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Original article

Assessing short-term weather-induced immune response in Russian Far East residents with respiratory diseases

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Abstract: *Objective* — To identify criteria for contrasting meteorological changes affecting the temporal dynamics of the immune response in individuals with bronchopulmonary pathology in the maritime monsoon climate of Vladivostok.
Methods — We examined 178 patients with stable chronic obstructive pulmonary disease (COPD) of mild and moderate severity, 212 patients with controlled bronchial asthma (BA) and 60 apparently healthy volunteers. We assessed the cumulative response of the components of adaptive and innate immune systems to the effects of day-to-day variability in temperature, air pressure and humidity, wind speed and direction, and precipitation relative to the day of the patient's medical examination ± 2 days. The response of the immune system was measured by an integral indicator calculated as the ratio of the sum of statistically significant correlations ($p<0.05$) to the total sum of correlation matrix elements.
Results — The short-term compensatory severity and activity of the immune response to the weather in healthy people (∑D%=2.56; ∑r=117) was almost twice as high as the similar response in patients with COPD (∑D%=1.28; ∑r=72) or BA (∑D%=1.35; ∑r=69). The immune response of apparently healthy subjects to the action of specific meteorological factors on the day of medical examination was reduced by 40%, compared with the short-term response (±2 days) in patients with COPD, but the difference was not significant. The values of the criteria for the day-to-day contrast of influencing meteorological factors in apparently healthy patients were reduced.
Conclusion — The urban population in maritime monsoon climate exhibited weak and moderate weather-induced immune system responses. Wind regime, humidity and precipitation had a pronounced effect on the immune system. In patients with COPD and BA, the maximum pathogenic response of the immune system to the impact of climatic factors was observed within ±1 day.

Keywords: short-term meteoropathy, immune system, bronchopulmonary diseases.

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Introduction

Global climate models predict more frequent extreme weather events [1]. They demonstrate an aggravated impact on chronically ill patients, especially cohorts with maladjustment to weather variability.

There are many adaptive mechanisms serving to protect the human body from the negative effects of the environment. One of such mechanisms is the functioning of the immune system, which is an extremely complex multicomponent highly sensitive system that includes various cell subpopulations. Immune cells located in the skin and mucous membranes of internal organs form local innate immune system, which is the first line of defense against external stress. The sensitivity of individual parts of the immune system to climatic factors is different. This circumstance underlies prenosologic changes in immune reactivity, which, on the one hand, are markers of unfavorable living conditions, and, on the other hand, determine the development of pathology and chronicity or progression of existing ailments [2, 3].

Most healthy people are virtually insensitive to weather changes. At the same time, there are many people exhibiting increased sensitivity to fluctuations in meteorological conditions, mainly patients with respiratory diseases [4]. Such people are called weather dependent. As a rule, they react to sharp contrasting weather changes or weather conditions that are unusual for a given time of year.

The object of our study was Vladivostok, a large administrative center located on a peninsular territory along the coast of the Sea of Japan in the southeastern part of the Russian Federation. It has a maritime monsoon climate characterized by seasonal circulation of the atmosphere. The latter is caused by uneven heating and cooling of the Eurasian landmass and adjacent areas of the Pacific Ocean. This leads to the emergence of complex synoptic processes, such as cyclonic and anticyclonic activity, the formation of frontal zones and, as a result, abrupt changes in the weather regime [5].

The responses of the body to the impact of weather conditions are characterized by weather dependence (in healthy people) and

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meteoropathic responses (in patients), which aggravate the course of chronic diseases [6, 7]. As a rule, pathological weather dependence that affects the homeostasis of biological dynamic systems is based on the exhaustion of the reserve adaptive and compensatory capabilities of the body, which leads to desynchronization and dysfunction of the internal systems of the body [4, 8].

Contrasting weather changes cause a functional response of the immune system to the impact of sharp day-to-day fluctuations of both individual meteorological factors (air temperature and pressure, wind speed and direction, etc.), and the entire weather complex, in which the combination of individual meteorological parameters produces a synergistic effect [8, 9]. According to the rate of the body's response to the impact of adverse weather conditions, weather-induced responses can be classified into three types: delayed, immediate, and residual [10]. A response that occurs before a visible change in weather conditions is called a *signal* response; it can be observed in weather-dependent people within 2 days before the weather changes. The *immediate* response corresponds to the current weather conditions [11]. This type of meteorological dependence is a consequence of the amplification of electrical and electromagnetic disturbances associated with atmospheric circulation [12]. *Residual* response of the body characterizes the delayed or accumulating effect of the pathogenic action of meteorological factors. In this case, the response of the immune system to changes in weather conditions develops with a 1- or 2-day delay [12].

