THE IMPACT OF BACKGROUND LYMPHOPENIA ON THE REACTIVITY OF NONSPECIFIC IMMUNITY IN RESPONSE TO TOTAL BODY COLD EXPOSURE

Patrakeeva VP ✉, Kontievskaya EV

N. Laverov Federal Center for Integrated Arctic Research, Ural Branch of the Russian Academy of Sciences, Arkhangelsk, Russia

Lymphopenia is a condition in which there are lower than normal counts of lymphocytes in the blood. Combination of lymphopenia and prolonged exposure to low temperatures leads to a reduction of adaptive resources, increasing risks of chronic inflammatory processes and secondary environmentally induced immunodeficiencies. The aim of the study was to compare characteristics of immune reactivity in response to cold exposure depending on background level of lymphocytes. Changes in hematologic and immunologic parameters in 203 participants before and immediately after short-term cold exposure were studied. Measurements included skin temperature (forehead, backside of palm), blood pressure, heart rate, leukogram, and hemogram. Levels of ferritin, lactoferrin, transferrin, interleukin-6, interleukin-1β, TNFα, erythropoietin, and irisin were determined using the enzyme immunoassay method. Apoptosis and necrosis of lymphocytes were assessed by flow cytometry analysis using AnV/PI double staining assay. Regardless of the background level of lymphocytes in peripheral blood, same-type responses to short-term cold exposure were observed in cardiovascular system as well as in irisin and ferritin levels, providing an evidence of activating thermoregulation and thermal homeostasis mechanisms. Lymphopenia is associated with a decrease in activity of nonspecific defense - in response to cold exposure there were no changes in level and functional activity of circulating neutrophil granulocytes that can increase the risks of chronicization of infectious processes in this group.

Keywords: lymphopenia, adaptation, human, NLR, ferritin, transferrin, lactoferrin, cold exposure

Funding: the study was performed within the Program of Fundamental Scientific Research on the topic of the environmental immunology laboratory, Institute of Physiology of Natural Adaptations, N. Laverov Federal Center for Integrated Arctic Research, Ural Branch of the Russian Academy of Sciences (project № 122011300377-5).

Author contribution: Patrakeeva VP — study planning, data collection, processing and interpretation, literature review, manuscript writing; Kontievskaya EV — data collection and processing.

Compliance with ethical standards: the study was conducted with the written consent of all participants and in accordance with the principles of the Declaration of Helsinki (1975, rev. 2013). The study was approved by the Ethics Committee of the N. Laverov Federal Center for Integrated Arctic Research, the Ural branch of RAS (protocol № 4 of 7 December 2016, protocol № 6 of 14 February 2022).

✉ **Correspondence should be addressed:** Veronika P. Patrakeeva
Nikolsky prospect, 20, Arkhangelsk, 163020, Russia; patrakeewa.veronika@yandex.ru

Received: 18.09.2023 **Accepted:** 02.02.2024 **Published online:** 19.03.2024

DOI: 10.47183/mes.2024.005

ВЛИЯНИЕ ФОНОВОЙ ЛИМФОПЕНИИ НА РЕАКТИВНОСТЬ ПОКАЗАТЕЛЕЙ НЕСПЕЦИФИЧЕСКОГО ИММУНИТЕТА В ОТВЕТ НА ОБЩЕЕ ХОЛОДОВОЕ ВОЗДЕЙСТВИЕ

В. П. Патракеева ✉, Е. В. Контиевская

Федеральный исследовательский центр комплексного изучения Арктики имени Н. П. Лаверова Уральского отделения Российской академии наук, Архангельск, Россия

Лимфопения — состояние, при котором концентрация лимфоцитов ниже физиологической нормы. Сочетание лимфопении и длительного воздействия низких температур приводит к сокращению резервов адаптационных ресурсов, повышая риск формирования хронических воспалительных процессов и вторичных экологически обусловленных иммунодефицитов. Цель исследования — сравнить особенности реактивности иммунных показателей в ответ на общее охлаждение в зависимости от фонового уровня лимфоцитов. Проведено изучение изменения гематологических и иммунологических показателей у 203 человек до и сразу после общего охлаждения. У обследованных проводили измерение температуры лба и тыльной стороны ладони, артериального давления и частоты сердечных сокращений, лейкограмму и гемограмму. Методом иммуноферментного анализа определено содержание ферритина, лактоферрина, трансферрина, интерлейкина-6, интерлейкина-1β и TNFα, эритропоэтина, ирисина. Уровень апоптоза и некроза лимфоцитов определяли методом проточной цитометрии двойным окрашиванием AnV/PI. Вне зависимости от фонового уровня лимфоцитов в периферической крови регистрировали однотипные реакции на общее кратковременное охлаждение со стороны сердечно-сосудистой системы, уровня ирисина и ферритина, что свидетельствует о включении механизмов терморегуляции и сохранении теплового гомеостаза. Лимфопения ассоциируется со снижением активности неспецифической защиты, в ответ на холодовое воздействие не происходит изменения уровня и функциональной активности циркулирующих нейтрофильных гранулоцитов, что повышает риск хронизации инфекционных процессов в данной группе.

Ключевые слова: лимфопения, адаптация, человек, NLR, ферритин, трансферрин, лактоферрин, холод

Финансирование: работа выполнена в рамках программы фундаментальных научных исследований по теме лаборатории экологической иммунологии Института физиологии природных адаптаций ФГБУН ФИЦКИА УрО РАН № гос. регистрации 122011300377-5.

