and HRV characteristics by factorial cell

Variable	CA + anxiety (CASA) (n=15)	CA + no anxiety (CA) (n=15)	UA + anxiety (UASA) (n=15)	UA + no anxiety (UA) (n=15)
ACQ-7	0.65 (0.43–0.86)	0.55 (0.50–0.61)	4.82 (4.18–5.47)	3.78 (3.34–4.22)
HADS-A	15.50 (12.80–18.40)	4.30 (3.80–4.90)	16.10 (12.90–19.50)	5.20 (4.40–6.00)
FEV_1 (%)	76.60 (72.40–81.20)	81.80 (76.60–87.30)	64.20 (59.70–68.80)	68.20 (64.30–72.10)
MHR (bpm)	87.60 (81.20–94.30)	80.10 (75.30–85.00)	71.20 (66.40–76.00)	61.40 (57.80–65.00)
SDNN (ms)	23.50 (17.90–29.30)	46.50 (35.80–56.70)	21.50 (16.20–26.80)	44.20 (36.40–52.30)
RMSSD (ms)	10.60 (8.10–13.20)	16.80 (13.40–20.10)	25.40 (20.50–30.20)	45.60 (34.80–56.90)
LF (ms^2)	838.50 (646.20–1034.10)	762.70 (588.30–939.80)	435.60 (324.50–546.80)	321.00 (196.40–444.20)
HF (ms^2)	421.50 (295.30–546.60)	386.50 (270.80–503.70)	698.70 (556.80–840.50)	835.60 (634.70–1037.20)
LF norm (n.u.)	40.60 (30.20–51.40)	50.40 (38.60–62.10)	43.80 (31.40–56.20)	33.20 (22.70–43.60)
HF norm (n.u.)	21.40 (15.80–27.20)	32.50 (24.90–40.30)	38.20 (27.50–48.90)	58.80 (46.50–71.40)
LF/HF ratio	1.96 (1.39–2.55)	1.52 (1.09–1.95)	1.04 (0.74–1.32)	0.64 (0.49–0.79)

Notes: CA, controlled asthma; UA, uncontrolled asthma; HADS-A, Hospital Anxiety and Depression Scale Anxiety subscale; FEV_1, forced expiratory volume in 1 second; MHR, mean heart rate; SDNN, standard deviation of normal-to-normal intervals; RMSSD, root mean square of successive differences; LF, low-frequency power; HF, high-frequency power; n.u., normalized units.

Autonomic and correlation patterns

Several distinct autonomic patterns across the factorial cells become evident from the consolidated data:

Anxiety and total HRV suppression: A notable finding across the factorial cells is the low SDNN in patients with clinically significant anxiety (CASA: 23.50 ms; UASA: 21.50 ms), reflecting a restricted range of beat-to-beat variation and an unadaptable autonomic nervous system (ANS). Statistical analysis revealed a strong inverse correlation between SDNN and HADS-A scores: Spearman's rank correlation coefficient for all 60 patients combined reached -0.882.

Parasympathetic regulation and vagal shifts: RMSSD and HF parameters-both specific indices of parasympathetic nervous system (PNS) tone-demonstrated unique behavior across asthma strata. Contrary to simplified models, PNS tone was higher in patients with uncontrolled asthma (UA branches) compared to those with controlled disease (CA branches), reflecting a pattern of increased vagal modulation in uncontrolled asthma. However, within both strata, the presence of anxiety was associated with reduced vagal activity. For instance, HF norm decreased from 32.50 n.u. (CA) to 21.40 n.u. (CASA), and from 58.80 n.u. (UA) to 38.20 n.u. (UASA).

Autonomic balance and disease control: The LF/HF ratio confirmed a marked predominance of sympathetic activity in patients with controlled asthma, which was further amplified by concurrent anxiety (LF/HF =1.96 in CASA). In contrast, the uncontrolled asthma group without anxiety showed a clear parasympathetic shift (LF/HF =0.64). Vagal suppression induced by anxiety shifted the autonomic balance toward a relative sympathetic increase in both groups, showing a strong direct correlation with HADS-A scores (Spearman's ρ=0.769 in Group 1; Spearman's ρ=0.875 in Group 3).

Interaction of control and autonomic status: Statistical evaluation exploring the relationship between asthma control (overall ACQ-7 score) and ANS status (LF/HF ratio) revealed a strong correlation. In the anxiety factorial cells (1 and 3), Spearman's ρ coefficient was 0.775, while in the non-anxiety factorial cells (2 and 4), it was even higher at 0.894, suggesting that anxiety shifts or confounds the direct relationship between asthma clinical control and autonomic regulation.

