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SEARCH FOR EARLY PRECLINICAL IMMUNE MARKERS OF B-CELL LYMPHOPROLIFERATIVE DISORDERS IN BIOBANK-BASED STUDIES: A REVIEW

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Introduction. Early diagnosis of malignant tumors, including those of lymphoid and hematopoietic tissues, is paramount for improving prognosis and survival outcomes. A key strategy for early detection involves the use of sensitive and specific biomarker-based screening tests. The identification of such biomarkers and the subsequent development of novel diagnostic assays can be achieved through the study of large-scale biorepositories.

Objective. To evaluate the feasibility of identifying early preclinical immune markers of B-cell lymphoproliferative disorders in retrospective studies drawing on data from global population-based biobanks.

Discussion. The most frequently identified early preclinical markers for non-Hodgkin lymphomas include sCD23, sCD27, sCD30, and CXCL13, along with several cytokines and their receptors, such as IL-10, TNF- α , sTNF-R2, and sIL-2R α . In multiple myeloma, early preclinical markers comprise IL-10, MIP-1 α , VEGF, and TGF- α . Notably, these biomarkers can be detected more than a decade prior to the clinical onset of B-cell lymphoproliferative disorders. Research into the association between these markers and cancer has been facilitated by population-based biobanks, which enable retrospective analysis following clinical diagnosis. Notable examples include the Janus Serum Bank (Norway), the PLCO biorepository (USA), the UK Biobank (United Kingdom), and repositories in Sweden and other countries.

Conclusions. Analysis of population-based biobank materials represents an effective tool for identifying associations between immune markers and cancer prognosis, thus facilitating the development of novel methods for early diagnosis. The proven success of global biorepositories demonstrates the potential for advancing biobanking infrastructure in Russia, as well as the need for fostering integration and collaboration with leading international institutions.

Keywords: early preclinical markers; biobanks; diagnostic biomarkers; B-cell lymphoproliferative disorders; non-Hodgkin lymphoma; multiple myeloma; immune marker

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ПОИСК ПРЕКЛИНИЧЕСКИХ ДИАГНОСТИЧЕСКИХ ИММУННЫХ МАРКЕРОВ В-КЛЕТОЧНЫХ ЛИМФОПРОЛИФЕРАТИВНЫХ ЗАБОЛЕВАНИЙ В ИССЛЕДОВАНИЯХ С ИСПОЛЬЗОВАНИЕМ БИОБАНКОВ: ОБЗОР

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Введение. Ранняя диагностика злокачественных опухолей, в том числе опухолей лимфоидной и кроветворной ткани, чрезвычайно важна для улучшения прогноза и исхода этих заболеваний. Одним из подходов к выявлению заболеваний на ранних стадиях являются чувствительные и специфичные, основанные на биомаркерах, скрининговые тесты. Установление биомаркеров заболеваний и состояний и создание на их основе новых диагностических тестов может быть реализовано путем исследований глобальных баз данных биологического материала.

Цель. Оценка возможности поиска преклинических диагностических иммунных маркеров В-клеточных лимфопролиферативных заболеваний в ретроспективных исследованиях на основе данных мировых популяционных биобанков.

Обсуждение. Наиболее часто выявляемыми ранними маркерами при неходжкинских лимфомах являются sCD23, sCD27, sCD30, CXCL13, а также ряд цитокинов и их рецепторов, в том числе IL-10, TNF- α и sTNF-R2, sIL-2R α . При множественной миеломе к таким маркерам отнесены IL-10, MIP-1 α , VEGF и TGF- α . Эти маркеры могут быть обнаружены у пациента более чем за 10 лет до дебюта В-клеточных лимфопролиферативных заболеваний. Поиск и изучение взаимосвязи данных маркеров с онкозаболеванием были проведены в популяционных биобанках, позволяющих проводить ретроспективные исследования после появления клинических признаков заболевания, таких как банки сывороток крови Janus (Норвегия), PLCO (США), UK Biobank (Великобритания), а также биобанки Швеции и ряда других стран.