Вклад авторов: В. П. Патракеева — планирование исследования, сбор, обработка и интерпретация данных, анализ литературы, подготовка рукописи; Е. В. Контиевская — сбор и обработка данных.

Соблюдение этических стандартов: исследование проводили с письменного согласия волонтеров, в соответствии с принципами Хельсинкской декларации 1975 г. (2013 г.). Исследование одобрено этической комиссией ИФПА ФГБУН ФИЦКИА УрО РАН (протокол № 4 от 7 декабря 2016 г., протокол № 6 от 14 февраля 2022 г.).

✉ **Для корреспонденции:** Вероника Павловна Патракеева
пр. Никольской, д. 20, г. Архангельск, 163020, Россия; patrakeewa.veronika@yandex.ru

Статья получена: 18.09.2023 **Статья принята к печати:** 02.02.2024 **Опубликована онлайн:** 19.03.2024

DOI: 10.47183/mes.2024.005

Described mechanisms of lymphopenia include impaired maturation and differentiation of lymphocytes, inhibition of lymphocyte release from lymphoid tissues, enhancement of lymphocyte migration into tissues as well as death of lymphocytes with increased sensitivity to complement-mediated cytolysis, activation of apoptosis and necrosis. Living in the North requires special adaptations to low temperatures resulting in a decrease in organism's reserve abilities. Cold exposure affects the thymus that is manifested as thymus hypotrophy, reducing lymphocyte abundance and increased intensity of apoptosis, which is further recorded as lymphopenia in peripheral blood [1, 2]. Cold stress leads to depletion of lymphoid tissue of mucous membranes with increasing degenerative processes thus reducing the effectiveness of defense at the "entrance gate" of infection [3, 4]. Decreased activity of cellular and humoral reactions in northern inhabitants is manifested in a higher frequency of acute and chronic infectious diseases, allergies, autoimmune processes and malignancies [5–7]. In pathological state, lymphopenia is accompanied by high levels of proinflammatory cytokines IL-6 and TNFα leading to activation of lymphocyte apoptosis and forming a destructive positive feedback loop [8]. Asymptomatic lymphopenia is often detected in people living in environmentally adverse areas and extreme climatic conditions; in the North, during periods of minimum daylight hours, the reported frequency of lymphopenia in working-age adults is up to 19.86% [9–11]. Adverse climatic effects exert stress on the body and impare the immune system. Prolonged decrease in the number of functionally active lymphocytes providing protective immune reactions significantly increases the risk of severe infectious diseases and their transition to chronic forms. In response to cold exposure, metabolic activity changes most rapidly with an increase in such biochemical parameters as concentrations of free fatty acids, C-reactive protein, glucose, etc. [12]. Factors of innate immunity are most resistant to the influence of cold exposure while for lymphocytes, glucose is a necessary substrate to increase their energy supply and active functioning. The aim of the study was to compare the characteristics of immune reactivity in response to total body cold exposure depending on background level of lymphocytes.

METHODS

Hematological and immunological parameters were measured before and immediately after total body cold exposure in two groups of volunteers (203 participants in total) depending on a background level of peripheral blood lymphocytes. The study included practically healthy individuals of working age who had no acute diseases or exacerbation of chronic diseases during the study period as well as previously and/or currently not engaged in hardening. Persons of working age who had acute chronic diseases and their exacerbations during the study period as well as previously or currently engaged in hardening were excluded accordingly. In the trial, the participants spent 5 minutes in USHZ-25N cold chamber (Xiron-Kholod; Russia) at –25 °C in cotton clothes under constant video monitoring. The first group of participants had a background lymphopenia (n = 70, including 59 women and 11 men; lymphocyte count 1.26 (1.09–1.37) × 10^9/L). The second group included participants having a normal lymphocyte count (n = 133, including 94 women and 39 men; with lymphocyte count 2,08 (1,81–2,45) × 10^9/L (p^{1-2} < 0,0001)). Skin temperatures at forehead and backside of palm, blood pressure and heart rate were measured before and immediately after the cold exposure. Blood samples were collected by qualified staff before and immediately after staying in cold chamber, from the ulnar vein using Vaccuette Blood Collection tubes (with EDTA for plasma and hematologic parameters; with clotting activator for getting serum). Serum and plasma were separated by centrifugation. The samples were frozen once at –20 °C. Hemograms and leukograms were determined using Automated Hematology Analyzer XS-500i (Sysmex; Japan). Ferritin (ORGENTEC Diagnostika; Germany), lactoferrin (HycultBiotech; USA), transferrin (AssayPro; USA), IL6, IL1β and TNFα (Bender MedSystems; Austria), erythropoietin (Vector Best; Russia), irisin (BioVendor; Czech Republic) levels were measured and analyzed using Thermo Scientific™ Multiskan™ FC Microplate Photometer (Thermo Fisher Scientific; Finland). The amounts of lymphocytes undergoing apoptosis or necrosis were determined by flow cytometry on Epics XL flow cytometer analyzer (Beckman Coulter; USA) by double staining with annexin-V (AnV) and propidium iodide (PI), counting at least 5000 cells. The results were evaluated by cell staining: live cells (AnV–/PI–), apoptosis (AnV+/PI–), necrosis (AnV–/PI+). Statistical analysis was carried out using Statistica 6.0 software package (StatSoft; USA). Shapiro–Wilk test was used for testing the normality of data. The data were presented as mean (M) ± standard deviation (SD) values. If the distribution was close to normal, t-test was used to compare the results; differences were considered significant at $p < 0.05$. If the distribution differed from normal, data were presented as median (Me) and 25–75% quartiles. Statistical significance of differences was assessed using the non-parametric Mann-Whitney test. The critical level of significance (p) for testing statistical hypotheses was assumed to be 0.05.