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Table 2

Aligned rank transformation (ART) ANOVA results for factorial effects

Outcome	Effect	F-value	p-value	Partial η^2
FEV_1	Asthma control	85.63	<0.001	0.605
	Anxiety	1.45	0.234	0.025
	Interaction	0.37	0.546	0.007
MHR	Asthma control	74.10	<0.001	0.570
	Anxiety	0.45	0.507	0.008
	Interaction	4.07	0.048	0.068
SDNN	Asthma control	0.29	0.595	0.005
	Anxiety	80.20	<0.001	0.589
	Interaction	0.00	0.989	0.000
RMSSD	Asthma control	218.27	<0.001	0.796
	Anxiety	20.13	<0.001	0.264
	Interaction	16.84	<0.001	0.231
LF norm	Asthma control	13.74	<0.001	0.197
	Anxiety	4.18	0.046	0.069
	Interaction	9.74	0.003	0.148
HF norm	Asthma control	63.06	<0.001	0.530
	Anxiety	11.06	0.002	0.165
	Interaction	2.79	0.101	0.047
LF/HF	Asthma control	54.86	<0.001	0.495
	Anxiety	4.96	0.030	0.081
	Interaction	0.61	0.437	0.011

Given the complexity of the relationships among asthma controllability, anxiety, and ANS parameters, a single correlation does not fully capture the nature of their interaction. Therefore, a multiple correlation coefficient was calculated to describe the combined relationship. The high multiple correlation coefficient of 0.914 indicates a strong joint association of anxiety severity (HADS-A) and autonomic balance (LF/HF ratio) with asthma controllability.

The principal finding of this study is the presence of a profound autonomic nervous system (ANS) imbalance in patients with bronchial asthma, which is compounded and structurally altered by the presence of clinically significant anxiety. By utilizing a rigorous Aligned Rank Transformation (ART) factorial design, we were able to isolate the independent main effects of asthma control and anxiety, as well as their significant interactions, on specific time- and frequency-domain heart rate variability (HRV) parameters.

A central finding across all asthma factorial cells is the severe suppression of total heart rate variability, indexed by low SDNN values, in patients with concomitant anxiety (CASA: 23.50 ms; UASA: 21.50 ms). Factorial ANOVA confirmed a highly significant main effect of anxiety on SDNN ($F=80.20$, $p<0.001$), while asthma control showed no significant independent impact on this parameter ($F=0.29$, $p=0.595$). This pattern is further supported by the secondary correlation analysis, which demonstrated a remarkably strong inverse relationship between total HRV and anxiety severity, both within the anxious cohort (Spearman's $\rho= -0.856$) and across the entire study cohort of 60 patients (Spearman's $\rho= -0.882$). These data align with compelling evidence from previous psychophysiological research indicating that low SDNN serves as a reliable and robust digital biomarker for clinical anxiety disorders, reflecting an unadaptable, rigid ANS unable to flexibly respond to environmental and internal stressors [3, 14].

However, evaluating ANS status solely through total variability provides an oversimplified view of the pathogenic mechanisms at play. Our analysis of parasympathetic nervous system (PNS) modulations via RMSSD and normalized high-frequency power (HF norm) revealed a far more complex, bi-directional dynamic. In contrast to traditional paradigms suggesting uniform autonomic suppression in chronic diseases, our data demonstrated a strong independent main effect of asthma control on both RMSSD ($F=218.27$, $p<0.001$) and HF norm ($F=63.06$, $p<0.001$). Patients with uncontrolled asthma without anxiety (the UA group) exhibited a marked predominance of parasympathetic modulation, characterized by the highest RMSSD (45.60 ms) and HF norm (58.80 n.u.) values, alongside the lowest mean heart rate (61.40 bpm). Physiologically, this hyper-vagal

state represents the classic autonomic hallmark of uncontrolled airway inflammation, driving bronchoconstriction, airway hyperresponsiveness, and mucus hypersecretion, which is consistent with several respiratory and functional studies [4, 19, 20].

The critical clinical insight, however, emerges from the significant interaction effects detected for RMSSD ($F=16.84$, $p<0.001$) and LF norm ($F=9.74$, $p=0.003$). These statistics indicate that the impact of anxiety on autonomic outcomes is not uniform across different asthma severity strata. Within both controlled and uncontrolled asthma branches, the presence of clinically significant anxiety actively dampens and suppresses the vagal component [3, 9, 10]. This is explicitly visible in the drop in HF norm from 32.50 n.u. (CA) to 21.40 n.u. (CASA), and from 58.80 n.u. (UA) to 38.20 n.u. (UASA).

This finding challenges simplified clinical assumptions regarding autonomic interactions [6, 7, 8, 9]. Theoretically, a shift toward sympathetic dominance (such as the highest LF/HF ratio of 1.96 observed in the CASA group) should promote bronchodilation via $\beta_1$adrenergic pathways. However, in the clinical reality of comorbid anxiety, this protective mechanism is absent. Instead, anxiety-induced sympathetic activation coupled with simultaneous parasympathetic withdrawal appears to cause a profound autonomic dysregulation or "arrhythmia" of the respiratory-cardiac axis. This mechanism is reflected in the ACQ-7 values: the score increased from 0.55 in the CA group to 0.65 in CASA, and from 3.78 in the UA group to 4.82 in UASA. This underscores that while anxiety increases SNS activity, it consistently leads to a simultaneous decline in asthma controllability, emphasizing the bidirectional relationship between the two conditions [1, 2].