Выводы. Исследование материалов популяционных биобанков является одним из эффективных инструментов для обнаружения связи между иммунными маркерами и прогнозом развития онкозаболевания и разработки новых методов ранней диагностики онкозаболеваний. Таким образом, опыт мировых биобанков свидетельствует о перспективности развития биобанков в России и необходимости их интеграции и сотрудничества с ведущими мировыми биобанками.

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Ключевые слова: ранние преклинические маркеры; диагностические маркеры; биобанки; В-клеточные лимфопрлиферативные заболевания; неходжкинская лимфома; множественная миелома; иммунный маркер

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INTRODUCTION

In 2024, the Russian Federation reported 698,693 new cases of malignant neoplasms, representing a 3.6% increase compared to 2023. Malignancies of lymphoid and hematopoietic tissues accounted for 4.8% of the total cancer incidence. Between 2014 and 2024, the absolute number of newly diagnosed malignant neoplasms of lymphoid and hematopoietic tissues rose from 12,441 to 15,375 cases¹.

Non-Hodgkin lymphomas (NHL) represent a heterogeneous group of malignant lymphoproliferative tumors characterized by diverse biological properties, morphological structures, clinical manifestations, therapeutic responses, and prognoses. B-cell lymphomas, clonal tumors of mature and immature B cells, constitute the majority (80–85%) of NHL cases. Non-Hodgkin lymphoma is most often diagnosed in individuals aged 65–74 years. Globally, the incidence of NHL ranges from 1 to 13 cases in men and from 1 to 7 cases in women per 100,000 population. In the Russian Federation, NHL accounts for 2.6% of all malignant neoplasms, with incidence rates of 8.2 and 7.2 per 100,000 for men and women, respectively. Notably, global NHL detection rates have been rising by 5–10% annually, having increased by more than 50% over the past 20–25 years, a growth rate that substantially outpaces that of Hodgkin lymphoma² [1].

Multiple myeloma is a malignant B-cell lymphoproliferative disorder characterized by clonal proliferation of plasma cells. It accounts for approximately 1% of all malignant tumors and 10–15% of all malignancies of hematopoietic and lymphoid tissues. The disease predominantly affects older individuals, with a median age at diagnosis of approximately 70 years; notably, the prevalence in individuals under 40 years of age does not exceed 2%³ [2].

Early diagnosis of malignant tumors, including those of lymphoid and hematopoietic tissues, is paramount for improving cancer patient outcomes, reducing the economic burden of therapy, and decreasing mortality rates. While early diagnostic protocols have

demonstrated clinical efficacy for several solid tumors (in particular, breast and cervical cancers), their translatability to other pathologies remains limited. The insufficient sensitivity and specificity of existing screening systems hinder their effective implementation for lymphoid and hematopoietic malignant neoplasms. Therefore, the search for novel biomarkers for various groups of cancers, as well as the development of a methodology for such a search, remains highly relevant. A promising approach to addressing this challenge lies in the use of biological materials stored in large biobanks⁴.

This study was aimed at evaluating the feasibility of identifying early preclinical immune markers of B-cell lymphoproliferative disorders in retrospective studies drawing on data from global biobanks.

A literature search was performed across Russian (eLIBRARY.RU, CyberLeninka) and English (Web of Science, Scopus, PubMed) databases, covering a 25-year period. Search queries included the following keywords: biobank, B-cell lymphoproliferative disorders, multiple myeloma, non-Hodgkin lymphoma, early preclinical (pre-diagnostic) markers, and plasma immune markers. Inclusion criteria were defined as the availability of data from studies that retrospectively compared patients with B-cell lymphoproliferative disorders to healthy controls matched for key characteristics.

Early preclinical markers refer to measurable laboratory parameters whose changes can be retrospectively identified in blood samples collected years prior to the clinical manifestation of the disease. This review focuses on markers detectable in blood plasma.

