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RESEARCH

Immune accentuations as a prognostic factor for adaptation in Antarctic conditions

Ievgen Dubrovskyi[1] · Dariia Zabara[1] · Yaroslava Anoshko[1] · Iryna Kozeretska[2] · Igor Deyneka[2] · Andrii Khytryi[2] · Vasyl Matkovskyi[2] · Dmytro Martynenko[2] · Boris Dons'koi[1]

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Abstract

Human presence and work in Antarctica occur under challenging climatic, psychophysiological, and social conditions. The health of expedition participants is a critical factor, and a pre-expedition medical assessment is extremely important. We evaluated the prognostic significance of previously identified immune accentuations on the health of Ukrainian Antarctic Expedition overwintering participants. Immunophenotyping was performed on 43 male winterers before the expedition. Their health and laboratory parameters of the immune system were tracked the entire expedition. According to the results, winterers with favorable and unfavorable kinds of adaptation showed differences in immunophenotypic indicators. The majority of winterers with favorable adaptation had T-helper (CD3+CD4+) levels (> 35%), balanced (< 24%) expression of HLA-DR on cytotoxic T-lymphocytes (CD3+CD8+), proportions and absolute levels of NK lymphocytes (5–18% and 100–400). In contrast, winterers with unfavorable adaptation exhibited balanced levels significantly less frequently. NK cell levels in the range of 5–18% were virtually absent in winterers with unfavorable adaptation. The combination of two diagnostically significant immune parameters yields higher accuracy. Increased expression of HLA-DR on cytotoxic T-lymphocytes and elevated NK-lymphocyte content significantly enhance the prognostic value of the diagnostic algorithm. In all winterers, cortisol levels significantly increased in the first quarter of the expedition compared to baseline, followed by fluctuations. Cortisol levels returned to baseline after the expedition. The results demonstrate that staying in Antarctica requires adaptive processes that are directly dependent on the balanced functioning of the immune system. Stressful environment condition, in conjunction with immune accentuations, complicates successful adaptation.

Keywords Polar expedition · NK lymphocytes · NK cytotoxicity · Chronic stress · HLA-DR

Introduction

Antarctic research holds significant importance for global science, particularly in the fields of climatology, biology, geology, and geophysics. Human presence and work in Antarctica occur under challenging climatic, physio-psychological, and social conditions. These stress factors impact the physiological state of the expedition participants (Salam 2020). The bodily response to prolonged exposure to extreme conditions evolves over time (Le Roy et al. 2024). Human adaptation to new extreme environments primarily results in some perturbation of a physiological process and a subsequent return to homeostasis (Ilardo and Nielson 2018). The adverse effects that occur in the human body during the stay in Antarctic conditions require thorough study for timely diagnosis and prevention (Srivastava et al. 2024; Moiseyenko et al. 2016).

The work capacity and health of expedition participants are influenced by numerous factors, including physical condition, mental resilience, circadian rhythm, health indicators, and the ability to adapt to the challenges of the Antarctic environment (Palinkas et al. 2000). Health is a critical factor, and a pre-expedition medical evaluation is crucial to ensure optimal adaptation processes, health and well-being during the stay in Antarctic conditions (Turner et al. 2014).

✉ Boris Dons'koi
boris_donskoy@ukr.net

[1] Institute of Pediatrics, Obstetrics and Gynecology of the National Academy of Medical Sciences of Ukraine, Kyiv 04050, Ukraine

[2] State Institution National Antarctic Scientific Center of Ministry of Education and Science of Ukraine, 01601 Kyiv, Ukraine

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The most thoroughly studied and substantiated changes are those in the psychophysiological state of the winterers (Sandal et al. 2018). Disruption of normal sleep patterns, sudden headaches, autonomic nervous system reactions, mood deterioration, and overall malaise are typical manifestations of the Antarctic syndrome. These symptoms are associated with the development of chronic stress and fatigue, slowing down the adaptation processes of psychophysiological functions, which increases the risk of psycho-emotional disorders and disruptions in interpersonal relationships within the small community.

The immune system is critically important for maintaining the body's homeostasis. It serves both protective and regulatory functions. It continuously responds to internal and external changes, ensuring the body's adaptation to various stress factors (McEwen 1998). This occurs through the close interaction of the immune system with the nervous and endocrine systems forming an integrated network that regulates responses to stress. According to Daëron, the immune system should not only be seen as a defense mechanism but also as a relational system that cooperates with other body systems to maintain health (Daëron 2022). This interaction highlights the immune system's ability to promote the body's adaptation to environmental changes.

Le Garff-Tavernier et al. (2010) demonstrated that its disruption can lead to chronic inflammatory conditions, which negatively impact health and contribute too many diseases.

The immune system also plays a crucial role in responding to stress. Chronic stress can impair immune function, reducing its ability to fight infections and oncological diseases. Fisher and Reason noted that prolonged stress disrupts the regulation of neuroendocrine-immune interactions, with possible repercussions for health (Fisher and Reason 1988).