RESULTS

The individuals with lymphopenia had a decreased level of neutrophils in peripheral blood: 2.44 (1.93–2.93) × 10^9 /L, with 38.57 ± 2.29% frequency of neutropenia. In individuals with physiologic lymphocyte levels, higher levels of neutrophil granulocytes were observed (3.02 (2.33–3.64) × 10^9/L ($p < 0.001$), neutropenia was detected in 15.79 ± 1.88% of cases. Low count of neutrophil granulocytes is associated with a decrease in their phagocytic activity. Thus, the rate of active phagocytes amounted to 68.53% in the first group (lymphopenia) while in practically healthy participants is was 72.25%. The neutrophil-to-lymphocyte ratio (NLR) was found to be 2.11 in group 1 and 1.49 in group 2. NLR is an important marker of conditions accompanied by systemic inflammation. Elevated NLR is known to be associated with infections, stroke, heart attack, cancer, autoimmune diseases, tissue damage and higher risk of morbidity [13–17]. In both groups, NLR was less than 3.0 which is normal. However, the higher NLR values in the group with lymphopenia evidenced imbalance of immune pathways of inflammation and can be considered as a criterion of increased systemic inflammation risks.

Assessement of apoptosis (AnV+/PI–) and lymphocyte necrosis (AnV–/PI+) showed that necrotic cells counts did not differ significantly in two groups: 0.74 % AnV–/PI+ lymphocytes in group 1, and 0.67% in group 2. The number of lymphocytes labeled for apoptosis was higher in individuals with normal lymphocyte levels in peripheral blood (5.43%), individuals with lymphopenia had 3.68% AnV+/PI– lymphocytes ($p < 0.01$). Thus, lymphopenia in this case is not associated with increased levels of cell death — it is rather a variant of compensatory adaptive reaction, and the impact of adverse factors leads to a shift of parameters out of normal physiological range.

In lymphopenia hemograms, we observed lower counts of erythrocytes (4.41 (4.08–4.73) and 4.68 (4.31–4.99) × 10^6 /L,

Table. Levels of iron-containing proteins in peripheral blood serum, M ± *m*, $p < 0.01$

	Ferritin, ng/mL	Lactoferrin, ng/mL	Transferrin, ug/mL
Group 1 (Lymphopenia)	43.91 (23.22–53.55)	394.85 (180.24–383.92)	827.35 (360.30–515.90)
Group 2 (Normal lymphocyte levels)	63.90 (24.38–87.21)	334.71 (169.80–470.80)	473.56 (351.40–549.6)

respectively, $p < 0.001$) and hemoglobin (127, 70 (118.00–138.00) and 137.19 (128.00–149) g/L, respectively, $p < 0.0001$) with no significant differences in mean hemoglobin concentrations in erythrocytes (340.33 (331.00–351.00) and 340.71 (332.00–349.00) g/L). The frequency of detection of less than 120 g/L hemoglobin concentration was 30.75 ± 2.15% in the first group and 16.67 ± 1.46% in the second group. Less than 4×10^6 erythrocytes/L values were actually four times more often detected in lymphopenia (in 20.51% and 6.06% of the participants, respectively). No significant differences in erythropoietin concentrations were observed in the two groups; it was 30.02 (13.25–35.48) mMe/mL in individuals with low lymphocyte counts and 29.68 (17.31–37.11) mMe/mL in individuals with normal lymphocyte counts.

Absorption and accumulation of iron play an important role in regulation of erythropoiesis as well as in adaptation to cold. Ferritin can serve as an indirect marker for total body iron store. Transcription of the ferritin H isoforms mRNA and accumulation of ferritin were enhanced by cold acclimation [18]. Levels of this iron-containing protein in lymphopenia occurred to be within the physiological norm with a tendency to lower concentrations as compared with individuals with normal lymphocyte counts (Table). No statistically significant differences in lactoferrin levels were found for the two groups. Lymphopenia is associated with the almost 2-fold higher transferrin levels in peripheral blood. Hypoxia and low temperatures are factors enhancing the expression of the transferrin gene and, consequently, transferrin blood level. High levels of transferrin, on the one hand, increases iron supply to tissues to compensate for oxygen deficiency but on the other hand, transferrin promotes the activation of thrombin which increases the risk of hypercoagulability and as a consequence, thromboembolic and cardiovascular pathologies [19, 20].

In both groups, levels of cytokines in peripheral blood were within the physiologic norm, no significant differences were found. In case of asymptomatic lymphopenia, IL6 levels were 2.48 ± 0.41 pg/mL in group 1 and 3.74 ± 0.35 pg/mL in group 2, IL1β levels 5.01 ± 0.61 and 4.46 ± 0.67 pg/mL, and TNFα levels 6.32 ± 1.03 and 7.32 ± 0.91 pg/mL, respectively.

After the cold exposure, an adaptive response of the cardiovascular system was recorded in both groups, with a tendency to increase blood pressure and decrease heart rate (Figure).