MAIN BODY

Blood biobanks

Markers that facilitate tumor detection at early stages, ideally prior to clinical manifestation, represent one of the most promising tools for improving prognosis in malignant neoplasms⁵ [3]. A critical question in this

¹ Kaprin AD, Starinsky VV, Shakhzadova AO, eds. *Malignant neoplasms in Russia in 2024 (incidence)*. Moscow: Hertsen MORI; 2025.

² Rukavitsyn OA. Hematology. National Guideline. Moscow: GEOTAR-Media; 2024.

³ Bessmeltsev SS, Sidorkevich SV. Federal Hematology Guideline. Moscow: SIMK; 2024.

⁴ Biobanking: National Guideline. Moscow: Triumph; 2022.

field is how long before a formal diagnosis these molecular changes can be reliably detected. Addressing such questions requires extensive sample repositories; consequently, large biobanks have been established worldwide, particularly over the past 20 years. In line with this global trend, the National Association of Biobanks and Biobanking Specialists was established in Russia in 2018, uniting over 20 biobanks and fostering their integration into the international community [4].

Among the world's largest and longest-established biobanks, the Janus Serum Bank (Oslo, Norway) stands out. It is a population-based biobank established for cancer research: it contains blood samples and medical examination data from 292,850 individuals who participated in major national studies conducted between 1972 and 2004 [5]. A primary advantage of the Janus Bank is its extensive sample size combined with the long storage and follow-up period, which allows for the selection of well-matched controls, even under stringent criteria. This capacity to identify matched pairs is critical for case-control studies, where each pair consists of a cancer patient and a healthy participant who remained cancer-free throughout the study period. Furthermore, the availability of repeated samples from participants enables the tracking of biomarker fluctuations over time during the pre-diagnostic stage.

The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer study conducted in the United States between 1993 and 2001 included 74,000 participants (37,000 men and 37,000 women aged 55–74 years) who underwent specific cancer screening, while a similar number of participants received usual medical care as a control group. This study offers a unique opportunity to investigate the etiology of cancer and other diseases, as well as to evaluate potential molecular markers at early stages of the disease. Beyond biological sample collection, the participants were surveyed to obtain information on medical history, familial cancer predisposition, medication use, and other risk factors. Notably, serum samples were collected during five subsequent annual screening examinations. Cancer incidence was monitored via annual follow-up questionnaires, with mortality data recorded through vital status tracking [6]. Detailed descriptions of the PLCO study are available in [7–9].

A number of biobanks in other countries operate on similar principles. In particular, the Northern Sweden Health and Disease Study (NSHDS), initiated in the mid-1980s, is a prospective longitudinal cohort study encompassing over 140,000 participants from two northern regions of Sweden. This repository comprises more than 240,000 blood samples and represents 1.5 million person-years of follow-up [10].

Prognostic immune markers of lymphoid malignancies

Certain subtypes of lymphoid malignancies are preceded by identifiable precursor conditions that manifest several years before clinical symptoms emerge. Examples include monoclonal B-cell lymphocytosis as a precursor to chronic lymphocytic leukemia; circulating t(14;18)-positive B-cells prior to the development of follicular lymphoma; non-IgM monoclonal gammopathy of undetermined significance preceding multiple myeloma; and IgM-MGUS as a precursor to Waldenström macroglobulinemia [11–13]. While pronounced immune dysregulation is a recognized risk factor for these conditions, the significance of subclinical immunological changes remains poorly understood. The detection of early pre-clinical signs, spanning several years or even several decades, alongside changes in biomarkers of cellular activation and inflammation, suggests a prolonged period of indolent progression. Studying the early stages of lymphoid neoplasm development may provide critical insights into disease etiology and the biological drivers of malignant transformation [14].