The role of immune factors in adaptation to the adverse conditions of the Antarctic region has been demonstrated in numerous scientific studies (Zabara et al. 2021; Palinkas et al. 2000; McElhaney and Effros 2009; Yadav et al. 2012). In our previous research, we identified individual immunophenotypes of Ukrainian Antarctic Expedition (UAE) members (winterers) that may be advantageous for certain challenges while disadvantageous for other physiological processes and determined the key accentuated immunological parameters: T-helper cells (CD3+CD4+), HLA-DR on T cytotoxic lymphocytes (Tc) (CD3+CD8+), and the amount of NK lymphocytes (Dons'koi 2023, Dons'koi et al. 2023).

It is well-known that chronic, psychological and social stress is associated with dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis activity, accompanied by an increase in cortisol levels (Spinelli and Werner 2022; O'Connor et al. 2020; Lee et al. 2015). Glucocorticoids and sex hormones affect immune responses, but also control the hematopoietic stem cell differentiation and subsequent maturation of immune cell subsets (Quatrini et al. 2021).

In the current study, we summarize the results of a four-year observation of winterers' health and investigate the relationship between the immunophenotype and adaptation.

Materials and methods

Study design

A total of 43 male overwintering participants from UAE at Akademik Vernadsky station, aged between 23 and 51 years (with an average age of 39.1 years), were studied during 2021–2024. The winterers were assessed for immunophenotypic indicators before the expedition. All participants passed a medical examination according to the order of the Ministry of Health of Ukraine No. 246 dated May 21, 2007 and were recognized as healthy 1 month before the trip. Since 2022, participants of the polar expedition have traveled to Europe, and then by plane to Chile. From Chile, participants of the polar expedition have traveled by ship to Antarctica. Now, with the outbreak of the war, logistics became more complicated and the journey took 10–11 days. To evaluate their adaptation status, we analyzed medical reports regarding the health of the UAE participants and their current visits and complaints to the doctor during the overwintering period. Complaints related to traumatic or dental issues were excluded from this analysis and were examined separately in another study. More than a third of the participants had previous experience of Antarctic expeditions. The time difference between Ukraine and Vernadsky station is 5 (6) h (65°14′44″ S, 64°15′28″ W.).

The majority ($n = 31$) exhibited favorable adaptation (FA), with a single complaint and a corresponding visit to the doctor within a month. However, 12 winterers demonstrated unfavorable adaptation (UfA). These winterers reported more than three complaints per month concerning general well-being (fever, catarrhal symptoms, weakness, blood pressure fluctuations, headaches, insomnia, infectious diseases, etc.). The most frequent reasons for seeking medical attention at the station were sleep disorders, various forms of nerve pain, cardiovascular disturbances, gastrointestinal issues, and viral reactivation.

All medical visits by expedition participants were documented by the physician, who examined the patients, made a diagnosis, and prescribed the treatment. Subjective symptoms were not taken into account; only those confirmed by the station doctor were considered. Data were compiled into monthly reports and sent to the research center for analysis.

Peripheral blood samples were collected in Vacutainer systems (BD Biosciences, USA). Samples that were collected before expedition were analyzed for immunophenotype. Serum samples were frozen and compared with serum samples taken during (on 3rd, 6th, 9th and 12th month) and

after the expedition. The wintering period for each group of participants spans one calendar year, from April to March. After this period, all winterers return to Europe while a new group arrives at the Antarctic station. All participants signed the informed consent form before being enrolled in the study (approved by the Biomedical Ethics Committee of Institute of Pediatrics, Obstetrics, and Gynecology, National Academy of Medical Sciences of Ukraine, No. 6, and Clinical Immunology and Allergology Committee of Ministry of Health, No. 11 dated February 14, 2013, according to Declaration of Helsinki).

The medical commission conducted a complete examination which included an interview, psychological testing, and all necessary laboratory tests for comprehensive screening during the selection stage. The strictly regulated list of examinations and exclusions defined by the Ministry of Health order ensures that no ill or insufficiently examined individual can be sent to the station. All expedition participants were screened for HIV and viral hepatitis.

Immunophenotyping of lymphocytes by flow cytometry

Flow cytometry was used for immunophenotype study (as shown in Zabara et al. 2021). Peripheral blood was incubated with monoclonal antibodies anti-CD3PeCy5 (555,341), CD8aFITC (551,303), CD4PE (347,327), CD56PE (340,363), HLA-DR- FITC (347,363), CD19FITC (340,719) and CD45 FITC/CD14 PE (340,040) with BD Trucount™ Trucount Absolute Counting Tubes (340,334) according to the manufacturer's instructions (BD Biosciences, USA).

Subsequently, the cells were lysed using lysing solution (BD Biosciences, USA) and analyzed on a FACScan flow cytometer with CellQuest software (BD Biosciences, USA).

Determination of cytotoxic activity of NK lymphocytes

Peripheral venous blood was collected and delivered to the laboratory within one hour under appropriate preservation conditions. The blood was analyzed no later than 4 h post-collection (Dons'koi et al. 2022).