In both groups, a significant decrease was observed in forehead skin temperatures (from 36.6 ± 0.06 to 34.05 ± 0.45 °C in group 1, $p < 0.0001$; from 36.4 ± 0.10 to 33.78 ± 0.32 °C, in group 2, $p < 0.0001$) as well as in back of the palm skin temperatures (from 33.2 ± 0.33 to 32.4 ± 0.24 °C in group 1, $p < 0.05$; from 33.61 ± 0.36 to 32.54 ± 0.23 °C in group 2, $p < 0.05$). Total body short-term cold exposure was accompanied by an increase in lymphocyte levels in individuals with lymphopenia up to 1.32 (1.13–1.48) × 10^9 /L ($p < 0.05$), with no significant change in the "control" group: 2.02 (1.76–2.35) × 10^9 /L. For neutrophil granulocytes, the opposite response was observed. In group 2 (normal lymphocyte levels) concentration of neutrophils increased by 11% up to 3.27 (2.57–4.01) × 10^9/L ($p < 0.05$) while in group 1 (lymphopenia) no changes in neutrophil content were observed. In both groups there was a decrease in the level of irisin (from 4.25 (1.81–6.70) to 3.52 (1.30–5.75) μg/mL in group 1; from 2.99 (1.63–7.14) to 2.38 (1.65–5.66) μg/mL in group 2 which may be an evidence of activating mechanisms of non-shivering thermogenesis.

Cold exposure was associated with an increase in ferritin concentration up to 57.67 (41.67–65.10) ng/mL($p < 0.01$) in group 1 (lymphopenia) and up to 76.46 (25.29–98.29) ng/mL ($p < 0.01$) in group 2 (normal lymphocyte level); lactoferrin content increased in group 2 only (up to 498.85 (124.68–485.97) ($p < 0.0001$); transferrin content did not change in both groups — 558.60 (421.70–940.70) mg/dL in group 1 and 423.30 (351.40–549.60) mg/dL in group 2).

DISCUSSION

Adaptive abilities depend on the levels of reactivity and resistance providing stress reaction or training reaction in response to environmental factors. Lymphopenia is known to be a negative prognostic marker in various pathological conditions, and its combination with the need to adapt to low temperatures leads to overstress of regulatory systems and failure of adaptation [21–23]. Asymptomatic lymphopenia commonly found in people living in the North is accompanied by neutropenia and lower activity of phagocytic defense.

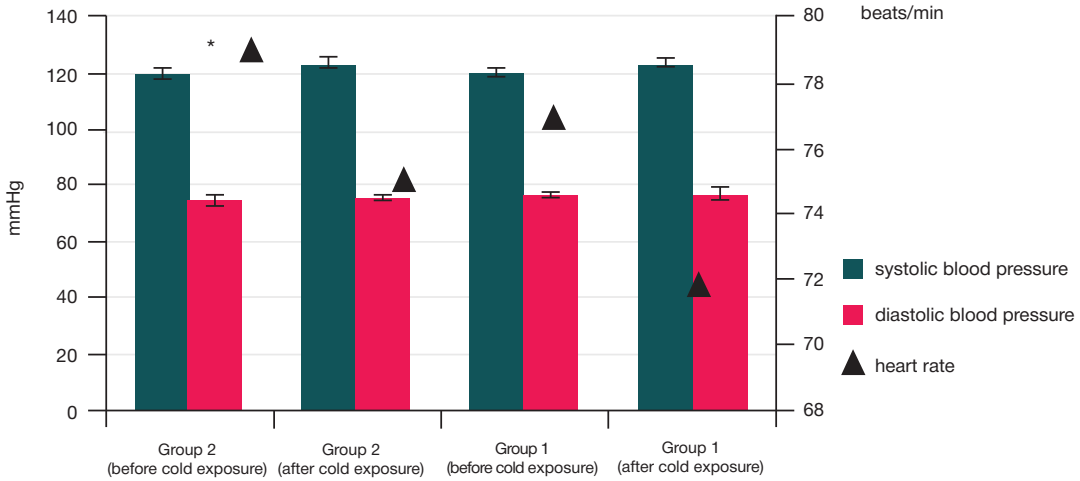

Fig. Changes in blood pressure and heart rate after short-term cold exposure. * — $p < 0.01$

Redistribution of leukocytes and increased transfer of neutrophil granulocytes to tissues under the influence of adverse climatic factors plays a role in the etiology of neutropenia in northerners [24, 25]. Low lymphocytes counts in peripheral blood are associated with tissue hypoxia which may be a consequence of abnormal morphofunctional state of erythrocytes caused by exposure to low temperatures and oxidative stress [26–28].

In addition, people living in the North are characterized by structural changes in erythrocyte membranes with increased membrane viscosity, and as a consequence, a decrease in the rate of gas diffusion and oxygen supply to tissues [29–31]. NLR is shown to be higher in individuals with lymphopenia as compared with individuals having normal lymphocyte levels. Combination of high NLR with insufficient oxygen supply is an adverse marker in patients with infectious inflammatory diseases [32]. In response to cold exposure, similar cardiovascular reactions have been observed in both groups regardless of the background level of lymphocytes, that are manifested in increased blood pressure and decreased heart rate. Decreased level of irisin, a protein involved in metabolism and thermoregulation is an evidence of activating thermoregulatory mechanisms [33, 34]. Irisin upregulates expression of uncoupling protein 1 (UCP1) and leads to non-shivering thermogenesis and increased heat production. No changes in lactoferrin concentration have been found in individuals with background lymphopenia after the short-term cold exposure. An increase in the concentration of this protein is associated with degranulation of neutrophils and reflects the level of their activation. Thus, lymphopenia combined with neutropenia and decreased functional activity of neutrophil granulocytes significantly increases the risk of adaptive failure, and systematic exposure to cold increases the probability of chronicization of infectious diseases. In addition, a high level of transferrin persisting after cold exposure increases risk of hypercoagulability, thrombosis and cardiovascular events. In both groups, actually the same increase in ferritin levels was observed (in + 21.10% in group 1 and + 19.96% in group 2) which may be an evidence of thermal homeostasis since the induction of ferritin heavy chain expression promotes survival in cold environments by detoxifying iron forms that generate reactive oxygen species [35].