Non-Hodgkin lymphomas. Emerging evidence suggests an association between circulating markers of immune activation (specifically sCD27, sCD30, and CXCL13) and the overall risk of NHL. However, studies into specific NHL subtypes have been constrained by limited sample sizes. To address this, Rhee et al. [15] performed a pooled analysis of eight studies encompassing 3,310 patients with various NHL subtypes. The analysis included patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL, $n = 623$), diffuse large B-cell lymphoma (DLBCL; $n = 621$), follicular lymphoma ($n = 398$), marginal zone lymphoma ($n = 138$), mantle cell lymphoma ($n = 82$), and T-cell lymphoma ($n = 92$). This analysis revealed associations between DLBCL and elevated levels of sCD27, sCD30, and CXCL13. Associations with sCD27 levels were observed in CLL/SLL, marginal zone lymphoma, and T-cell lymphoma, while follicular lymphoma showed a correlation with sCD30. Notably, when stratified by the time from blood collection to diagnosis, the associations of T-cell lymphoma with sCD27 and the associations of DLBCL with all three markers remained consistent across observation periods of varying duration (<7.5 and ≥ 7.5 years). For other NHL subtypes, particularly indolent lymphomas, the correlations with the studied soluble markers are more pronounced in samples collected closer to the time of clinical manifestation [15].

A study comparing baseline serum levels of 67 immune and inflammatory markers in 301 NHL patients, diagnosed five or more years after sample collection, with a control group revealed a statistically significant

⁵ Vale AJ, Filho IA, Pinheiro FI, de Azevedo P, Guzen FP, Cobucci RN. Role of tumor markers in early detection and prevention of complications in oncology. In: Rezaei N, ed. *Handbook of Cancer and Immunology*. Springer Nature Switzerland AG; 2025. https://doi.org/10.1007/978-3-030-80962-1_324-1

association of NHL with elevated levels of B-cell-attracting chemokine 1 (BCA-1 also known as CXCL13), soluble tumor necrosis factor receptor 2 (sTNF-R2), and soluble vascular endothelial growth factor receptor 2 (sVEGFR2). Notably, elevations in these markers were detected well in advance of NHL diagnosis [16].

Sustained B-cell activation is a key mechanism contributing to NHL development. Elevated pre-diagnostic serum levels of immune activation markers, such as sCD27 and sCD30, are associated with the risk of this disease. An increase in serum sCD27 levels as the disease progresses has also been documented in patients with advanced chronic lymphocytic leukemia [17]. However, the analysis of only a single sample from each participant limits etiological inferences. Using the Janus Serum Bank, which provides two serial samples collected on average five years apart, enabled the analysis of markers in 422 NHL patients (including subgroups by NHL subtype) and 434 controls. The longitudinal analysis revealed that CLL/SLL was associated with elevated sCD27 levels only in the later sample, whereas follicular lymphoma was linked to elevated sCD30 levels in both samples. In the pooled analysis, NHL patients frequently transitioned from below-median sCD27 levels in early samples to above-median levels in later samples. In follicular lymphoma patients, sCD30 levels remained above the median in both samples. These findings suggest that sCD27 reflects disease-induced changes, while sCD30 may serve as a marker of increased susceptibility to follicular lymphoma [18].

In another study aimed at validating B-cell activation markers for NHL risk prediction, Saberi Hosnijeh et al. [19] evaluated serum levels of sCD23, sCD27, sCD30, and CXCL13 in 517 NHL patients and 525 control subjects. While all markers initially correlated with an increased risk of CLL, follicular lymphoma, and DLBCL, mutual adjustment for other immune markers revealed that sCD23 retained its association with all disease subtypes, whereas CXCL13 remained specifically associated with follicular lymphoma and DLBCL. Notably, the associations of sCD23 with CLL and DLBCL, as well as CXCL13 with DLBCL, persisted in samples collected more than nine years prior to diagnosis. Furthermore, sCD23 demonstrated strong predictive value for CLL, particularly in older male participants. Interestingly, sCD23 and CXCL13 were found to mediate the association between body mass index and DLBCL risk, while CXCL13 contributed to the inverse association between physical activity and DLBCL development [19].