Enzyme-linked immunosorbent assay (ELISA)

Solid-phase enzyme-linked immunosorbent assay (ELISA) was used to determine the levels of testosterone and cortisol, employing test systems from "Xema ELISA" K210, K209 (Ukraine). The tests were performed according to the manufacturer's instructions.

Methods for statistical analysis of results

All obtained results were analyzed and recorded in Microsoft Excel spreadsheets. Statistical analysis, including Woolf's approximation for Odds Ratio (OR) and 95% confidence intervals (CI), Fisher's exact test (unpaired, non-parametric, two-sided P value), and Spearman's correlation, was performed using InStat version 3.0 for Windows (GraphPad Software Inc., San Diego, CA, USA).

Results

Immune parameters and health status during stay at the station

Ukrainian Antarctic Expedition winterers with FA and UfA exhibited differences in immunophenotypic parameters. The majority of winterers with FA had levels of T-helper cells (CD3+CD4+) exceeding 35%, balanced HLA-DR expression on T-cytotoxic lymphocytes (CD3+CD8+) below 24%, and NK lymphocyte proportions within 5–18%, respectively. In contrast, winterers with UfA exhibited these balanced levels significantly less frequently (Table 1).

These parameters, within their reference ranges, were significantly associated with FA in winterers (Table 1). Conversely, accentuated levels of these parameters were observed in winterers with UfA (Table 1). For instance, NK cell levels within the reference (favorable) range of 5–18% were almost never found in winterers with UfA (1/12), whereas they were typical in participants with FA (Fig. 1).

The combination of two diagnostically significant immune parameters provided higher diagnostic predictive accuracy. Elevated HLA-DR expression on cytotoxic T-lymphocytes or an increased percentage of NK lymphocytes significantly enhanced the predictive value of the diagnostic algorithm. Among winterers with UfA, only 9 (30%) exhibited one of these accentuations, whereas in the FA group, all 12 participants had one of these accentuations ($p < 0.0001$, OR = 59.211 95% CI 3.170–1106.0) (Fig. 2).

The combination of accentuations—a reduced percentage of T-helper cells (CD3+CD4+) and elevated HLA-DR expression on cytotoxic T-lymphocytes—was highly associated with the UfA status. In the UfA group, 6 out of 12 participants (50%) exhibited one of these accentuations, while only 2 out of 31 participants (6.5%) in the FA group had one of these ($p = 0.0031$, OR = 14.500 95% CI 2.335–90.057) (Fig. 3).

We did not find any significant difference in NK cytotoxicity levels, absolute numbers of leucocytes, lymphocytes, monocytes, T and B lymphocytes between the FA and UfA groups.

Table 1 Association between elevated immunophenotype parameters and prediction of unfavorable adaptation to conditions of increased stress exposure

Favorable range	Participants with favorable course within reference range ($n=31$)	Participants with unfavorable course within reference range ($n=12$)	Significance of association with favorable course
Level of T-helper cells (CD3+CD4+) (> 35%)	30/31 (96.7%)	8/12 (66.7%)	OR 15.0 $p=0.0168$ 95% CI 1.46–153.63
Expression level of HLA-DR on T-cytotoxic cells (CD3+CD8+) (< 24%)	30/31 (96.7%)	7/12 (58.4%)	OR 21.4 $p=0.0042$ 95% CI 2.14–213.70
NK lymphocyte level (5–18%)	22/31 (70.9%)	1/12 (8.3%)	OR 26.9 $p=0.0003$ 95% CI 3.01–240.17