CONCLUSIONS

Asymptomatic background lymphopenia is associated with insufficient oxygen supply and higher levels of neutropenia. Regardless of the background level of lymphocytes in peripheral blood, same-type responses to short-term cold exposure are observed in cardiovascular system as well as in irisin and ferritin levels, providing an evidence of activating thermoregulation mechanisms. Cold exposure did not induced activation of nonspecific defense and did not change level and functional activity of circulating neutrophil granulocytes that can increase risks of chronicization of infectious processes in this group. The obtained data can be used in monitoring related to environmental physiology, for developing methods for assessing risks of maladaptive reactions to cold exposure and correcting immunity disorders in people living in the North.

References

1. Garmaeva DK, Belolyubskaya DS, Fyodorova AI, Arzhakova LI, Afanasieva OG. The effect of the cold stress on morphological and functional parameters of the thymus in the experiment. Morphological Newsletter. 2019; 27 (2): 19–23. DOI: 10.20340/mv-mn.19(27).02.19-23. Russian.
2. Matkina OV. Patogeneticheskie izmeneniya v timuse i selezenke neinbrednykh belykh krys pri ostrom stresse. Permskiy meditsinskiy zhurnal. 2014; 31 (1): 121–8. Russian.
3. Buzinaeva MT. Immunomorfologicheskaya kharakteristika limfoidnoy tkani gortani pri vozdeystvii nizkikh prirodnykh temperatur [dissertation]. Ul'yanovsk, 2013. Russian.
4. Devonaev OT. Strukturno-funktsional'nye kharakteristiki i osobennosti morfogeneza limfoidnogo apparata mochevyvodyashchikh putey v norme i pri vozdeystvii kholodovogo stressa i vysokogor'ya [dissertation]. Novosibirsk, 2007. Russian.
5. Gosudarstvennyy doklad «O sostoyanii sanitarno-epidemiologicheskogo blagopoluchiya naseleniya v Arkhangel'skoy oblasti v 2022 godu». Arkhangel'sk, 2023. Russian.
6. Ob itogakh raboty Ministerstva zdravookhraneniya Rossiyskoy Federatsii v 2022 godu i zadachakh na 2023 god. M.: Ministerstvo zdravookhraneniya Rossiyskoy Federatsii, 2023. Russian.
7. Krasilnikov SV. Analysis of tendencies of population morbidity of Arkhangelsk region as a result of diseases of blood circulation system as the basis of cardiac-surgery organization. International Research Journal. 2017;5–2 (59). C. 145–7. DOI: 10.23670/IRJ.2017.59.077. Russian.
8. Fathi N, Rezaei N. Lymphopenia in COVID-19: Therapeutic opportunities. Cell Biol Int. 2020; 44 (9): 1792–7. DOI: 10.1002/cbin.11403.
9. Dobrodeeva LK. Immunologicheskoe rayonirovanie. Syktyvkar: KNTs, 2004; 101 p. Russian.
10. Dobrodeeva LK, Patrakeeva VP. Vliyanie migratsionnykh i proliferativnykh protsessov limfotsitov na sostoyanie immunnogo fona cheloveka, prozhivayushchego v usloviyakh vysokikh shirot. Ekaterinburg: UrO RAN, 2018; 203 p. Russian.
11. Gubkina LV, Samodova AV, Dobrodeeva LK. Distinctive aspects of the immune status of the kola Saami and Russians living in the far North. American Journal of Human Biology. 2023; 23969. DOI: 10.1002/ajhb.23969.
12. Juravlyova OA, Markin AA, Kuzichkin DS, Saltuikova MM, Loginov VI, Zabolotskaya IV, et al. Features of Human Metabolic Reactions under Extreme Cold Exposure. Human Physiology. 2018; 44 (3): 109–15. DOI: 10.7868/S0131164618030128. Russian.
13. De Jager CP, van Wijk PT, Mathoera RB, de Jongh-Leuvenink J, van der Poll T, Wever PC. Lymphocytopenia and neutrophil-lymphocyte count ratio predict bacteremia better than conventional infection markers in an emergency care unit. Crit Care. 2010; 14 (5): R192. DOI: 10.1186/cc9309.
14. Kabak M, Çil B, Hocanlı I. Relationship between leukocyte, neutrophil, lymphocyte, platelet counts, and neutrophil to lymphocyte ratio and polymerase chain reaction positivity. International Immunopharmacology. 2021; 93: 107390. DOI: 10.1016/j.intimp.2021.107390.
15. Sejópoles MD, Souza-Silva JP, Silva-Santos C, Paula-Duarte MM, Fontes CJF, Gomes LT. Prognostic value of neutrophil and lymphocyte counts and neutrophil/lymphocyte ratio for predicting death in patients hospitalized for COVID-19. Heliyon. 2023; 9 (6): e16964. DOI: 10.1016/j.heliyon.2023.e16964.
16. Shusterman E, Prozan L, Ablin JN, Weiss-Meilik A, Adler A, Choshen G, et al. Neutrophil-to-lymphocyte ratio trend at admission predicts adverse outcome in hospitalized respiratory syncytial virus patients. Heliyon. 2023; 9 (6): e16482. DOI: 10.1016/j.heliyon.2023.e16482.
17. Mehta S, Ketkar M, Jain DK. Role of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in predicting carcinoma prostate (CaP) in patients with lower urinary tract symptoms and raised serum prostate-specific antigen (sr.PSA). Medical Journal Armed Forces India. 2023. DOI: 10.1016/j.mjafi.2023.03.001.