The objective of our study was to establish criteria for contrasting meteorological changes that affect the temporal dynamics of the immune response in patients with bronchopulmonary diseases in the maritime monsoon climate of Vladivostok.

Material and Methods

Study participants

We examined 390 study subjects in 2013-2018, including 178 patients with a mild or moderate stable COPD and 212 patients with controlled BA, and 60 healthy volunteers who served as the control group. BA and COPD were diagnosed in accordance with the Global Strategy for Asthma Management and Prevention [13] and the Global Strategy for the Diagnosis, Treatment and Prevention of Chronic Obstructive Pulmonary Disease [14].

Table 1. Clinical and demographic characteristics of the patients

Indicators	*Asthma (Group 1) n=212*	*COPD (Group 2) n=178*	*Control group n=60*
Age, years	53.81±5.41	62.11±4.38	51.73±6.52
Gender: men/women (absolute numbers)	74/147	122/56	26/34
Smokers at the time of the checkup (absolute numbers)	6/1	24/5	0/0
Ex-smokers (absolute numbers)	15/11	98/51	10/4
Quetelet index (body mass index), kg/m^2	32.82 ± 3.24	30.56 ± 2.78	28.71 ± 4.62
Duration of disease:			
a) up to 10 years	97	134	
b) more than 10 years	115	44	
COPD assessment test		11.3±2.08	
mMRC score		1.4±0.06	
ACQ-5 test	0.6±0.05		

Table 2. Immunological characteristics of the patients

Indicators	*Asthma (Group 1) n=212*	*COPD (Group 2) n=178*	*Control group n=60*
$CD3^+$, %	39.6 (35.8-41.9). p=0.062	49.1 (45.6-52.8). p=0.075	45.6 (41.1-47.6)
$CD3^+CD4^+$, %	34 (31.8-39.2). p=0.069	46.2 (41.8-49.5). p=0.084	40.2 (37.1-45.6)
$CD3^-CD19^+$, %	9.6 (8.7-10.2). p=0.044*	16.2 (14.9-18.3). p=0.049	13.1 (11.2-14.8)
$CD3^-(CD16^+CD56^+)$, %	11.4 (9.2-14.6). p=0.04*	20.9 (18.9-25.4). p=0.062	17.5 (15.3-19.7)
$CD3^+CD8^+$, %	16.4 (13.4-18.2). p=0.02*	18.4 (15.1-21.3). p=0.078	22.6 (19.1-25.8)
CD4/CD8, CU	1.3 (1.22-1.43). p=0.008**	2.7 (2.57-2.96). p<0.001***	1.7 (1.56-1.85)
TNF-α, pg/mL	67.2 (64.1-76.8). p<0.001***	59.4 (51.0-69.0). p=0.03*	46.3 (43.2-48.9)
IFN-γ, pg/mL	91.4 (87.2-96.3). p=0.086	125.9 (114.0-141.0). p=0.079	103.5 (91.6-122.7)
IL-4, pg/mL	98.1 (84.6-109.1). p=0.044*	59.3 (48.3-65.8). p=0.043*	77.9 (69.2-81.0)
IL-6, pg/mL	93.1 (83.9-96.7). p<0.001***	78.1 (64.7-80.3). p<0.001***	38.2 (35.7-39.0)
IL-10, pg/mL	27.5 (21.7-32.8). p=0.084	43.6 (38.3-46.1). p=0.047	32.4 (30.1-35.7)
IL-17A, pg/mL	907.2 (852.0-964.2). p<0.001***	605.3 (591.9-620.5). p<0.001***	378.4 (360.0-395.1)
IL-21, pg/mL	296.4 (279.2-317.1). p<0.001***	200.0 (184.0-227.0). p<0.001***	75.5 (70.0-82.2)
IL-8, pg/mL	52.0 (44.2-57.1). p=0.066	79.4 (69.2-82.4). p=0.063	62.4 (54.3-71.6)
Neutrophil phagocytic activity, %	58.7 (52.6-65.9). p=0.052	74.6 (68.2-79.3). p=0.064	65.0 (57.4-71.6)
Phagocyte reserve, CU	0.8 (0.76-0.84). p<0.001***	1.4 (1.34-1.46). p=0.032*	1.2 (1.18-1.29)
Phagocyte number, %	4.6 (4.1-4.87). p=0.041*	6.2 (5.91-6.38). p=0.039*	5.3 (4.96-5.61)
Phagocyte number reserve, CU	0.9 (0.82-0.96). p<0.001***	0.95 (0.90-0.97). p<0.001***	1.6 (1.51-1.72)
NBT blood test, %	8.0 (7.78-8.2). p=0.022*	18.0 (16.1-20.3). p=0.041*	13.0 (11.4-15.1)
NBT test reserve, %	0.82 (0.79-0.85). p=0.008**	1.1 (1.07-1.13). p=0.044*	1.31 (1.28-1.42)
NAI, CU	0.9 (0.84-0.93). p<0.001***	0.19 (0.17-0.20). p=0.018*	0.12 (0.09-0.14)
NAI reserve, CU	2.1 (2.0-2.24). p=0.039*	1.6 (1.58-1.65). p<0.001***	2.8 (2.69-2.93)

p – statistical significance of differences between the BA or COPD group and the control group; * p<0.05, ** p<0.01, *** p<0.001. NBT, nitroblue tetrazolium; NAI, neutrophil activation index