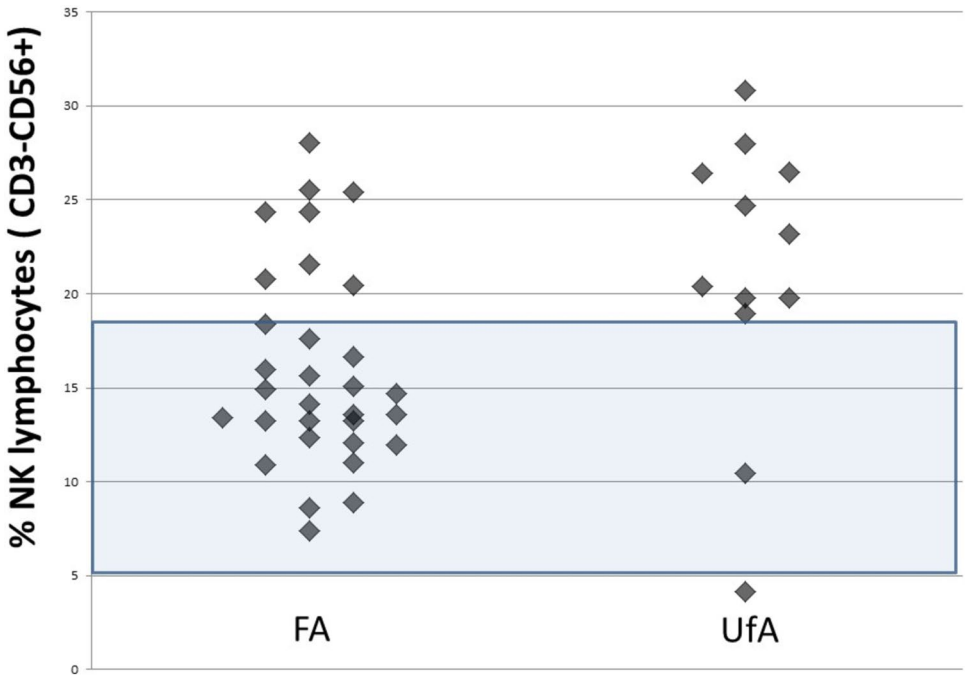


Fig. 1 The distribution of NK lymphocyte levels in Ukrainian Antarctic Expedition winterers with Favorable Adaptation (FA) and Unfavorable Adaptation (UfA). Blue rectangle shows the favorable course within reference range (each dot represent data of one participant)

Dynamics of cortisol levels

In all winterers, cortisol levels significantly increased in the first quarter compared to the baseline ($p < 0.01$), followed by a decrease in the second quarter. The average level then rose again in the third quarter, which is 1.7 times higher than the initial level. Average cortisol levels upon return from the expedition reverted to baseline values. Cortisol levels in all winterers exhibited individual dynamics during the expedition, yet all participants also demonstrated elevated levels during expedition (Fig. 4A).

Testosterone levels exhibited a similar trend (Fig. 4C). Hormonal changes confirm the presence of stress adaptation during the stay at the station in all members of the Antarctic expedition.

Discussion

One-year-long Antarctic expedition offers many stressful challenges such the climate, circadian rhythms, nutrition, lifestyle, microbiological/allergen/antigen environment. Moreover, it is difficult to find aspects of human life that do not change in the Antarctic. The immune system must adapt itself and adapt the host to all these changes (Ilardo and Nielsen 2018).

The immune system receives a huge amount of information about the antigenic environment, activity and changes in the state of the body's systems, tissues and individual cells through T and B lymphocyte antigen receptors, systems of killer cell immunoglobulin-like receptors, lectin-like receptors, Toll-like receptors, and cytokine receptors. In response

