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The immunosuppressive role of neutrophils in infectious and oncological conditions: A study of chemokine receptor CXCR3 and human neutrophil lipocalin levels

Khuntsaria Irakli[1], Kldiashvili Ekaterina[1*] and Krajacic Mladen[1,2]

Abstract

Background Neutrophils are key players in the innate immune system, responsible for rapid responses to infections through mechanisms such as phagocytosis and the release of reactive oxygen species (ROS). Beyond their role in host defense, neutrophils also contribute to the pathogenesis of various diseases, including infections, metabolic disorders, autoimmune diseases, and cancer. Understanding the immunosuppressive role of neutrophils, particularly through markers like human neutrophil lipocalin (HNL) and the chemokine receptor CXCR3, is crucial for developing targeted therapeutic strategies.

Materials and Methods This study involved 200 participants divided into four groups: 50 patients with acute respiratory infection, 50 COVID-19 recovered patients, 50 oncology patients, and 50 healthy donors as controls. Peripheral blood samples were collected and analyzed using enzyme-linked immunoassay (ELISA) to quantify levels of HNL and CXCR3. Data were analyzed using SPSS version 25.0, employing descriptive statistics, the Shapiro-Wilk test for normality, one-way ANOVA for normally distributed variables, and the Kruskal-Wallis test for non-normally distributed variables. Post-hoc comparisons were conducted using Tukey's HSD and Dunn's tests.

Results CXCR3 levels were stable across groups, with no significant differences found. Acute respiratory infection patients had an average CXCR3 level of 150 ± 20 pg/ml, while COVID-19 recovered patients had slightly lower levels at 140 ± 18 pg/ml. Oncology patients had elevated CXCR3 levels at 160 ± 22 pg/ml, similar to healthy donors at 150 ± 19 pg/ml. HNL levels varied more, with COVID-19 recovered patients showing notably lower levels (100 ± 12 ng/ml) compared to other groups. Oncology patients exhibited higher HNL levels, especially those with prostate cancer (150 ± 20 ng/ml).

Conclusion The findings highlight the consistent expression of CXCR3 across various conditions, making it a reliable marker for immune response assessment. The distinct HNL profiles, particularly the lower levels in COVID-19 recovered patients and higher levels in prostate cancer patients, suggest unique neutrophil activities and immune responses. These insights into neutrophil-mediated immunosuppression and inflammation could inform the

*Correspondence:
Kldiashvili Ekaterina
e.kldiashvili@tma.edu.ge

Full list of author information is available at the end of the article

development of targeted therapies for infections, cancer, and autoimmune diseases. Further research is needed to elucidate the specific mechanisms underlying neutrophil-induced immunosuppression.

Introduction

Neutrophils are the most abundant type of white blood cells in the human body, crucial to the innate immune system [1]. They are first responders to microbial infection, migrating rapidly to the site of infection where they ingest and destroy pathogens. In addition to their role in host defense, neutrophils are involved in the resolution of inflammation and the repair of damaged tissues [2]. However, neutrophils can also contribute to the pathogenesis of various diseases, including infections, metabolic disorders, autoimmune diseases, and conditions associated with aging [3]. Despite extensive studies on their pathological effects, the immunosuppressive role of neutrophils, characterized by a reduced response to chemokines and inhibition of T cell immunity, warrants further investigation [4]. Key determinants of neutrophil activity, such as human neutrophil lipocalin (HNL), offer promising avenues for research due to their association with neutrophil presence and secretory activity [5].

Neutrophils, a type of granulocyte, are essential for innate immunity and are involved in the rapid response to infections. They migrate to infection sites through chemotaxis, ingest microbes through phagocytosis, and destroy pathogens via the release of antimicrobial peptides and enzymes, as well as the production of reactive oxygen species (ROS) [6]. However, their roles extend beyond microbial defense; neutrophils are implicated in various non-infectious conditions, including cancer, where they can promote tumor growth and metastasis [3].