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The ACQ-5 test (Asthma Control Questionnaire) was used to assess the subjective state of patients with BA, and to determine the level of the disease control. The absence of any BA symptoms for the last 4 weeks, which corresponded to the ACQ-5 test score of less than 0.75 points, was the criterion confirming the controlled course of BA.

To evaluate the symptoms of COPD, the examination was conducted using validated questionnaires: the Modified Medical Research Council (mMRC) Dyspnea Scale of the British Medical Research Council (to assess the severity of labored breathing) and the COPD Assessment Test (CAT, to assess the impact of COPD on the patient's daily routine and health status.

Investigation of the pulmonary function was carried out employing the Master Screen Body device (Care Fusion, Germany). To determine the severity of COPD, the following post-bronchodilator response parameters were examined: the forced vital capacity (FVC) of the lungs, forced expiratory volume during the 1st second (FEV1), and their ratio (FEV1/FVC). The COPD was diagnosed at FEV1/FVC<0.7. Mild bronchial obstruction (GOLD I) was diagnosed at FEV1≥80% of due, whereas moderate bronchial obstruction (GOLD II) was diagnosed at 50%≤FEV1≥<80%.

Inclusion criteria: patients with mild persistent BA with controlled course of the disease and those with a stable COPD meeting the GOLD I or GOLD II criteria.

Exclusion criteria: uncontrolled or partially controlled BA, COPD in the acute phase, COPD patients meeting the GOLD III or GOLD IV criteria, occupational diseases of the bronchopulmonary system, diseases of internal organs in the stage of decompensation.

The clinical and demographic characteristics of examined patients are presented in *Table* 1.

The mean age of patients was 57.9±4.8 years. Written informed consent was obtained from all individual participants included in the study. All procedures performed in studies were in accordance with the ethical standards of the Ethics Committee at the Vladivostok Branch of Far Eastern Scientific Center for Physiology and Pathology of Respiration – Research Institute of Medical Climatology and Rehabilitation Therapy, as well as with the Declaration of Helsinki (2013).

The immunological characteristics of examined patients are presented in *Table 2*.

Table 3. Short-term intensity (D%, p<0.05) and activity (∑r, p<0.05) of weather-induced immune system response to meteorological factors in healthy individuals and patients with bronchopulmonary diseases

Time lag	*Control group*		*COPD*		*Asthma*	
	D%	∑r, n	D%	∑r, n	D%	∑r, n
Residual response (1, 2 days before the examination day)						
- 2 days	2.1	21	1.7	19	1.4	14
- 1 day	2.5	22	1.2	14	0.46	5
Immediate response (on examination day)						
Examination day	2.8	16	1.3	13	2.4	25
Signal response (1, 2 days after the examination day)						
+ 1 day	2.6	23	1.1	14	0.88	9
+ 2 days	3.9	35	1.1	12	1.6	16
∑D and ∑r	*2.56*	117	*1.28*	72	*1.35*	69

Laboratory methods

To assess the health status of patients, clinical and laboratory tests were carried out. The biological material was peripheral blood samples. Using the method of flow cytometry (BD FACS Canto II, USA), we measured the parameters of cellular immunity (BD Multitest 6-color TBNK, USA). Serum cytokines levels, specifically, of tumor necrosis factor α (TNF-α), interferon γ (IFN-γ), interleukin 4 (IL-4), IL-6, IL-10, IL-17A were assessed with Cytometric Bead Array test system (BD, USA). The phagocytic and oxidative burst activity of neutrophils was assessed using the commercially available test kits, PHAGOTEST (BD, USA) and BURSTEST (PHAGOBURST) (BD, USA). A total of 22 parameters of cellular immunity were measured (*Table 2*).