Within the European Prospective Investigation into Cancer and Nutrition project, a large-scale prospective cohort study evaluated the levels of markers associated with early lymphoid malignancy pathogenesis (sB-CMA, CXCL13, sCD23, CD28, CD72, FCRL1, FCRL3, SEMA4A, and SEMA7A). A total of 6,412 circulating proteins were assessed in 4,565 participants. Analysis of

identified 484 cases of lymphoid malignancies revealed key pre-diagnostic serum markers: CD72, CD28, and SLAMF6 for CLL; FDCSP, CD72, CD28, LAG3, and INSL4 for DLBCL; FDCSP, CD72, and CD28 for FL; and TACI and FCRLB for multiple myeloma. The predominance of cell-surface proteins among markers associated with lymphoid malignancy risk raises questions as to whether these proteins are actively secreted or represent membrane shedding by malignant or pre-malignant cells. While the utility of a protein as a risk factor does not strictly depend on its origin, understanding the mechanism underlying these changes in circulating molecule levels is essential for the future interpretation of such fluctuations in the diagnosis of lymphoid malignancies [14].

As expected, certain identified protein-lymphoma associations were consistent with previous findings. Specifically, serum sCD23 has previously been linked to the early development of B-cell lymphomas, particularly CLL, while CXCL13 is associated with DLBCL risk. For instance, a study of 170 individuals who provided two blood samples prior to diagnosis and 170 matched healthy controls from the NSHDS biobank evaluated the associations between lymphoma risk and marker levels at baseline, at the time of repeated sample collection, and their rate of change. Notably, strong associations of CXCL13, sCD23, sCD27, and sCD30 with lymphoma risk were observed even in blood samples collected 15–25 years prior to diagnosis. While marker levels remained stable in the control group, they exhibited an increase over time in individuals who subsequently developed lymphoma. The strongest correlations were observed for indolent lymphoma subtypes, with a pronounced association between sCD23 and CLL. Among aggressive lymphomas, the association between risk and the rate of change was limited to CXCL13 for DLBCL. These findings suggest that B-cell activation plays a role in the early stages of various B-cell lymphoma subtypes. Furthermore, these biomarkers demonstrate potential for predicting an early occult form of the disease and/or could enhance screening and monitoring strategies for indolent lymphoma in individual patients [20].

The association of circulating cytokine levels and other immune markers with the subsequent risk of NHL was also investigated within the PLCO trial [18]. Pre-diagnostic serum samples from 297 patients with newly diagnosed NHL and 297 matched controls were analyzed for levels of individual cytokines (IL-4, IL-6, IL-10, and TNF- α) and other immune markers, including soluble TNF receptors (sTNF-R1 and sTNF-R2), C-reactive protein, and sCD27. Elevated serum levels of sTNF-R1 ($p = 0.02$) and sCD27 ($p < 0.0001$) were significantly associated with NHL risk. Notably, these associations persisted for cases diagnosed more than six years after blood collection (sTNF-R1, $p = 0.01$; sCD27,

$p = 0.0001$). While elevated IL-10, TNF- α , and sTNF-R2 were also initially linked to increased overall NHL risk, these associations weakened over time and were no longer significant for cases diagnosed more than six years after blood collection. These findings regarding sTNF-R1 and sCD27 (potential indicators of inflammation and B-cell stimulation, respectively) support the role of subclinical inflammation and chronic B-cell stimulation in lymphomagenesis [21].

Previously, the same authors examined 234 individuals who developed NHL and 234 control subjects. The researchers reported a strong dose-response relationship between pre-diagnostic sCD30 concentrations and NHL risk ($p < 0.001$). This association persisted for cases diagnosed six to ten years after blood sample collection [22].

By the end of the follow-up period, 297 NHL cases were identified among 54,829 participants in the screening group (inclusion required the absence of malignancy during the first year of follow-up). The control group was individually matched to the case group in a 1:1 ratio based on age at study entry (within five years), sex, race, PLCO study center, and baseline blood draw date (within three months) among subjects with no malignancies other than non-melanoma skin cancer at the time of diagnosis. The number of individuals with elevated levels of IL-10, TNF- α , sTNF-R1, sTNF-R2, and sCD27 in the NHL group was significantly higher compared to the matched controls (p -values ranging from 0.003 to <0.0001). Conversely, the levels of IL-4, IL-6, and CRP did not differ between the two groups [21].