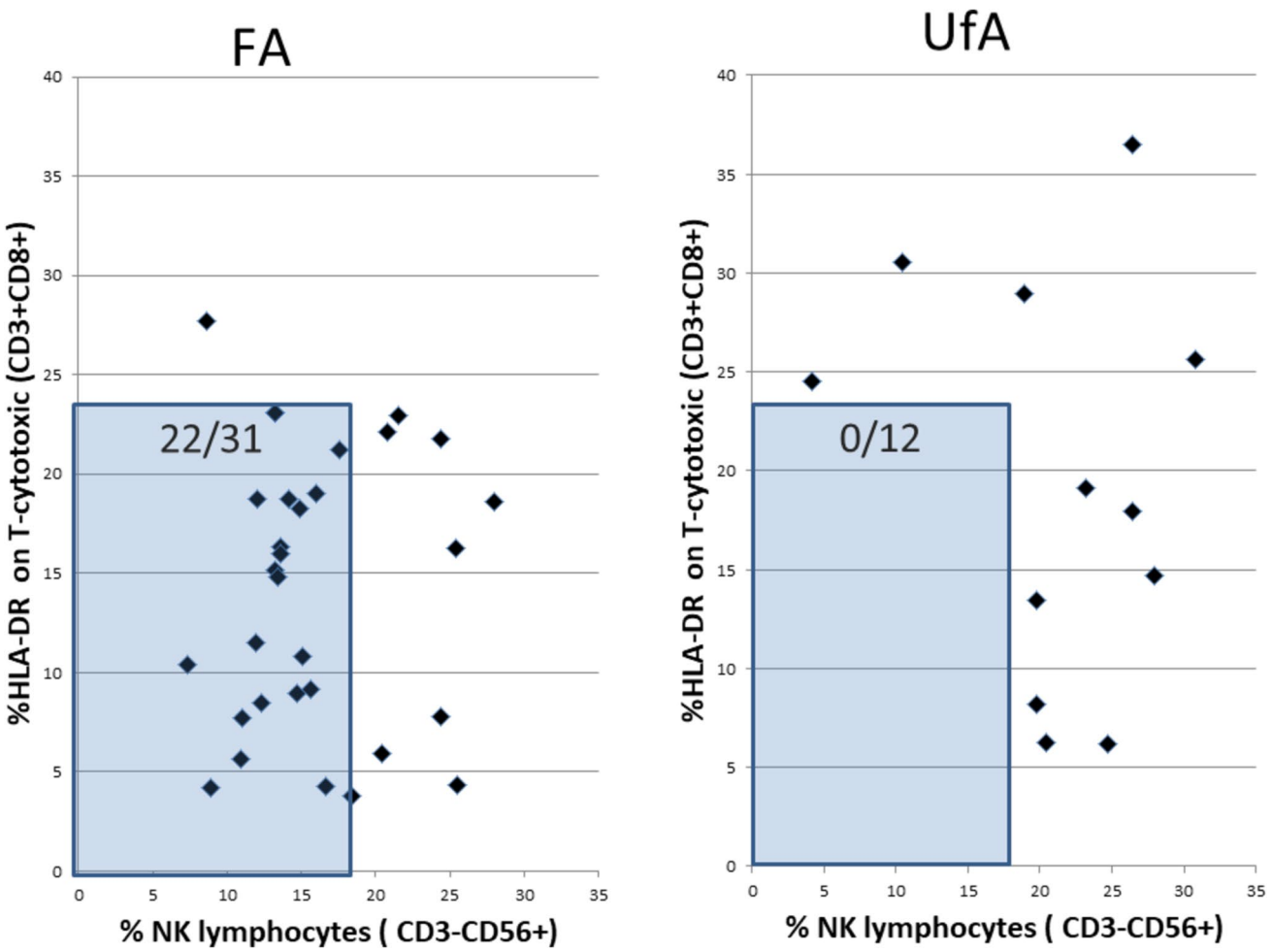


Fig. 2 Distribution of HLA-DR on Tc (CD3+CD8+) and NK (CD3-CD56+) levels in Ukrainian Antarctic Expedition winterers with Favorable Adaptation (FA) and Unfavorable Adaptation (UfA). Blue rectangles show the favorable course within reference range (each dot represent data of one participant)

to this information, cells of the immune system produce pro- or anti-inflammatory cytokines, growth factors, differentiation factors and angiogenic factors that regulate both the immune system's own links and the activity of individual cells and tissues of the body (Borish and Steinke 2003).

The idea of "allostasis" or "stability through change" was proposed by Sterling and Eyer (Fisher and Reason 1988). The immune system is a system of relations rather than as a defense system. The immune system has powerful adaptive properties that enable the organism to live in peace with itself and with other living beings, whether pathogens or commensals (Daëron 2022). Individual features of the immune system can help or hinder the adaptation process. This is especially true for increased levels of certain parameters. Accentuated immune parameters can be unfavorable because they escape the possibility of being regulated. This becomes especially critical when environmental conditions change. Quantitative and qualitative assessment of lymphocytes and their phenotypic characteristics allow to determine the state of cellular, humoral, and innate immunity (Blom and Spits 2006). Combined assessment of quantitative and functional lymphocyte characteristics becomes a practical method for evaluating immunity (Williams and Bevan 2007; Wingender and Kronenberg 2015; Lucas et al. 1995).

Our pilot study (Zabara et al. 2021) found a correlation between immunophenotypic indicators of UAE participants and their overall health status and adaptation during wintering. Specifically, accentuated immune parameters (high levels of NK lymphocytes, increased cytotoxic activity of NK cells, and the expression level of CD8aa on NK lymphocytes, in combination with high levels of HLA-DR expression on T-cytotoxic cells) may serve as markers of adverse health conditions in UAE participants and contribute to complications in adaptation processes.