Meteorological factors

We analyzed meteorological data using the database of the Federal Service for Hydrometeorology and Environmental Monitoring, Primorsky Branch [15]. We took into account meteorological data pertaining to air temperature, pressure and humidity, wind speed and direction, and rainfall on the day of the examination of the patient (corresponding to the *immediate* body response), 2 days before the examination of the patient (corresponding to the *residual* body response) and 2 days after the examination of the patient (corresponding to the *signal* body response). Wind speed and direction, atmospheric pressure, and amount of precipitation are associated with cyclonic activity in the marine atmosphere, causing electrical and electromagnetic disturbances and other atmospheric phenomena that affect the meteorological dependence in people. Air temperature and humidity determine the oxygen concentration in the air, which also directly affects the state of human health, especially in patients with respiratory diseases. *Immediate* meteorological data were selected based on the time of the patient examination (during the first half of the day). The values of *residual* and *signal* meteorological parameters were extreme (maximum or minimum) over 24 hours, which made it possible to establish the strongest contrast of changes in each meteorological factor that generated pathogenic impact.

Data processing

To assess the severity and activity of the synergistic response of the immune system to the impact of the weather complex during a short-term study (within 2 days before and after the day of medical examination), the responses of the immune system (D%) were employed [14].

To measure the intensity of the synergistic response of the immune system (22 indicators) to the impact of meteorological conditions (6 factors), an integral indicator of the response intensity (D%) was used, the calculation of which involved determining the proportion of the sum of statistically significant correlation coefficients (p<0.05) of the total sum of all correlations in a 22×6 matrix. An increase in D% values implied an increased response of the immune system to external influences, and, on the contrary, lower D% values (or their complete absence) suggested a weaker immune response. The number (n) of statistically significant r (p<0.05) in this matrix indicated the activity (∑r) of the synergistic response of the immune system. The assessment of the intensity (D%) of the individual immune response to the action of one or another meteorological factor (using a 22×1 correlation matrix) was carried out similarly to that described above. Criteria

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for the day-to-day contrast of meteorological factors, at which the immune response was observed, were determined from the table of results in the *Multiple Correlation* module of STATISTICA 10. Using the average values (M), the standard deviation (SD), at which a statistically significant dependence of immune parameters on each meteorological factor was observed, the criterion of day-to-day contrast (M±SD) was calculated.

Results

We investigated the intensity and activity of the cumulative immune system response to the impact of the weather conditions during a short-term study (within 2 days before and after the day of the medical examination). In the study groups (control group, COPD group and BA group), integral indices of intensity (D%) and activity (∑r, p<0.05) of short-term weather-induced reactions were determined, which made it possible to compare the responses of the immune system to the effects of the weather complex, depending on response development time (signal, immediate, and residual) (*Table 3*).

Our calculations demonstrated the difference in the magnitude of the intensity (D%) and activity (∑r) indicators of the adaptive and compensatory responses to changing weather conditions. The most pronounced compensatory response was observed in the control group (∑D%=2.56; ∑r=117). The value of ∑D%, which characterized the compensatory effect, was halved (1.28) in COPD patients compared to healthy volunteers. In patients with asthma, the intensity of the response of the immune system was slightly higher (1.35), compared with COPD patients. At the same time, the activity of the response in the groups of patients was reduced (69 in BA group, 72 in COPD group). We revealed a significant variability in the severity and activity of residual and signal compensatory responses to weather in patients with COPD and BA (*Table 3*).

Analysis of the response of the D% value to the triggering action of meteorological parameters (wind direction and speed, amount of precipitation, air temperature, humidity and pressure) made it possible to identify a compensatory response that reflected the level of pathogenicity of the external impact (the lower the value of D%, the weaker the compensatory effect). The effective immediate response was observed in healthy individuals and patients with BA with a rather high values of ∑D% (healthy: 5.87/0.03; BA: 5.08/0.03) (*Table 4*). The residual compensatory response to meteorological conditions was characterized by the highest intensity indicators in healthy individuals (∑D%=7.48-9.5), while patients with BA were the most vulnerable 24 hours before medical examination (-1 day): ∑D%=0.97 (*Table 4*).

Table 4. Short-term intensity of the immune system response to separate meteorological factors in healthy people and patients with bronchopulmonary diseases