The association of inflammatory markers and adipokines with the NHL risk was investigated under the hypothesis that immune dysfunction underlies disease development, and obesity and chronic inflammation may play a role in its etiology [23]. In a multiethnic cohort study (272 NHL cases and 541 matched controls), with a median follow-up of 2.7 years from blood collection to diagnosis, IL-10 levels were found to be significantly associated with NHL risk ($p < 0.001$). While TNF- α and IL-8 showed borderline elevated risk, no associations were found for IFN- γ , IL-1 β , IL-2, IL-4, IL-5, IL-6, and CRP. Leptin (but not adiponectin) was linked to NHL risk ($p < 0.001$). Adjustment for body mass index did not substantially affect the risk estimates. Subtype stratification revealed significant correlations of IL-10 and leptin with follicular lymphoma, but not DLBCL. Notably, excluding cases diagnosed within one year after blood collection weakened all associations. Thus, IL-10 and leptin were the only cytokine and adipokine, respectively, associated with NHL; however, given the short follow-up period, the influence of preclinical effects on these markers could not be ruled out. While markers of inflammation and obesity may provide new insights into the etiology of

NHL, they need to be assessed many years prior to clinical diagnosis [23].

In another study analyzing serum samples from the US Department of Defense Serum Repository [24], elevated levels of sCD30, CXCL13, and, to a lesser extent, IL-10 were also associated with the subsequent development of follicular lymphoma and DLBCL. Compared to the control group, the median follow-up period from the first sample collection to diagnosis was 5.5 years. Notably, a significant increase in sCD30 and CXCL13 levels was observed from the earliest time points, whereas IL-10 levels rose significantly only as the date of diagnosis approached.

Chronic inflammation leads to the continuous release of various mediators. Cytokines of the TNF- α family and IL-6 play pivotal roles in mediating inflammation, whereas IL-10 is characterized by its anti-inflammatory functions. TGF exhibits broad biological activity in tumor invasion, cell proliferation, and adhesion, while CXCL13 is involved in the accumulation of malignant B-cells [25]. Given the association of inflammatory processes and B-cell hyperactivation with NHL development, a prospective analysis was conducted within the Nurses' Health Study and the Health Professionals Follow-up Study to further investigate the profiles of plasma immune markers [26]. The authors identified 598 newly diagnosed lymphoma cases and compared them with 601 matched controls using archived pre-diagnostic plasma samples. Levels of 13 immune markers were measured via multiplex immunoassay, with stratification by time to diagnosis (<5 , 5–10, and ≥ 10 years). Positive associations with overall NHL and specific subtypes were established for sIL-2R α , CXCL13, sCD30, and sTNF-R2. Conversely, a negative association was found for B-cell activating factor (BAFF), a member of the TNF ligand superfamily also known as CD257. While biomarker combinations independently associated with lymphoma varied by subtype and time since collection, the unexpected inverse association between BAFF and CLL/SLL risk persisted for more than ten years. Thus, immune system activation precedes NHL diagnosis by at least several years, and a decrease in BAFF levels may serve as an early indicator of CLL development long before diagnosis [26].

Profound immune suppression is a serious risk factor for NHL development, while B-cell activation and inflammation are associated with an increased risk of AIDS-related NHL. In HIV-positive individuals, elevated pre-diagnosis plasma levels of B-cell stimulation markers (CXCL13, IL-6, and sCD30) serve as predictive biomarkers for the development of AIDS-related NHL. In some instances, elevated levels of these markers were observed as early as five years prior to diagnosis [27].