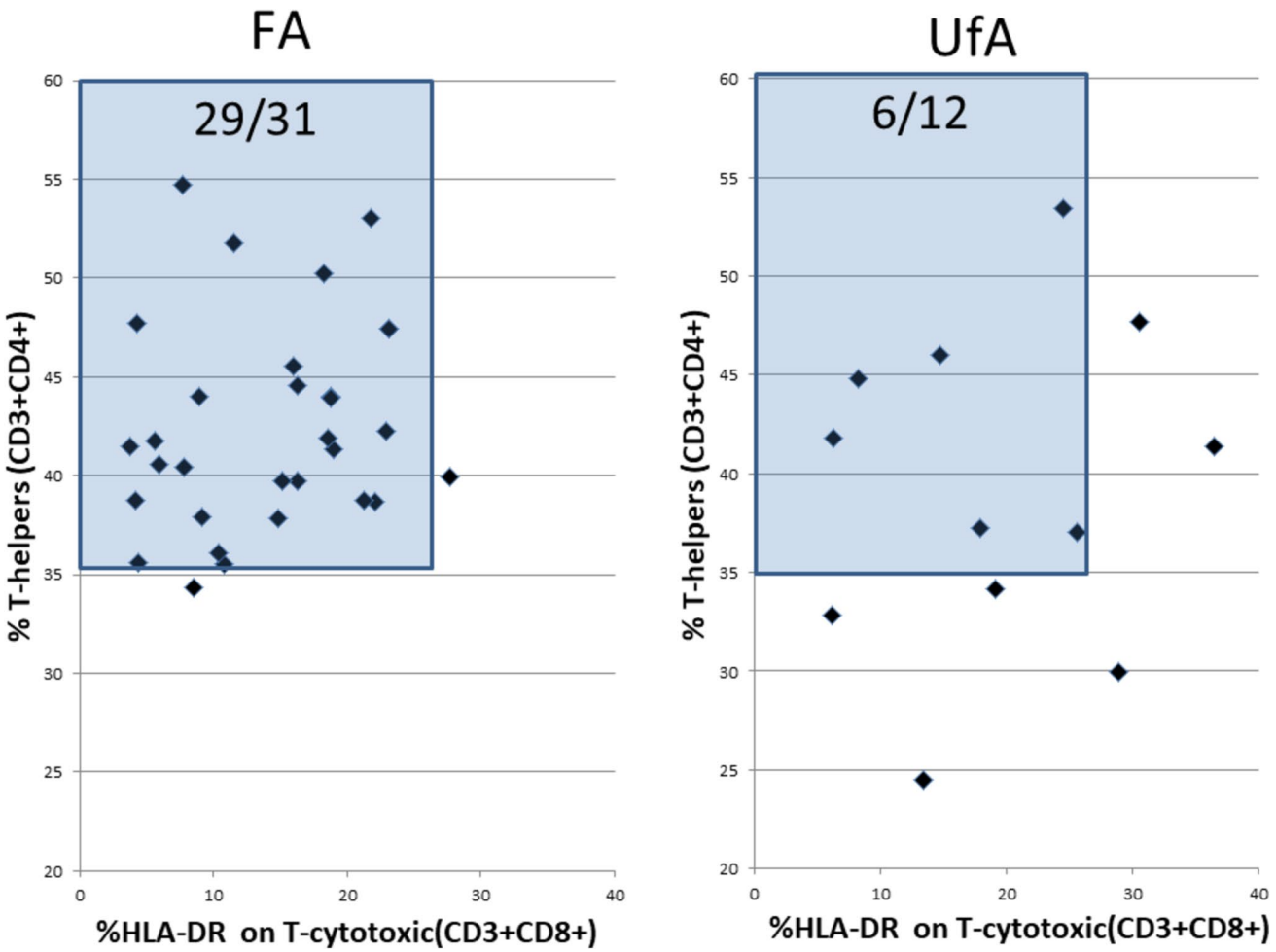


Fig. 3 Distribution of T-helpers (CD3+CD4+) and NK (CD3-CD56+) levels between Ukrainian Antarctic Expedition winterers with Favorable Adaptation (FA) and Unfavorable Adaptation (UfA). Blue rectangles show the favorable course within reference range (each dot represent data of one participant)

In the current study, the data regarding the possible association of specific immunophenotypes with normal adaptation in UAE participants confirm most of the previous conclusions. We show here that reduced percentages of T-helper cells (CD3+CD4+), increased expression of HLA-DR on T cytotoxic lymphocytes (Tc) (CD3+CD8+), and increased percentages of NK lymphocytes are among the key accentuated immunological parameters.

All these parameters, within certain reference ranges, are significantly associated with normal adaptation in UAE participants, while their accentuated levels are observed in the winterers with complicated adaptation. Combining parameters such as HLA-DR expression on Tc, increased percentages of NK lymphocytes, or decreased percentages of T-helper cells (CD3+CD4+), may be used to develop a diagnostic algorithm for predicting adaptation success.

NK cells are active producers of cytokines and chemokines, interacting with a variety of other immune cells, and may contribute to the pathogenesis of various inflammatory, infectious, and autoimmune diseases (Jiao and Wang 2016). An accentuated level of NK cells may be necessary for enhanced control over infectious or autoimmune processes, also favorable in patients with actual myeloid leucosis (Penman et al. 2016; Bernson et al. 2017). High levels of innate resistance and "stressfulness" of immune effectors and regulations links (accentuated levels of NK lymphocytes, increase HLA-DR activation marker on Tc, downregulation of helper T cell content) may reduce the development of normal adaptability. In the absence of infectious agents, high natural resistance is not effectively engaged in function execution but may lead to problems of adaptation to increased stress factors. Interestingly, similar immunophenotypes characterized by high resistance levels are also observed in women with reproductive complications, particularly recurrent pregnancy losses and embryo implantation failures (Dons'koi et al. 2022, 2023b).