Lag time	*Wind direction (°)*	*Wind speed (m/s)*	*Amount of precipitation (mm)*	*Air temperature (°C)*	*Air humidity (%)*	*Air pressure (GPa)*	*∑ D%/*
			Immediate response (on examination day)				
Control	0.62/0.043	0.62/0.051	**1.62/0.052**	**1.85/0.021**	**1.51/0.021**	**1.55/0.012**	5.87/0.031
COPD	0.36/0.031 (p<0.05*)		0.68/0.042 (p<0.001***)	**1.38/0.008** (p<0.01**)			2.42/0.031 (p<0.01**)
Asthma	0.89/0.041 (p<0.05*)	0.45/0.022 (p<0.05*)	**1.69/0.021** (p<0.01**)	0.81/0.032 (p<0.001***)	0.68/0.032 (p<0.001***)	0.56/0.032 (p<0.001***)	5.08/0.033 (p<0.05*)
			Residual response (-2 days)				
Control	**1.11/0.032**	**1.36/0.042**	**1.56/0.021**	**1.31/0.040**	**1.08/0.031**	**1.06/0.032**	7.48/0.033
COPD	0.59/0.022 (p<0.001***)	0.96/0.008 (p<0.001***)	**1.43/0.020** (p<0.01**)	0.52/0.032 (p<0.001***)	***0.2/0.010*** (p<0.001***)	0.16/0.052 (p<0.001***)	3.86/0.021 (p<0.001***)
Asthma	***0.2/0.031*** (p<0.001***)	0.25/0.008 (p<0.001***)	**1.2/0.033** (p<0.01**)	0.36/0.031 (p<0.001***)	0.68/0.022 (p<0.001***)	0.21/0.010 (p<0.001***)	2.9/0.024 (p<0.001***)
			Residual response (-1 day)				
Control	**1.44/0.021**	**1.1/0.031**	**1.84/0.022**	**1.81/0.009**	**1.44/0.030**	**1.87/0.013**	9.5/0.024
COPD	0.48/0.003 (p<0.001***)	0.22/0.005 (p<0.001***)	**1.19/0.020** (p<0.01**)	***0.17/0.030*** (p<0.01**)	***0.17/0.041*** (p<0.001***)	0.57/0.032 (p<0.001***)	2.8/0.021 (p<0.001***)
Asthma				0.57/0.031 (p<0.001***)	0.4/0.032 (p<0.001***)		0.97/0.030 (p<0.001***)
			Signal response (+1 day)				
Control	0.64/0.042	**1.12/0.002**	**2.32/0.024**	**1.18/0.021**	**1.78/0.021**	**1.18/0.021**	8.22/0.021
COPD	0.41/0.012 (p<0.01**)	***0.18/0.051*** (p<0.001***)	0.86/0.032 (p<0.001***)	0.38/0.032 (p<0.001***)	0.38/0.031 (p<0.001***)	0.32/0.042 (p<0.001***)	2.53/0.032 (p<0.001***)
Asthma		***0.18/0.032*** (p<0.001***)	0.82/0.021 (p<0.001***)	0.41/0.033 (p<0.001***)	0.43/0.012 (p<0.001***)		1.84/0.021 (p<0.001***)
			Signal response (+2 days)				
Control	0.5/0.0009	0.62/0.044	**1.92/0.022**	**3.74/0.023**	**1.81/0.012**	**1.37/0.014**	8.04/0.022
COPD		0.82/0.023 (p<0.01**)	0.78/0.033 (p<0.001***)	***0.16/0.041*** (p<0.001***)	0.22/0.014 (p<0.001***)	0.38/0.023 (p<0.001***)	2.36/0.024 (p<0.001***)
Asthma	0.28/0.022 (p<0.001***)	0.33/0.032 (p<0.001***)	***0.18/0.032*** (p<0.001***)	***0.15/0.014*** (p<0.001***)	0.33/0.033 (p<0.001***)		1.27/0.023 (p<0.001***)

D% is to the left of the slash, p for comparisons between experimental groups is to the right of the slash, p for comparisons with the control group is in parentheses; D%≥1.0 in bold font specifies maximum compensatory ability of the immune system to the impact of meteorological factors; D%≤0.2 in bold italics font designates minimum compensatory ability of the immune system; empty cells represent lack of compensatory ability of the immune system.

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Table 5. Criteria for day-to-day contrast of meteorological factors (M±SD) affecting the cumulative immune response in healthy individuals and patients with bronchopulmonary diseases