Some of these markers have also demonstrated an association with NHL risk in immunocompetent

individuals within prospective studies. Interestingly, plasma sCD30 levels were positively associated with the risk of developing NHL 6–10 [13] and even 15–23 years prior to diagnosis [28]. In another small cohort study, a significant (2.5-fold) increase in NHL risk was found in women with elevated levels of sIL-2R α (a marker of T-cell activation and increased IL-2 levels), as well as a small but significant increase in NHL risk for those with higher pre-diagnosis levels of TNF- α and sTNF-R2 [29]. Collectively, these results suggest that chronic B-cell stimulation plays a role in lymphomagenesis in immunocompetent individuals.

In recent years, research has focused on the study of microRNAs, which play a pivotal role in regulating immunological reactions, including the development, maturation, activation, function, and aging of various immune cells [30]. Findings by Abu-Halima et al. [31] indicate that malignancy may be detected via serum microRNA analysis decades prior to clinical manifestations. Given that CLL was the first human malignancy linked to microRNA dysfunction [32], identifying these markers long before the onset of clinical symptoms is of paramount importance.

Multiple myeloma. Multiple myeloma is often preceded by monoclonal gammopathy of undetermined significance (MGUS). Although only a minority of MGUS patients progress to multiple myeloma, accurately predicting this transition using standard clinical biomarkers remains a challenge. In a large prospective population-based screening study involving over 75,000 individuals, 3,725 (4.9%) were identified with monoclonal gammopathy. Following a three-year follow-up period, 194 of these individuals progressed to multiple myeloma or another lymphoproliferative disorder [33].

Data regarding certain potential biomarkers, including monocyte chemoattractant protein-3 (MCP-3), macrophage inflammatory protein-1 α (MIP-1 α), fibroblast growth factor-2 (FGF-2), VEGF, fractalkine, and transforming growth factor- α (TGF- α), remain conflicting. To evaluate the association between the serum levels of these biomarkers and the subsequent risk of multiple myeloma, as well as their longitudinal dynamics, a study was conducted using prospective samples from the Janus Serum Bank [34]. This study included 293 patients who subsequently developed multiple myeloma, with serum samples collected up to 20 years (median) prior to diagnosis, alongside 293 matched healthy controls. For multiple myeloma patients, additional samples collected up to 20 years prior to diagnosis were available to assess marker dynamics. Statistical analysis focused on markers with detection rates >60% (MIP-1 α , VEGF, and TGF- α). While no statistically significant associations were found between the risk of developing multiple myeloma and the levels of these markers in serum samples

collected up to 20 years prior to diagnosis, TGF- α levels significantly declined in multiple myeloma patients as the time to diagnosis decreased ($p < 0.001$). The authors suggest that this decline may reflect subtle changes in the microenvironment associated with multiple myeloma progression [34].

Within the PLCO trial, the concentrations of 45 immunological and pro-angiogenic markers were measured in serum from multiple myeloma patients ($n = 241$), individuals with stable MGUS ($n = 441$), and MGUS-free controls ($n = 258$) [21]. The researchers showed that the levels of six markers (EGF, HGF, Ang-2, CXCL12, CCL8, and BMP-9) were statistically significantly elevated in multiple myeloma patients compared to the MGUS-free control group, with a false discovery rate of 10%. Of these, three angiogenic markers were associated with subsequent progression from MGUS to multiple myeloma: EGF ($p = 0.00028$), HGF ($p = 0.015$), and Ang-2 ($p = 0.07$) [35].

In a prospective analysis of samples within the European Prospective Investigation into Cancer and Nutrition study, associations were observed between the risk of multiple myeloma and low circulating levels of MCP-3, MIP-1 α , FGF-2, VEGF, fractalkine, and TGF- α [36].

Analyzing data collected over ten years from a large prospective cohort within the UK Biobank project (378,930 individuals, 980 of whom developed multiple myeloma during follow-up), Bingjie et al. showed that the laboratory CRAB features (calcium elevation, renal impairment, anemia, and bone lesions) characteristic of this disease precede full clinical manifestation by several years [37].

Recently, research has also focused on the early detection of systemic pre-cancerous changes using complete blood count parameters: the neutrophil-to-lymphocyte ratio, the platelet-to-lymphocyte ratio, and the red cell distribution width. Changes in these parameters may be caused by persistent inflammation within the pre-malignant tissue microenvironment, manifesting several years prior to the clinical onset of hematologic malignancies [38–40].