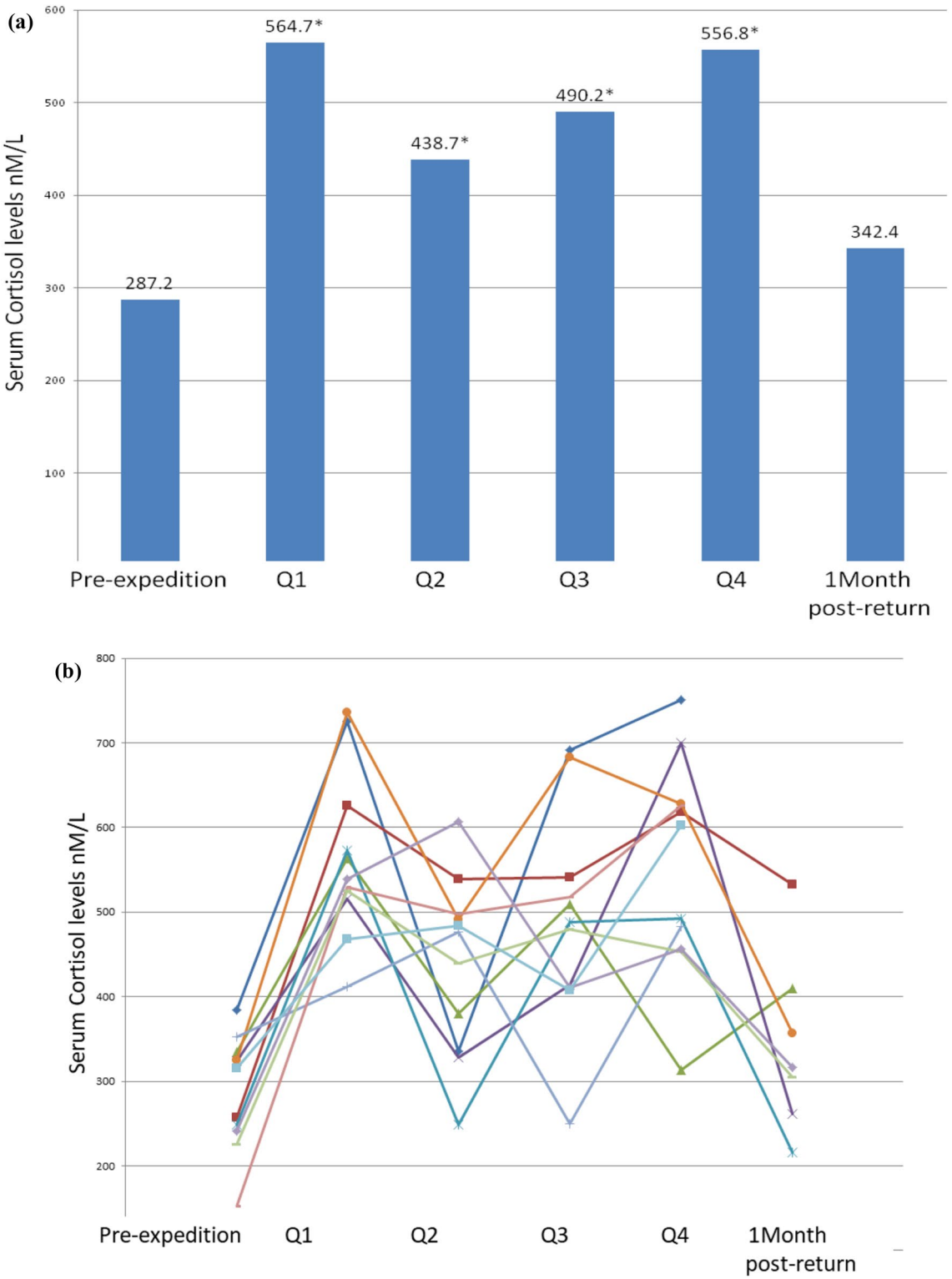


Fig. 4 **a** Dynamics of serum cortisol levels in winterers. **b** Individual dynamics of serum cortisol levels in 26UAE participants (each line represent dynamic of cortisol level of one participant). **c** Individual dynamics of serum testosterone levels in 26UAE participants (each line represent dynamic of cortisol level of one participant). *$p < 0.05$ compared to Pre-expedition levels. Q1 = April–June, Q2 = July–September, Q3 = October–December, Q4 = January–March

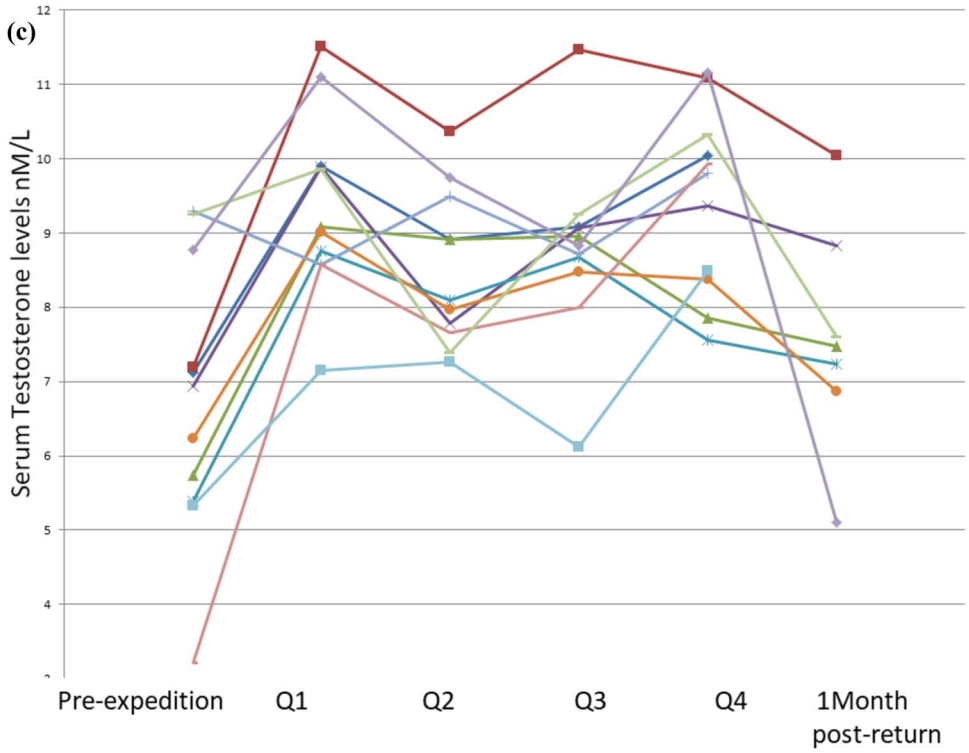


Fig. 4 (continued)