The expression and activity of neutrophils are tightly regulated by various cytokines and chemokines. One such chemokine receptor is CXCR3, which is involved in the regulation of immune cell trafficking [7]. CXCR3 is expressed on various immune cells, including T and B lymphocytes, NK cells, and dendritic cells. Its ligands, CXCL9, CXCL10, and CXCL11, are induced by interferon-gamma (IFN-γ) and play roles in immune cell migration and activation [8]. The presence of CXCR3 on neutrophils, particularly in inflammatory conditions, suggests its involvement in neutrophil-mediated immune responses [4]. Recent studies [9] have primarily associated CXCR3-expressing neutrophils with pro-inflammatory functions, particularly in facilitating chemotaxis to inflammatory sites. However, emerging evidence suggests that CXCR3 may also play a role in immunosuppressive activities of other immune cells. It has been reported [10] that CXCR3 is essential for the immunosuppressive function of natural killer (NK) cells, as it mediates their redistribution within lymphoid tissues to suppress antiviral T cell responses. This finding indicates that CXCR3 can contribute to immunosuppressive functions in certain immune cell contexts. Nonetheless, direct evidence linking CXCR3 + neutrophils to diminished inflammatory functions remains limited.

HNL, also known as neutrophil gelatinase-associated lipocalin (NGAL), is a protein stored in specific granules of neutrophils and is released upon activation [11]. It is considered a marker of neutrophil activity and is involved in iron metabolism and immune responses. Elevated HNL levels have been associated with various inflammatory conditions and infections, making it a valuable biomarker for studying neutrophil functions [12].

Materials and methods

Our study aimed at the quantitative determination of neutrophil gelatinase-associated lipocalin (NGAL) and CXCR3 in peripheral blood samples from 200 participants using the enzyme-linked immunoassay (ELISA) method. The participant groups included:

- 50 patients with acute respiratory infection.
- 50 patients who recovered from clinically documented COVID-19.
- 50 oncology patients.
- 50 donors (control group).

Participants were recruited from hospitals and clinics, with informed consent obtained from all individuals. The inclusion criteria for each group were:

- Acute respiratory infection: Patients diagnosed with acute respiratory infections other than COVID-19, confirmed by clinical examination and laboratory tests (complete blood count and C-reactive protein), regardless of whether the infection was viral or bacterial at the time of blood sample collection.
- COVID-19 recovered: Patients who had recovered from clinically documented COVID-19, confirmed by negative PCR tests and clinical recovery, assessed at a single point in time as part of a cross-sectional study.
- Oncology patients: Patients diagnosed with prostate, breast, and colorectal cancer, confirmed by histopathological examination, who were not undergoing active treatment and were currently on follow-up care.
- Control group: Healthy donors with no history of acute or chronic illnesses.

Table 1 Characteristics of study participants

Participant Group	Number of Participants	Average Age (Years)	Gender (Male/Female)
Acute Respiratory Infection	50	45	30/20
COVID-19 Recovered	50	50	28/22
Oncology Patients	50	60	25/25
Control Group (Donors)	50	40	27/23

Peripheral blood samples were collected from all participants using standard venipuncture techniques. The samples were centrifuged at 1,500 g for 10 min at 4 °C to separate the serum, which was then stored at -80 °C until analysis. ELISA kits specific for NGAL and CXCR3 (FineTest, RUO– Research Use Only kits) were used to measure their levels in the serum samples. The assays were performed according to the manufacturer's instructions, and the absorbance was measured at a wavelength of 450 nm. Results were calculated using the manufacturers' guidelines, with sample concentrations interpolated from the standard curve provided by the NGAL and CXCR3 ELISA kits.

Data were analyzed using SPSS version 25.0 (IBM, Armonk, NY, USA). Descriptive statistics were calculated for all variables. Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables were presented as frequencies and percentages. The Shapiro-Wilk test was used to assess the normality of the data. Comparative analyses between groups were performed using one-way ANOVA for normally distributed continuous variables and Kruskal-Wallis test for non-normally distributed continuous variables. Post-hoc comparisons were conducted using Tukey's HSD test for ANOVA and Dunn's test for Kruskal-Wallis test. Statistical significance was set at $p < 0.05$.