The data presented above are summarized in the table.

CONCLUSIONS

Immune markers of B-cell lymphoproliferative disorders can be detected in plasma more than a decade prior to clinical onset, as evidenced by studies using biorepositories such as Janus (Norway), PLCO (USA), and UK Biobank (United Kingdom), as well as biobanks established in Sweden and several other countries. For NHL, the most common prognostic markers include sCD23, sCD27, sCD30, and CXCL13, alongside a number of cytokines and their receptors,

Table. Changes in the levels of early preclinical immune markers in B-cell lymphoproliferative disorders

Marker	Disorder	Direction of change	Reference
sCD23	Non-Hodgkin lymphoma	↑	[20]
	Chronic lymphocytic leukemia	↑	[19], [20]
	Follicular lymphoma, diffuse large B-cell lymphoma	↑	[19]
sCD27	Non-Hodgkin lymphoma	↑	[16], [20], [21]
	Diffuse large B-cell lymphoma	↑	[15]
sCD30	Non-Hodgkin lymphoma	↑	[15], [20], [22], [26], [28]
	Non-Hodgkin lymphoma in HIV-positive individuals	↑	[27]
	Diffuse large B-cell lymphoma	↑	[15], [24]
	Follicular lymphoma	↑	[15], [18], [24]
CXCL13	Non-Hodgkin lymphoma	↑	[20], [26], [27]
	Non-Hodgkin lymphoma in HIV-positive individuals	↑	[27]
	Diffuse large B-cell lymphoma	↑	[15], [19], [24]
	Follicular lymphoma	↑	[19], [24]
TNF-α	Non-Hodgkin lymphoma	↑	[21], [25]
	Non-Hodgkin lymphoma in women	↑	[29]
sTNF-R1	Non-Hodgkin lymphoma	↑	[21]
sTNF-R2	Non-Hodgkin lymphoma	↑	[16], [21], [26]
	Non-Hodgkin lymphoma in women	↑	[29]
IL-2	Non-Hodgkin lymphoma in women	↑	[29]
sIL-2Rα	Non-Hodgkin lymphoma	↑	[26]
	Non-Hodgkin lymphoma in women	↑	[29]
IL-6	Non-Hodgkin lymphoma in HIV-positive individuals	↑	[27]
IL-8	Non-Hodgkin lymphoma (borderline risk)	↑	[23]
IL-10	Non-Hodgkin lymphoma	↑	[21]
	Follicular lymphoma	↑	[23], [24]
	Diffuse large B-cell lymphoma	↑	[24]
TGF-α	Multiple myeloma	↓	[34], [36]
BCA-1, sVEGFR2	Non-Hodgkin lymphoma	↑	[16]
BAFF (B-cell activating factor)	Non-Hodgkin lymphoma, chronic lymphocytic leukemia	↓	[26]
EGF, HGF, Ang-2, CXCL12, CCL8, BMP-9	Multiple myeloma	↑	[25]
MCP-3, MIP-1α, FGF-2, VEGF, fractalkine	Multiple myeloma	↓	[35]
Leptin	Follicular lymphoma	↑	[23]

Table compiled by the authors based on data from literature sources

Note: ↑ — increase; ↓ — decrease.

including IL-10, TNF- α , sTNF-R2, and sIL-2R α . For multiple myeloma, these include IL-10, MIP-1 α , VEGF, and TGF- α . The conducted analysis demonstrates the pivotal role of biobanks that collect and store blood samples long-term in the discovery of novel biomarkers for hematological malignancies. While the stage at which irreversible malignant transformation occurs

remains to be elucidated, the pathogenetic significance of the established changes is substantial. The identification and clinical integration of novel plasma immune markers for early diagnosis hold the potential to improve diagnosis and treatment outcomes for cancer patients, alleviate the economic burden of cancer care, and reduce cancer mortality.

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