This is more evidence that such immunophenotypes are difficult to regulate and adapt in response to changes in internal and external factors. Women whose NK cells levels do not decrease in the early weeks of pregnancy have significantly higher chances of miscarriage compared to women whose NK levels decrease by even a small percentage (OU 2024). Combining such an accentuated level with an increased content of HLA-DR+CD8+T lymphocytes supports the presence of a possible chronic inflammatory process. This inflammation marker (percentage of HLA-DR+CD8+T lymphocytes) correlates with other routine biochemical indicators of overall health status, primarily with low-density lipoproteins (LDL), which are a factor in the development of cardiovascular diseases (Liu et al. 2022).

We demonstrated here that immunophenotype can be extremely favorable in certain physiological conditions and simultaneously unfavorable for the course of another process (Dons'koi 2023). We described immunophenotypes that may be unfavorable for embryo implantation and successful pregnancy outcomes (Dons'koi et al. 2023), and that associated with latent CMV infection (Dons'koi et al. 2020). Thus, based on an accentuated immunophenotype, it is possible to predict with a certain probability the possibility of a specific adverse physiological process.

Hoyme and Meyer-Rochow investigated and described the frequency of complaints among passengers and crew during long polar voyages on cruise ships (Hoyme and Meyer-Rochow 2011).

Comparing the complaints of the winterers those described in the article by Hoyme and Meyer-Rochow (2011), we observe significant differences. Passengers of cruise ships most often had respiratory diseases (34%). In our study, such diseases were extremely rare, which can be explained by the isolation of winterers during most of the year and by the strict medical selection before entering the polar station. Participants of the polar expedition spend the winter with minimal external interference and without contact with the outside world. In contrast, cruise ship passengers are part of a large group and constantly interact with many people. In addition, the participants of the Antarctic stations are relatively young and do not have chronic diseases. Additionally, cruise ship passengers tend to be older people who can afford such an expensive trip and do not have any health or age restrictions.

Complaints described by Hoyme and Meyer-Rochow in cruise ship passengers and crew (respiratory illnesses such as bronchitis, sinusitis and colds (34%) and seasickness (9.8%) are not typical of Ukrainian Antarctic winterers. Infections and respiratory illnesses do not predominate among complaints. Instead, the doctor mainly deals with issues that Hoyme and Meyer-Rochow classifies as "general" complaints (psychological stress, sleep disorders, dental problems, various forms of neuralgia, cardiovascular

disorders), which account for only 13.2% of cases among cruise passengers (Hoyme and Meyer-Rochow 2011). Thus, the conditions of the isolated stay of a small group of winterers at the polar station, are profoundly different from those of cruise ship passengers and their health complaints.

Chronic stress is associated with dysregulation of HPA axis, accompanied by an increase in cortisol (Spinelli and Werner 2022; Palinkas and Houseal 2000; Lee et al. 2015). Cortisol levels do not differ from globally recognized data (Strewe et al. 2019; Wright et al. 2015), an increase in cortisol levels during wintering was registered compared to the pre-expedition's outset. However, elevated cortisol in all expedition members did not correlate within UfA and FA groups. It seems that the success of adaptation is influenced not by the elevated level of cortisol, but by the individual sensitivity and the ability to return the immune regulations process to homeostasis.

Testosterone fluctuations are undoubtedly associated with changes in other hormone levels, including cortisol. The increase in testosterone levels in men does not exceed reference ranges. Similar to cortisol fluctuations, the most significant increase in men is observed in the first 3 month of wintering, followed by a moderate decrease and stabilization.

Thus, this study shows that studying immunophenotype features can be a useful method of predicting the development of adaptations to adverse conditions during an Antarctic expedition.

Limitations of study

For 4 years, we were able to analyze only 43 cases, although 154 applicants for participation were examined. Almost half were not selected to participate in the expedition (medical and competitive reasons).

A quarter of the applicants group was women; they were removed from the study and it is not yet possible to analyze them separately because the group of is too small. Another large part stayed at the station for 3–6 months, and it is also impossible to assess their adaptation.

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Author contributions ID—analysis and manuscript preparation, reviewed, contributed to, and approved the final draft of the manuscript. DZ, YaA—laboratory investigation, analysis and manuscript preparation. ID, AK, VM, DM—collection of clinical data and blood samples during UAE. IK—idea of investigation, moderation of investigation and group formation, reviewed, contributed to, and approved the final draft of the manuscript. BD—laboratory investigation, analysis and manuscript preparation, reviewed, contributed to, and approved the final draft of the manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

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