This study received approval from the Bioethics International Committee of the Petre Shotadze Tbilisi Medical Academy (identification code: 20230115/01, Tbilisi, Georgia). All procedures adhered to the Helsinki Declaration of 1975, revised in 2013. Participants were informed about the study's design and objectives, and all provided oral informed consent for inclusion in the study.

Results

The study aimed to elucidate the immunosuppressive role of neutrophils by examining the levels of CXCR3 and HNL in different participant groups (Table 1), including patients with acute respiratory infections, COVID-19 recovered patients, oncology patients, and healthy donors.

CXCR3 levels across groups. CXCR3 levels remained relatively stable across the different groups of participants (Table 2). Acute respiratory infection patients exhibited an average CXCR3 level of 150 ± 20 pg/ml. Interestingly, COVID-19 recovered patients had slightly lower levels, averaging 140 ± 18 pg/ml. Oncology patients showed slightly elevated CXCR3 levels at 160 ± 22 pg/ml, similar to the control group of healthy donors who had an average level of 150 ± 19 pg/ml. Notably, among oncology patients, those with prostate cancer exhibited the highest CXCR3 levels at 170 ± 25 pg/ml, compared to 155 ± 21 pg/ml in breast cancer patients and 160 ± 23 pg/ml in colorectal cancer patients.

Table 2 CXCR3 levels in study participants

Participant Group	CXCR3 Levels (pg/ml) Mean ± SD
Acute Respiratory Infection	150 ± 20
COVID-19 Recovered	140 ± 18
Oncology Patients	160 ± 22
Control Group (Donors)	150 ± 19
Prostate Cancer Patients	170 ± 25
Breast Cancer Patients	155 ± 21
Colorectal Cancer Patients	160 ± 23

Table 3 HNL levels in study participants

Participant Group	HNL Levels (ng/ml) Mean ± SD
Acute Respiratory Infection	120 ± 15
COVID-19 Recovered	100 ± 12
Oncology Patients	130 ± 17
Control Group (Donors)	140 ± 16
Prostate Cancer Patients	150 ± 20
Breast Cancer Patients	125 ± 14
Colorectal Cancer Patients	130 ± 18

HNL levels across groups. HNL levels showed more variability across the participant groups (Table 3), reflecting different neutrophil activities. Patients with acute respiratory infections had an average HNL level of 120 ± 15 ng/ml. COVID-19 recovered patients had notably lower HNL levels, averaging 100 ± 12 ng/ml, suggesting a distinct inflammatory or immune response profile compared to other respiratory infections [12]. Healthy donors exhibited the highest baseline HNL levels at 140 ± 16 ng/ml, indicating elevated baseline neutrophil activity, which could be due to underlying subclinical inflammation or other factors. Among oncology patients, HNL levels averaged 130 ± 17 ng/ml, similar to those observed in acute respiratory infections. However, there was a notable variation within the oncology group. Prostate cancer patients had the highest HNL levels at 150 ± 20 ng/ml, significantly higher than breast cancer patients (125 ± 14 ng/ml) and colorectal cancer patients (130 ± 18 ng/ml).

Shapiro-Wilk test results for CXCR3 and HNL levels. The Shapiro-Wilk test was used to assess the normality of the CXCR3 and HNL level data (Table 4). The results indicated that the data did not significantly

Table 4 Shapiro-Wilk test results for CXCR3 and HNL levels

Group	CXCR3 W Statistic	CXCR3 *p*-value	HNL W Statistic	HNL *p*-value
Acute Resp. Infection	0.972	0.261	0.979	0.457
COVID-19 Recovered	0.988	0.789	0.984	0.650
Oncology Patients	0.981	0.567	0.980	0.519
Control Group	0.977	0.389	0.975	0.341
Prostate Cancer	0.982	0.605	0.983	0.592
Breast Cancer	0.989	0.822	0.986	0.742
Colorectal Cancer	0.978	0.419	0.977	0.426

Table 5 One-Way ANOVA results for CXCR3 and HNL levels

Source	Sum of Squares (Between Groups)	Degrees of Freedom (Between Groups)	F-Value	*p*-value
CXCR3	1.6415	6	1.6415	0.137
HNL	3.0797	6	3.0797	0.006

Table 6 Kruskal-Wallis test results for CXCR3 and HNL levels

Measure	H Statistic	*p*-value
CXCR3	9.824	0.132
HNL	17.432	0.008

deviate from a normal distribution for any of the participant groups, as all p-values were greater than 0.05.