18. Yamashita M, Ojima N, Sakamoto T. Molecular cloning and cold-inducible gene expression of ferritin H subunit isoforms in rainbow trout cells. J Biol Chem. 1997; 271 (43): 26908–13. DOI: 10.1074/jbc.271.43.26908.
19. Li M, Tang X, Liao Z, Shen C, Cheng R, Fang M, et al. Hypoxia and low temperature upregulate transferrin to induce hypercoagulability at high altitude. Blood. 2022; 140 (19): 2063–75. DOI: 10.1182/blood.2022016410.
20. Tang X, Zhang Z, Fang M, Han Y, Wang G, Wang S, et al. Transferrin plays a central role in coagulation balance by interacting with clotting factors. Cell Res. 2020; 30 (2): 119–32. DOI: 10.1038/s41422-019-0260-6.
21. Streltsova EI, Peshkova IV, Samatov IYu, Valeeva VA, Vereshchagin EI. Lymphopenia as a determinant factor of sepsis severity, as an exact diagnostic criterion, and as an object of therapy. Journal of Siberian Medical Sciences. 2020; 3: 108–25. DOI: 10.31549/2542-1174-2020-3-108-125. Russian.
22. Osmanova AS, Amirov GN, Asadulayeva MN, Shakhbanov RK, Asadulayeva ZM. The effect of lymphopenia in COVID-19 patients on the severity of infection. Journal Technologies of Living Systems. 2022; 19 (1): 14–9. DOI: 10.18127/j20700997-202201-02. Russian.
23. Abdullaev RYu, Komissarova OG. Changes in markers of hematological, biochemical and coagulological blood tests with coronavirus COVID-19 infections. Consilium Medicum. 2020; 22 (11): 51–5. Russian.
24. Balashova SN, Dobrodeeva LK. Influence of neutropenia on the state of the immune status in persons working on the Svalbard Archipelago. Vestn Ural Med Akad Nauki. 2019; 16 (2): 71–7. DOI: 10.22138/2500-0918-2019-16-2-71-77. Russian.
25. Gubkina LV, Samodova AV, Dobrodeeva LK. Distinctive aspects of the immune status of the kola Saami and Russians living in the far North. American Journal of Human Biology. 2023; 23969. DOI: 10.1002/ajhb.23969.
26. Lutsenko MM. Gas-transport metabolism in the peripheral blood at general cooling of the organism. Bulletin Physiology and Pathology of Respiration. 2012; 44: 85–9. Russian.
27. Alekseev RZ, Golderova AS, Mamaeva SN, Platonova VA, Savvinova LN, Afanasyeva SS, et al. Main features of erythrocytes morphology in persons dead of hypothermia. International Research Journal. 2018; 12 (78): 169–72. DOI: 10.23670/IRJ.2018.78.12.030. Russian.
28. Nagibovich OA, Ukhovsky DM, Zhekalov AN, Tkachuk NA, Arzhavkina LG, Bogdanova EG, et al. Mechanisms of hypoxia in Arctic zone of Russian Federation. Bulletin of the Russian Military Medical Academy. 2016; 2 (54): 202–5. Russian.
29. Kunitsyn VG, Panin LE, Osipova LP, Tabikhanova LE, Churkina TV, Rozumenko AA. Izmenenie struktury gemoglobina v ekstremal'nykh usloviyakh Arktiki. Journal of Ural Medical Academic Science. 2014; 2 (48): 37–9. Russian.
30. Kim LB. Transport kisloroda pri adaptatsii cheloveka k usloviyam Arktiki i kardiorespiratornoy patologii. Novosibirsk: Nauka, 2015; 216 p. Russian.
31. Kim LB. Vliyanie polyarnogo stazha na kislorodotransportnuyu funktsiyu krovi u severyan razlichnogo vozrasta. Arktika i Sever. 2014; 17: 150–62. Russian.
32. Ozawa T, Asakura T, Chubachi S, Namkoong H, Tanaka H, Lee K, et al. Use of the neutrophil-to-lymphocyte ratio and an oxygen requirement to predict disease severity in patients with COVID-19. Respiratory Investigation. 2023; 61 (4): 454–9. DOI: 10.1016/j.resinv.2023.03.007.
33. Vliora M, Grillo E, Corsini M, Ravelli C, Nintou E, Karligiotou E, et al. Irisin regulates thermogenesis and lipolysis in 3T3-L1 adipocytes. Biochimica et Biophysica Acta (BBA). 2022; 1866 (4): 130085. DOI: 10.1016/j.bbagen.2022.130085.
34. Gheit REAE, Younis RL, El-Saka MH, Emam MN, Soliman NA, El-Sayed RM, et al. Irisin improves adiposity and exercise tolerance in a rat model of postmenopausal obesity through enhancing adipo-myocyte thermogenesis. J Physiol Biochem. 2022; 78 (4): 897–913. DOI: 10.1007/s13105-022-00915-3.
35. Blankenhaus B, Braza F, Martins R, Bastos-Amador P, González-García I, Carlos AR, et al. Ferritin regulates organismal energy balance and thermogenesis. Molecular Metabolism. 2019; 24: 64–79. DOI: 10.1016/j.molmet.2019.03.008.
36. Blankenhaus B, Braza F, Martins R, Bastos-Amador P, González-García I, Carlos AR, et al. Ferritin regulates organismal energy balance and thermogenesis. Molecular Metabolism. 2019. 24: 64–79. DOI: 10.1016/j.molmet.2019.03.008.