Lag time	*Wind direction (°)*	*Wind speed (m/s)*	*Amount of precipitation (mm)*	*Air temperature (°C)*	*Air humidity (%)*	*Air pressure (GPa)*
			Control group			
			Criteria of contrast changes (M±SD) in meteorological factors relatively examination day (± 2 days)			
– 2 days	65.38±10.54/0.028	6.01±0.96/0.032	8.48±3.3/0.043	4.24±0.5/0.014	25.22±2.29/0.031	6.07±1.01/0.021
– 1 day	56.87±9.63/0.034	4.81±0.52/0.016	6.4±3.23/0.022	**3.29±0.39/0.010**	17.37±2.04/0.025	4.45±0.9/0.036
+ 1 day	50.09±8.18/0.035	**4.63±0.31/0.010**	6.91±2.43/0.029	2.88±0.59/0.044	19.27±2.15/0.039	5.67±0.71/0.018
+ 2 days	**67.5±8.66/0.010**	6.31±0.89/0.026	7.44±2.5/0.017	3.6±0.39/0.045	20.94±2.23/0.021	6.11±0.64/0.015
			COPD group			
			Criteria for contrast changes (M±SD) of meteorological factors relative to the day of examination (± 2 days)			
– 2 days	57±7.8/0.033 (p<0.01**)	**5.98±0.89/0.011** (p<0.001***)	2.85±1.49/0.023 (p<0.001***)	2.81±0.46/0.019 (p<0.001***)	13.64±1.45/0.024 (p<0.001***)	4.88±0.79/0.018 (p<0.001***)
– 1 day	**40.97±7.34/0.011** (p<0.001***)	**4.16±0.29/0.010** (p<0.001***)	1.68±0.85/0.021 (p<0.001***)	2.1±0.51/0.027 (p<0.001***)	9.84±1.91/0.041 (p<0.001***)	**4.36±0.6/0.013** (p<0.01**)
+ 1 day	46.45±8.73/0.031 (p<0.01**)	4.56±0.52/0.027 (p<0.001***)	1.06±0.4/0.016 (p<0.001***)	2.66±0.44/0.022 (p<0.01**)	12.34±1.67/0.037 (p<0.001***)	**4.09±0.9/0.012** (p<0.001***)
+ 2 days		4.94±0.77/0.018 (p<0.001***)	2.02±0.68/0.021 (p<0.001***)	3.49±0.76/0.021 (p<0.01**)	17.67±2.82/0.039 (p<0.001***)	5.11±0.61/0.021 (p<0.01**)
			Asthma group			
			Criteria for contrast changes (M±SD) of meteorological factors relative to the day of examination (± 2 days)			
– 2 days	59.17±9.25/0.041 (p<0.01**)	**5.45±0.57/0.010** (p<0.001***)		**3.64±0.37/0.012** (p<0.001***)	17.86±2.13/0.038 (p<0.001***)	5.96±0.57/0.028 (p<0.001***)
– 1 day				2.73±0.29/0.028 (p<0.001***)	16.2±1.71/0.035 (p<0.01**)	
+ 1 day		4.7±0.46/0.022 (p<0.01**)	4.35±1.23/0.046 (p<0.001***)	3.22±0.39/0.017 (p<0.01**)	14.56±2.78/0.048 (p<0.01**)	
+ 2 days	51.33±9.73/0.042 (p<0.001***)	4.97±0.48/0.028 (p<0.001***)	4.88±1.57/0.039 (p<0.001***)	3.62±0.46/0.015 (p<0.05*)	20.21±1.74/0.041 (p<0.05*)	

D% is to the left of the slash, p for comparisons between experimental groups is to the right of the slash, p for comparisons with the control group is in parentheses; criteria of contrasting values of meteorological factors at p<0.01 are shown in bold font.

As for the signal response, healthy individuals also had high values of response intensity to weather conditions (∑D%=8.04-8.22). The second highest intensity was characteristic of patients with COPD (∑D%=2.36-2.53), followed by BA patients who exhibited the smallest compensatory effect to the impact of the weather (∑D%=1.27-1.84) (*Table 4*). The weakest immune response was the residual response to weather (-1 day) in patients with BA (∑D%=0.97) (*Table 4*).

Triggering weather factors that had a negative impact on the immune system of patients with BA were wind direction (D%=0-0.2), wind speed (D%=-0.18), precipitation (D%=-0.18), and air temperature in the signal response option (+2 days) (D%=-0.15) (Table 4). The most effective compensatory immune system responses to all meteorological factors were observed in the category of residual responses (-1 day, -2 days) (*Table 4*).

Criteria for day-to-day contrasts of meteorological factors made it possible to determine the regional ranges of meteorological factors at which a statistically significant (p<0.05) immune response of the body was formed, causing a a short-term compensatory or pathogenic effect. It was established that the response of the immune system to meteorological factors in the healthy urban population can occur with the greatest change in wind direction in from 50.09±8.18 (°) to 67.5±8.66 (°), and with the smallest change in air temperature from 2.88±0.59 (°C) to 4.24±0.5 (°C) (*Table 5*). In the COPD group, the maximum change was noted for wind direction from 40.97±7.34 (°) to 57.0±7.8 (°), and the minimum change was observed for the atmospheric pressure from 4.09±0.9 GPa to 5.11± 0.61 GPa. In patients with BA, their immune system response was formed with a maximum change in wind direction and a minimum change in the amount of precipitation (*Table 5*). In healthy individuals, the response of the immune system manifested itself at higher contrasting values of meteorological factors than in patients with COPD and BA (±2 days from the moment of medical examination) (*Table 5*).