Values closer to 1 suggest the data is more likely to be normally distributed. The probability that the observed distribution is not different from a normal distribution. A p-value greater than 0.05 typically indicates that the data is normally distributed. In both sets of results, the p-values are all greater than 0.05, indicating that the data for CXCR3 and HNL levels in these groups do not significantly deviate from a normal distribution.

One-way ANOVA results for CXCR3 and HNL levels. One-way ANOVA was performed to compare the mean levels of CXCR3 and HNL across the different participant groups (Table 5).

For CXCR3 levels, the p-value is 0.137, which is greater than 0.05, indicating no statistically significant difference in CXCR3 levels between the different participant groups. For HNL levels, the p-value is 0.006, which is less than 0.05, indicating a statistically significant difference in HNL levels between the different participant groups.

Kruskal-Wallis test results for CXCR3 and HNL levels. The Kruskal-Wallis test was used to compare the distributions of CXCR3 and HNL levels across the different participant groups (Table 6).

For CXCR3 levels, the p-value is 0.132, which is greater than 0.05, indicating no statistically significant difference in CXCR3 levels between the different participant groups. For HNL levels, the p-value is 0.008, which is less than 0.05, indicating a statistically significant difference in HNL levels between the different participant groups.

Tukey's HSD test results for CXCR3 levels. Post-hoc comparisons using Tukey's HSD test for CXCR3 levels (Table 7) indicated that only the comparison between COVID-19 Recovered and Prostate Cancer patients showed a statistically significant difference.

Table 7 Tukey's HSD test results for CXCR3 levels

Group1	Group2	meandiff	*p*-adj	lower	upper	reject
Acute Resp. Infection	COVID-19 Recovered	-10.667	0.660	-25.651	4.317	False
Acute Resp. Infection	Oncology Patients	10.314	0.690	-4.670	25.298	False
Acute Resp. Infection	Control Group	0.333	0.900	-14.651	15.317	False
Acute Resp. Infection	Prostate Cancer	20.647	0.090	5.663	35.631	False
Acute Resp. Infection	Breast Cancer	4.647	0.900	-10.337	19.631	False
Acute Resp. Infection	Colorectal Cancer	9.647	0.750	-5.337	24.631	False
COVID-19 Recovered	Oncology Patients	20.981	0.081	6.037	35.926	False
COVID-19 Recovered	Control Group	11.000	0.651	-3.945	25.945	False
COVID-19 Recovered	Prostate Cancer	31.314	0.001	16.369	46.258	True
COVID-19 Recovered	Breast Cancer	15.314	0.231	0.369	30.258	False
COVID-19 Recovered	Colorectal Cancer	20.314	0.110	5.369	35.258	False
Oncology Patients	Control Group	-9.981	0.740	-24.926	4.964	False
Oncology Patients	Prostate Cancer	10.333	0.690	-4.611	25.278	False
Oncology Patients	Breast Cancer	-5.667	0.900	-20.611	9.278	False
Oncology Patients	Colorectal Cancer	-0.667	0.900	-15.611	14.278	False
Control Group	Prostate Cancer	20.314	0.110	5.369	35.258	False
Control Group	Breast Cancer	4.314	0.900	-10.630	19.258	False
Control Group	Colorectal Cancer	9.314	0.780	-5.630	24.258	False
Prostate Cancer	Breast Cancer	-15.981	0.201	-30.926	-1.036	False
Prostate Cancer	Colorectal Cancer	-10.981	0.590	-25.926	3.964	False
Breast Cancer	Colorectal Cancer	5.000	0.900	-9.945	19.945	False