Литература

1. Гармаева Д. К., Белолюбская Д. С., Федорова А. И., Аржакова Л. И., Афанасьева О. Г. Влияние холодового стресса на морфофункциональные показатели тимуса в эксперименте. Морфологические ведомости. 2019; 27 (2): 19–23. DOI: 10.20340/mv-mn.19(27).02.19-23.
2. Маткина О. В. Патогенетические изменения в тимусе и селезенке неинбредных белых крыс при остром стрессе. Пермский медицинский журнал. 2014; 31 (1): 121–8.
3. Бузинаева М. Т. Иммуноморфологическая характеристика лимфоидной ткани гортани при воздействии низких природных температур [диссертация]. Ульяновск, 2013.
4. Девонаев О. Т. Структурно-функциональные характеристики и особенности морфогенеза лимфоидного аппарата мочевыводящих путей в норме и при воздействии холодового стресса и высокогорья [диссертация]. Новосибирск, 2007.
5. Государственный доклад «О состоянии санитарно-эпидемиологического благополучия населения в Архангельской области в 2022 году». Архангельск, 2023.
6. Об итогах работы Министерства здравоохранения Российской Федерации в 2022 году и задачах на 2023 год. М.: Министерство здравоохранения Российской Федерации, 2023.
7. Красильников С. В. Анализ тенденций заболеваемости населения Архангельской области болезнями системы кровообращения как основа организации кардиохирургической помощи. Международный научно-исследовательский журнал. 2017; 5–2 (59): 145–7. DOI: 10.23670/IRJ.2017.59.077.
8. Fathi N, Rezaei N. Lymphopenia in COVID-19: Therapeutic opportunities. Cell Biol Int. 2020; 44 (9): 1792–7. DOI: 10.1002/cbin.11403.
9. Добродеева Л. К. Иммунологическое районирование. Сыктывкар: КНЦ, 2004; 101 с.
10. Добродеева Л. К., Патракеева В. П. Влияние миграционных и пролиферативных процессов лимфоцитов на состояние иммунного фона человека, проживающего в условиях высоких широт. Екатеринбург: УрО РАН, 2018; 203 с.
11. Gubkina LV, Samodova AV, Dobrodeeva LK. Distinctive aspects of the immune status of the kola Saami and Russians living in the far North. American Journal of Human Biology. 2023; 23969. DOI: 10.1002/ajhb.23969.
12. Журавлева О. А., Маркин А. А., Кузичкин Д. С., Салтыкова М. М., Логинов В. И., Заболотская И. В. и др. Особенности метаболических реакций человека при экстремальном холодовом воздействии. Физиология человека. 2018; 44 (3): 109–15. DOI: 10.7868/S0131164618030128.
13. De Jager CP, van Wijk PT, Mathoera RB, de Jongh-Leuvenink J, van der Poll T, Wever PC. Lymphocytopenia and neutrophil-lymphocyte count ratio predict bacteremia better than conventional infection markers in an emergency care unit. Crit Care. 2010; 14 (5): R192. DOI: 10.1186/cc9309.
14. Kabak M, Çil B, Hocanlı I. Relationship between leukocyte, neutrophil, lymphocyte, platelet counts, and neutrophil to lymphocyte ratio and polymerase chain reaction positivity. International Immunopharmacology. 2021; 93: 107390. DOI: 10.1016/j.intimp.2021.107390.
15. Sejópoles MD, Souza-Silva JP, Silva-Santos C, Paula-Duarte MM, Fontes CJF, Gomes LT. Prognostic value of neutrophil and lymphocyte counts and neutrophil/lymphocyte ratio for predicting death in patients hospitalized for COVID-19. Heliyon. 2023; 9 (6): e16964. DOI: 10.1016/j.heliyon.2023.e16964.
16. Shusterman E, Prozan L, Ablin JN, Weiss-Meilik A, Adler A,