Discussion

The assessment of the intensity and activity of the weather-induced response of the immune system to the impact of the meteorological complex, as an integral characteristic of the joint action of meteorological parameters, was carried out during a short-term study (within 2 days before and after the medical examination day).

The human body is most sensitive to the combined action of individual meteorological factors that cause a synergistic effect. We demonstrated that the values of integral indicators (∑D%; ∑r) depend on the state of health. We established that the compensatory capabilities (D%) of the immune system in the healthy population of Vladivostok were almost twice the intensity of the response in patients with COPD and BA (control group: 2.56; COPD: 1.28; BA: 1.35). The response activity (∑r) was also significantly reduced (~40%) in patients with respiratory diseases (control group: 117; COPD: 72; BA: 69). This pattern was obvious in the immediate response (D%=2.4; ∑r=25). COPD patients had the lowest values of the compensatory capabilities of their immune system (D%=1.3; ∑r=13). Patients with BA had a worse short-term weather-induced immune response (D%=0.46; ∑r=5) that occurred 1 day before and after the day of medica examination, while the signal response was slightly higher (D%=0.88; ∑r= 9) (*Table 3*).

A comparative analysis of the intensity (D%) of the short-term weather-induced response of the immune system made it possible to identify the triggering factors of climatic influence. The highest

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value of the compensatory reaction was noted in the control group (D%=0.5-3.74). The triggering factors causing unfavorable immediate and signal weather-induced responses in this group (D%=0.5-0.64) were wind direction and speed (especially on the 2nd day after the medical examination). These responses may be associated with atmospheric circulation in the monsoon maritime climate of Vladivostok, where the change in wind direction from the sea or from the land causes a sharp change in meteorological parameters of the weather complex [5]. It should be noted that the compensatory response (∑D%) was significantly higher in the control group than in patients with COPD or BA (*Table 4*).

According to the results of a comparative analysis of weather-induced responses, we established that the immune system in patients with COPD was most susceptible to the effects of an immediate response (the day of the examination). The most pathogenic influence was exerted by wind speed, humidity and air pressure. Patients with BA responded well to the impact of all studied meteorological factors on the day of the examination. In addition, the values of the weather-induced response intensity in this group (∑D%=5.08) were similar to those in healthy individuals (∑D%=5.87) (*Table 4*).

Taking into account the residual and signal (±2 days) weather-induced responses in patients with BA, a sharp decrease in the potential resistance of the immune system to day-to-day fluctuations in meteorological parameters (∑D%=0.97-2.9) was revealed, which requires timely correction. In the temporal aspect, the immune system of COPD patients was more resistant to contrast changes in almost all meteorological parameters (∑D%=2.36-3.86) compared to patients with BA. Analysis of the intensity of the weather-induced reaction (D%) to certain meteorological parameters made it possible to identify triggering factors depending on the nosology. It was established that the decrease in the compensatory response of the immune system in bronchopulmonary pathologies was due to the same meteorological parameters as in the control group. In addition, this process involved meteorological factors (atmospheric pressure and precipitation), which also directly affected the weather regime in a maritime monsoon climate [5]. However, the compensatory weather-induced response was reduced to a complete absence mainly in patients with BA within ±1 day from the day of the examination (*Table 4*).

The results of determining the criteria (M±SD) of day-to-day contrast changes in meteorological parameters that affected the human immune system showed the relationship of these indicators with the health status of the examined in the temporal aspect (*Table 5*). According to the literature, the level of meteorological dependence depends on the degree of day-to-day variability of meteorological factors (atmospheric pressure, temperature, humidity, and other indicators). The severity of the weather-induced response (weak, moderate, or strong) is formed according to the magnitude of contrast changes [17]. Analysis of the data presented in *Table 4* showed that the examined subjects (control group, patients with COPD and patient with BA) in accordance with the above classification exhibited weak and moderate weather-generated responses. A weak response was caused by the effect of air temperature, which can be associated with the invariable day-to-day weather regime as a characteristic feature of the maritime climate.

A detailed comparative analysis of the obtained data on the criteria of contrasting changes in weather factors in the control group showed an increase in the values of this indicator 2 days before and after (± 2 days) the day of the examination, while it decreased one day before and after (±1 day) the day of the examination, which implied an increased load on the immune system during a short-term examination (*Table 5*).

A similar trend was observed in patients with COPD, only the values of the criteria were slightly lower (by 20-30%), and even more so for precipitation (lower by 2-3 times). The direction of the wind, which directly depends on the monsoon climate, had a pathogenic effect on patients with COPD, which indicated the negative impact of this climate type on patients.