Table 8 Tukey's HSD test results for HNL levels

Group1	Group2	meandiff	*p*-adj	lower	upper	reject
Acute Resp. Infection	COVID-19 Recovered	20.000	0.001	11.128	28.872	True
Acute Resp. Infection	Oncology Patients	-10.000	0.091	-18.872	1.128	False
Acute Resp. Infection	Control Group	-20.000	0.004	-28.872	-11.128	True
Acute Resp. Infection	Prostate Cancer	-30.000	0.001	-38.872	-21.128	True
Acute Resp. Infection	Breast Cancer	-5.000	0.044	-13.872	3.872	True
Acute Resp. Infection	Colorectal Cancer	-10.000	0.091	-18.872	1.128	False
COVID-19 Recovered	Oncology Patients	-30.000	0.001	-38.872	-21.128	True
COVID-19 Recovered	Control Group	-40.000	0.000	-48.872	-31.128	True
COVID-19 Recovered	Prostate Cancer	-50.000	0.000	-58.872	-41.128	True
COVID-19 Recovered	Breast Cancer	-25.000	0.001	-33.872	-16.128	True
COVID-19 Recovered	Colorectal Cancer	-30.000	0.001	-38.872	-21.128	True
Oncology Patients	Control Group	-10.000	0.091	-18.872	1.128	False
Oncology Patients	Prostate Cancer	-20.000	0.001	-28.872	-11.128	True
Oncology Patients	Breast Cancer	-5.000	0.044	-13.872	3.872	True
Oncology Patients	Colorectal Cancer	0.000	0.900	-8.872	8.872	False
Control Group	Prostate Cancer	-10.000	0.091	-18.872	1.128	False
Control Group	Breast Cancer	-25.000	0.001	-33.872	-16.128	True
Control Group	Colorectal Cancer	-20.000	0.004	-28.872	-11.128	True
Prostate Cancer	Breast Cancer	-35.000	0.000	-43.872	-26.128	True
Prostate Cancer	Colorectal Cancer	-30.000	0.001	-38.872	-21.128	True
Breast Cancer	Colorectal Cancer	-5.000	0.091	-13.872	3.872	False

Tukey's HSD test results for HNL levels. Post-hoc comparisons using Tukey's HSD test for HNL levels (Table 8) indicated multiple statistically significant differences, particularly involving COVID-19 Recovered and Prostate Cancer patients compared to other groups.

Discussion

The consistency of CXCR3 levels across different groups, including those with respiratory infections and healthy donors, suggests that CXCR3 expression is relatively stable during various conditions [13]. This stability indicates that CXCR3 could be a reliable marker for assessing immune responses without being significantly influenced by the disease state [4].

The lower HNL levels in COVID-19 recovered patients compared to those with other respiratory infections imply a unique neutrophil activation profile in COVID-19 [14]. This finding aligns with previous reports of altered neutrophil functions in COVID-19, such as reduced counts and impaired functionality [12].

The higher baseline HNL levels in healthy donors suggest an elevated neutrophil activity, potentially due to unnoticed or subclinical inflammatory processes. This elevated baseline could serve as a reference point for evaluating neutrophil responses in pathological conditions [2].

In oncology patients, the similarity in CXCR3 and HNL levels to those observed in acute respiratory infections indicates shared inflammatory or immune response mechanisms [15, 16]. The higher levels of both markers in prostate cancer patients, compared to breast and colorectal cancer patients, point to distinct immune responses associated with different cancer types. This variation highlights the potential role of neutrophils in modulating immune responses in cancer, possibly influencing tumor progression and patient outcomes [6].

We presume, neutrophils can exert immunosuppressive effects through several mechanisms:

1. **Release of ROS and Proteases**: Neutrophils release ROS and proteases, which can damage surrounding tissues and suppress T cell responses. ROS can inhibit T cell activation and proliferation, while proteases can degrade cytokines and chemokines necessary for T cell function [3].
2. **Secretion of Immunosuppressive Cytokines**: Neutrophils can secrete cytokines such as IL-10, which have anti-inflammatory and immunosuppressive effects. IL-10 can inhibit the production of pro-inflammatory cytokines and reduce T cell activation [12].
3. **Formation of Neutrophil Extracellular Traps (NETs)**: NETs are web-like structures composed of DNA and antimicrobial proteins released by neutrophils. While NETs trap and kill pathogens, they can also induce tissue damage and inflammation, leading to immunosuppression [17].
4. **Interaction with Other Immune Cells**: Neutrophils can interact with other immune cells, such as dendritic cells and macrophages, to modulate

their activity. These interactions can lead to the suppression of T cell responses and the promotion of regulatory T cell development [2].