The tight physiological coupling between autonomic balance and asthma control is further highlighted by the strong inverse correlation between the ACQ-7 overall score and the LF/HF ratio, which was particularly prominent in the non-anxiety groups (Spearman's $\rho= -0.894$) compared to the anxiety groups ($\rho= -0.775$). This discrepancy suggests that while autonomic tone directly mirrors asthma control under stable psychological conditions, the presence of clinical anxiety acts as a profound confounding and disruptive factor that distorts the predictable physiological relationship between the lungs and the ANS.

Ultimately, because chronic asthma controllability, psychological distress, and autonomic tone are inherently interwoven, a simple double-factor analysis cannot fully capture the clinical picture. A multiple rank correlation analysis showed a strong combined association of HADS-A and the LF/HF ratio with ACQ-7 (multiple correlation coefficient, $R=0.914$), indicating that anxiety severity (HADS-A) and autonomic imbalance (the LF/HF ratio) are jointly and strongly associated with overall asthma controllability [5, 19, 20].Consequently, optimizing therapeutic outcomes in bronchial asthma requires a holistic approach that moves beyond basic bronchodilation to actively screen for and manage comorbid anxiety, thereby stabilizing the underlying autonomic equilibrium.

Limitations. The present study has several limitations. First, it was a single-center study with a relatively small sample size and no control group, which may have influenced the results. Additionally, the respiratory rate, as it is known to impact HRV analysis, was not recorded in this study. Efforts were made to reduce any potential effects, but this remains a limitation. Furthermore, although the non-parametric Aligned Rank Transformation (ART) ANOVA design is highly robust for non-normal data, it evaluates significance based on rank-based transformations rather than the original physical metrics (raw milliseconds or percentages). Furthermore, although the non-parametric Aligned Rank Transformation (ART) ANOVA design is highly robust for non-normal data, it evaluates significance based on rank-based transformations rather than the original physical metrics (raw milliseconds or percentages). This approach establishes the statistical presence of factorial interactions but inherently limits direct parametric modeling of raw effect sizes. On the positive side, the strength of this study was the formation of age- and sex-matched groups of asthma patients, categorized according to their level of asthma control and anxiety. When analyzing the HRV assessment results, we attempted to minimize the influence of inhalation therapy: patients refrained from using ICS, LABA or LAMA for several hours before the study. However, patients with UA were allowed to use salbutamol. The existing data on the effects of inhaled LABA and LAMA on HRV are contradictory. For instance, Sarah Elhage et al. concluded that LABA and LAMA do not significantly affect HRV in asthma patients [21]. In contrast, Hajar Ali et al. reported that the administration of salbutamol within two hours prior to HRV testing or the use of LABA within two weeks prior resulted in decreased PNS activity and increased SNS activity in asthma patients [20]. Furthermore, Ching-Hui Tsou et al. found prolonged SNS activation following β2-agonist inhalation [22]. In their review of recent studies, Lorena Soto-Retes et al. concluded that, currently, there is no reliable evidence regarding the impact of LABA and LAMA on the ANS in asthma patients [7].

CONCLUSIONS

1. Patients with bronchial asthma and comorbid, clinically significant anxiety exhibit severe autonomic

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dysfunction characterized by marked sympathetic hyperactivity, profound withdrawal of parasympathetic modulation, and a critical suppression of total heart rate variability. This rigid autonomic profile indicates a diminished regulatory capacity and impaired systemic adaptability to psychophysiological stress.

2. A state of uncontrolled asthma is fundamentally associated with a hyper-vagal shift and elevated parasympathetic activity, reflecting the pathophysiological mechanisms of airway inflammation and bronchial hyperresponsiveness. However, the chronic suppression of overall heart rate variability (low SDNN) induced by concurrent anxiety strongly correlates with poorer clinical control of the disease, establishing a distinct relationship between autonomic dysregulation and clinical severity.

3. Clinically significant anxiety actively disrupts the predictable physiological equilibrium between the respiratory system and the autonomic nervous system, contributing to a profound autonomic imbalance across all asthma factorial cells. Psychological distress does not merely act as an isolated comorbidity but serves as a disruptive factor that impairs autonomic stability, directly exacerbating the clinical course and controllability of bronchial asthma.

4. Routine screening for anxiety and emotional distress in patients with bronchial asthma is highly recommended in clinical practice to facilitate the early identification of individuals at an increased risk of poor disease control, thereby allowing for the timely implementation of targeted, individualized management strategies.

5. Short-term heart rate variability assessment using standard electrocardiography or validated wearable sensors represents a practical, non-invasive, and cost-effective digital method for evaluating autonomic function. Incorporating short-term HRV monitoring into clinical protocols may serve as a valuable additional tool for the comprehensive and objective assessment of asthma patients in routine clinical settings.

Acknowledgement. This research is not currently receiving funding from any source. We would like to thank the authors who contributed to this work

Contributors:

Vysochyna I.L. – conceptualization, methodology, formal analysis;

Berezutskyi I.V. – resources, data curation, investigation, software.

Funding. Thisresearchreceivednoexternalfunding.

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

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Стаття надійшла до редакції 24.03.2026;
затверджена до публікації 05.09.2026

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