Choshen G, et al. Neutrophil-to-lymphocyte ratio trend at admission predicts adverse outcome in hospitalized respiratory syncytial virus patients. Heliyon. 2023; 9 (6): e16482. DOI: 10.1016/j.heliyon.2023.e16482.
17. Mehta S, Ketkar M, Jain DK. Role of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in predicting carcinoma prostate (CaP) in patients with lower urinary tract symptoms and raised serum prostate-specific antigen (sr.PSA). Medical Journal Armed Forces India. 2023. DOI: 10.1016/j.mjafi.2023.03.001.
18. Yamashita M, Ojima N, Sakamoto T. Molecular cloning and cold-inducible gene expression of ferritin H subunit isoforms in rainbow trout cells. J Biol Chem. 1997; 271 (43): 26908–13. DOI: 10.1074/jbc.271.43.26908.
19. Li M, Tang X, Liao Z, Shen C, Cheng R, Fang M, et al. Hypoxia and low temperature upregulate transferrin to induce hypercoagulability at high altitude. Blood. 2022; 140 (19): 2063–75. DOI: 10.1182/blood.2022016410.
20. Tang X, Zhang Z, Fang M, Han Y, Wang G, Wang S, et al. Transferrin plays a central role in coagulation balance by interacting with clotting factors. Cell Res. 2020; 30 (2): 119–32. DOI: 10.1038/s41422-019-0260-6.
21. Стрельцова Е. И., Пешкова И. В., Саматов И. Ю., Валеева В. А., Верещагин Е. И. Лимфопения как фактор, определяющий тяжесть сепсиса, как точный критерий диагностики и как объект терапии. Journal of Siberian Medical Sciences. 2020; 3: 108–25. DOI: 10.31549/2542-1174-2020-3-108-125.
22. Османова А. С., Амиров Г. Н., Асадулаева М. Н., Шахбанов Р. К., Асадулаева З. М. Влияние лимфопении у больных covid-19 на тяжесть протекания инфекции. Технологии живых систем. 2022; 19 (1): 14–9. DOI: 10.18127/j20700997-202201-02.
23. Абдуллаев Р. Ю. О., Комиссарова О. Г. Изменения маркеров гематологического, биохимического и коагулологического анализов крови при новой коронавирусной инфекции covid-19. Consilium Medicum. 2020; 22 (11): 51–5.
24. Балашова С. Н., Добродеева Л. К. Влияние нейтропении на состояние иммунного статуса у лиц, работающих на архипелаге Шпицберген. Вестник Уральской медицинской академической науки. 2019; 16 (2): 71–7. DOI: 10.22138/2500-0918-2019-16-2-71-77.
25. Gubkina LV, Samodova AV, Dobrodeeva LK. Distinctive aspects of the immune status of the kola Saami and Russians living in the far North. American Journal of Human Biology. 2023; 23969. DOI: 10.1002/ajhb.23969.
26. Луценко М. М. Газотранспортный обмен в периферической крови при общем охлаждении организма. Бюллетень физиологии и патологии дыхания. 2012; 44: 85–9.
27. Алексеев Р. З., Гольдерова А. С., Мамаева С. Н., Платонова В. А., Саввинова Л. Н., Афанасьева С. С. и др. Особенности морфологии эритроцитов у лиц, умерших от переохлаждения. Международный научно-исследовательский журнал. 2018; 12 (78): 169–72. DOI: 10.23670/IRJ.2018.78.12.030.
28. Нагибович О. А., Уховский Д. М., Жекалов А. Н., Ткачук Н. А., Аржавкина Л. Г., Богданова Е. Г. и др. Механизмы гипоксии в Арктической зоне Российской Федерации. Вестник Российской военно-медицинской академии. 2016; 2 (54): 202–5.
29. Куницын В. Г., Панин Л. Е., Осипова Л. П., Табиханова Л. Э., Чуркина Т. В., Розуменко А. А. Изменение структуры гемоглобина в экстремальных условиях Арктики. Вестник Уральской медицинской академической науки. 2014; 2 (48): 37–9.
30. Ким Л. Б. Транспорт кислорода при адаптации человека к условиям Арктики и кардиореспираторной патологии. Новосибирск: Наука, 2015; 216 с.
31. Ким Л. Б. Влияние полярного стажа на кислородотранспортную функцию крови у северян различного возраста. Арктика и Север. 2014; 17: 150–62.
32. Ozawa T, Asakura T, Chubachi S, Namkoong H, Tanaka H, Lee K, et al. Use of the neutrophil-to-lymphocyte ratio and an oxygen requirement to predict disease severity in patients with COVID-19. Respiratory Investigation. 2023; 61 (4): 454–9. DOI: 10.1016/j.resinv.2023.03.007.
33. Vliora M, Grillo E, Corsini M, Ravelli C, Nintou E, Karligiotou E, et al. Irisin regulates thermogenesis and lipolysis in 3T3-L1 adipocytes. Biochimica et Biophysica Acta (BBA). 2022; 1866 (4): 130085. DOI: 10.1016/j.bbagen.2022.130085.
34. Gheit REAE, Younis RL, El-Saka MH, Emam MN, Soliman NA, El-Sayed RM, et al. Irisin improves adiposity and exercise tolerance in a rat model of postmenopausal obesity through enhancing adipo-myocyte thermogenesis. J Physiol Biochem. 2022; 78 (4): 897–913. DOI: 10.1007/s13105-022-00915-3.
35. Blankenhaus B, Braza F, Martins R, Bastos-Amador P, González-García I, Carlos AR, et al. Ferritin regulates organismal energy balance and thermogenesis. Molecular Metabolism. 2019; 24: 64–79. DOI: 10.1016/j.molmet.2019.03.008.
36. Blankenhaus B, Braza F, Martins R, Bastos-Amador P, González-García I, Carlos AR, et al. Ferritin regulates organismal energy balance and thermogenesis. Molecular Metabolism. 2019. 24: 64–79. DOI: 10.1016/j.molmet.2019.03.008.