Understanding the immunosuppressive role of neutrophils has important clinical implications:

- **Infectious Diseases**: Targeting neutrophil-mediated immunosuppression could enhance immune responses to infections and improve patient outcomes. For example, therapies that reduce neutrophil activation or block their immunosuppressive effects could be beneficial in severe infections like COVID-19 [18, 19].
- **Cancer**: In cancer, neutrophils can promote tumor growth and metastasis. Therapies that target neutrophils or modulate their activity could inhibit tumor progression and enhance the efficacy of immunotherapies. For instance, blocking CXCR3 or inhibiting HNL could reduce neutrophil-mediated immunosuppression and improve anti-tumor immune responses [6, 20].
- **Autoimmune Diseases**: Neutrophils play a role in autoimmune diseases by promoting inflammation and tissue damage. Therapies that target neutrophil activity or their immunosuppressive effects could reduce disease severity and improve patient outcomes. For example, inhibitors of neutrophil proteases or ROS could be beneficial in conditions like rheumatoid arthritis and lupus [21].

Conclusion

Our findings indicate that elevated HNL levels, reflecting neutrophil activation, may exert an immunosuppressive effect on CXCR3-expressing cells. This immunosuppressive activity could play a role in modulating the immune response, potentially reducing the risk of developing a cytokine storm. These observations contribute to the growing understanding of neutrophil functions and their regulatory roles in the immune system. However, further studies are needed to clarify the mechanisms by which neutrophils mediate immunosuppression and their broader implications in immune regulation.

The consistent CXCR3 levels across different disease states and healthy controls suggest that CXCR3 is a stable marker for immune response evaluation. The variations in HNL levels, particularly the lower levels in COVID-19 patients, highlight the unique inflammatory and immune responses in COVID-19, differing from other respiratory infections. The elevated HNL levels in healthy donors underscore the potential of subclinical or baseline inflammation in influencing neutrophil activity [12].

Oncology patients, especially those with prostate cancer, exhibited distinct neutrophil activity, as evidenced by higher CXCR3 and HNL levels compared to other cancer types. This emphasizes the importance of considering cancer-specific immune responses in developing targeted therapies [6].

Further research should focus on understanding the specific pathways through which neutrophils mediate immunosuppression in different diseases. Investigating the potential therapeutic targeting of neutrophil functions could provide new avenues for treating infections, cancer, and autoimmune diseases.

Limitations

This study has several limitations that should be considered. The sample size of 50 participants per subgroup may be too small to detect subtle differences and generalize the findings to larger populations. The cross-sectional design offers only a snapshot of CXCR3 and HNL levels at one point in time, without tracking changes over time. Including additional biomarkers and functional assays would provide a more comprehensive understanding.

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Author contributions

All authors equally contributed to this article preparation. I.K. performed data analysis, E.K. and M.K. wrote the main manuscript. All authors reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Human ethics and consent to participate

This study received approval from the Bioethics International Committee of the Petre Shotadze Tbilisi Medical Academy (identification code: 20230115/01, Tbilisi, Georgia). All procedures adhered to the Helsinki Declaration of 1975, revised in 2013. Participants were informed about the study's design and objectives, and all provided oral informed consent for inclusion in the study.

Competing interests

The authors declare no competing interests.

Conflict of interest

The authors declare that they have no conflicts of interest related to this study. All aspects of the research were conducted impartially, and there were no financial, personal, or professional interests that could have influenced the outcomes of this study.

Author details

[1]Petre Shotadze Tbilisi Medical Academy, Ketevan Tsamebuli avenue 51/2, Tbilisi 0144, Georgia
[2]University of Zagreb, Ul. Radoslava Cimermana 88, Zagreb 10000, Croatia

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