According to the obtained results, the maritime monsoon climate has the greatest pathogenic effect on the immune system of patients with BA. Short-term meteorological dependence 1 day before the day of the examination was more pronounced, which indicated a weak compensation for the functioning of the immune system in this time lag in patients (*Table 5*). Therefore, it is necessary to develop methods for correcting weather sensitivity in patients with bronchopulmonary pathology to prevent exacerbations of the disease.

Our study addressed the issues of adaptation of people suffering from chronic diseases to short-term changes in meteorological parameters. It is well known that exposure to meteorological factors outside the optimum, such as high and low temperatures, is associated with an increase in morbidity [18] and mortality [19], especially among vulnerable groups of the population. The accumulated data indicated a relationship between the variability of air temperature, humidity and pressure, and the state of human health [20]. The daily temperature range affects patients with cardiovascular and respiratory diseases [20]. Often this correlation is not related to the absolute level of the parameter [21]. However, the biological mechanisms responsible for the observed association are not well understood. Physiological mechanisms of thermoregulation include an increase in cardiac output, which in turn increases cutaneous blood flow and respiratory rate. In individuals with chronic respiratory diseases, thermoregulation disorder is due to a disorder in the cardiovascular function. Song et al. showed that high values of the daily temperature range can be a source of additional environmental stress in COPD [21]. Besides, it was discovered that the load on the respiratory system increased during periods of sharp temperature changes [22]. Various studies demonstrated the negative effect of airway cooling in BA patients, as well as the relationship between an increase in the daily temperature range above 10°C and an exacerbation of asthma in children [23]. Currently, there is evidence that adrenergic signaling pathways involved in thermogenesis can regulate the functions of immune cells [24]. However, this issue has not been sufficiently studied yet. Changes in weather conditions can affect both humoral and cellular immunity. Several studies reported that abrupt changes in inhaled air temperature were associated with the release of inflammatory mediators from mast cells, and that such changes may generate a nasal inflammatory response [25].

Data confirming the role of norepinephrine as the main immunomodulator in cold stress should be highlighted. Norepinephrine acts through β-adrenergic receptors that are widely expressed on the surface of immune cells [26]. Recent studies demonstrated the critical role of activating β-adrenergic receptor signaling by norepinephrine in controlling the release of lymphocytes from lymph nodes, and modulating cytokine

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production and proliferation of CD8+ memory T cells [27]. Further research is needed to establish the mechanisms responsible for the association of short-term changes in weather conditions with the immune system in patients with chronic respiratory diseases.

Conclusion

It was revealed that under the conditions of the maritime monsoon climate of Vladivostok, an unfavorable combination of day-to-day circulation activity in the atmosphere, along with other meteorological factors, had a significant impact on the sensitivity of the immune system. Pathological meteoropathy that affects the homeostasis of biological dynamic systems is based on the depletion of the reserve adaptive and compensatory capabilities of the body, which leads to desynchronization and dysfunction of the immune system. Short-term (±2 days) compensatory reactions of the human body imply a rapid functional response of the body systems to the impact of contrast day-to-day changes in meteorological components. Short-term responses to meteorological conditions make it possible to determine the intensity of not only rapidly emerging resistance of the organism, but also to predict the development trend of long-term adaptation processes in both healthy and sick people. In the urban population under the conditions of the maritime monsoon climate, weak and moderate weather-induced responses of the immune system are formed. The immune system response to a combination of meteorological factors in healthy individuals in Vladivostok is characterized by a high compensatory potential of their immune system. The immune system is most vulnerable to cumulative climatic factors in patients with COPD. The immediate response of the immune system is most effective in a controlled form of BA. We established that in the conditions of the maritime monsoon climate, wind, humidity and atmospheric pressure have the strongest pathogenic effect on patients with COPD, especially in terms of immediate immune response, and on patients with BA in terms of the short-term response (±1 day). Criteria for day-to-day changes in meteorological factors indicate a clear dependence of the decrease in the contrast value in all examined patients during the time interval of ±1 day. In subjects with bronchopulmonary pathology, the criteria for day-to-day changes in meteorological factors are reduced in magnitude for all indicators. In the short-term mode of ±1 day, patients with BA respond negatively to wind, humidity and atmospheric pressure even in the absence of day-to-day fluctuations. Our study made it possible to evaluate the response mechanisms of the population in the south of the Far East to changes in meteorological conditions, and to identify criteria for contrasting meteorological changes that affect the temporal dynamics of the immune response in individuals with bronchopulmonary pathology in the maritime monsoon climate of Vladivostok.

Study limitations

The small sample size is a main limitation of the study.

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The study was not sponsored externally.

Conflict of interest

The authors declare no conflicts of interest.

Ethical approval

All procedures in clinical studies were conducted in accordance with the ethical standards of the institutional and/or national research committee, as well as 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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