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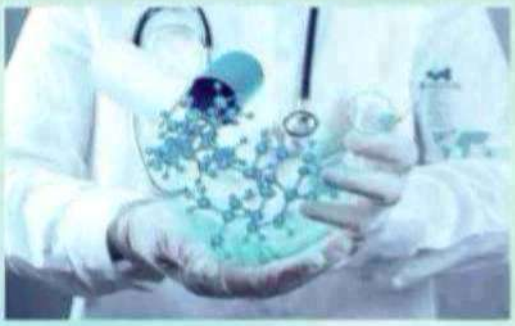

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ANALYSIS OF HEMATOLOGICAL INDICES OF SYSTEMIC INFLAMMATION IN THYROID CANCER

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✓ ***Resume***

In patients with thyroid cancer (TC), a statistically significant increase in all studied hematological indices of systemic inflammation was observed even at the early stages of the disease compared to practically healthy individuals. At the early stages of TC, the SIRI increased by 2.85 times, AISI by 2.79 times, and dNLR by 3.36 times relative to the control group. At advanced stages of the disease, the index values increased even more significantly: SIRI exceeded the norm by 7.12 times, AISI by 6.52 times, and dNLR by 9.31 times. Statistically significant differences were found between the early and advanced stages of the disease: SIRI increased by 2.50 times, AISI by 2.34 times, and dNLR by 2.77 times. The dNLR demonstrated the most pronounced association with tumor progression, which allows considering it as the most sensitive hematological marker of the clinical severity of TC. The obtained results confirm the high diagnostic and prognostic value of SIRI, AISI, and dNLR. Their determination based on a standard complete blood count can be utilized for the early assessment of tumor biological aggressiveness, prediction of clinical severity and metastasis risk, and personalization of treatment strategies in TC patients.

Keywords: thyroid cancer, complete blood count, hematological indices, systemic inflammation, oncological process prediction.

АНАЛИЗ ГЕМАТОЛОГИЧЕСКИХ ПОКАЗАТЕЛЕЙ СИСТЕМНОГО ВОСПАЛЕНИЯ ПРИ РАКЕ ЩИТОВИДНОЙ ЖЕЛЕЗЫ

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✓ ***Резюме***

У пациентов с раком щитовидной железы (РЩЖ) наблюдалось статистически значимое повышение всех изученных гематологических показателей системного воспаления уже на ранних стадиях заболевания по сравнению с практически здоровыми людьми. На ранних стадиях РЩЖ SIRI увеличился в 2,85 раза, AISI — в 2,79 раза, а dNLR — в 3,36 раза относительно контрольной группы. На поздних стадиях заболевания значения индексов увеличивались еще более значимо: SIRI превышал норму в 7,12 раза, AISI — в 6,52 раза, а dNLR — в 9,31 раза. Были выявлены статистически значимые различия между ранними и поздними стадиями заболевания: SIRI увеличился в 2,50 раза, AISI — в 2,34 раза, а dNLR — в 2,77 раза. dNLR показал наиболее выраженную связь с прогрессированием опухоли, что позволяет рассматривать его как самый чувствительный гематологический маркер клинической тяжести РЩЖ. Полученные результаты подтверждают высокую диагностическую и прогностическую ценность SIRI, AISI и dNLR.

Их определение на основе стандартного общего анализа крови может использоваться для ранней оценки биологической агрессивности опухоли, прогнозирования тяжести течения болезни и риска метастазов, а также для персонализации стратегий лечения у пациентов с раком щитовидной железы.

Ключевые слова: рак щитовидной железы, общий анализ крови, гематологические показатели, системное воспаление, прогнозирование онкологического процесса.

QON GEMATOLOGIK KO‘RSATKICHLARINI QALQON BEZI SARATONIDAGI SISTEMALI YALQINANISH BO‘YICHA TAHLIKASI

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✓ ***Rezyume***

Qalqoncha bezi saratoni (TC) bo‘lgan bemorlarda, kasallikning dastlabki bosqichlarida ham tizimli yallig‘lanishning barcha o‘rganilgan gematologik ko‘rsatkichlarida statistika jihatdan sezilarli ortish qayd etildi, bu esa amalda sog‘lom odamlar bilan solishtirganda kuzatiladi. TCning dastlabki bosqichlarida SIRI 2,85 martaga, AISI 2,79 martaga va dNLR 3,36 martaga o‘sdi. Kasallikning rivojlangan bosqichlarida esa indeks qiymatlari yanada kengroq oshdi: SIRI normadan 7,12 martaga, AISI 6,52 martaga va dNLR 9,31 martaga oshdi. Kasallikning dastlabki va rivojlangan bosqichlari orasida statistik jihatdan sezilarli farqlar aniqlangan: SIRI 2,50 martaga, AISI 2,34 martaga va dNLR 2,77 martaga oshdi. dNLR o‘smaning rivojlanishi bilan eng aniq bog‘liqlikni ko‘rsatdi, bu esa uni TC klinik og‘irligini aniqlaydigan eng sezgir gematologik marker sifatida ko‘rib chiqish imkonini beradi. Olingan natijalar SIRI, AISI va dNLRning yuqori diagnostik va prognostik qiymatini tasdiqlaydi.

Ularning standart to‘liq qon hisoblashga asoslangan aniqlanishi, TC bemorlarida saratonning biologik agressivligini erta baholash, klinik og‘irligini va metastaz xavfini oldindan aytish hamda davolash strategiyalarini shaxsiylashtirish uchun ishlatilishi mumkin.

Kalit so‘zlar: qalqonsimon bez saratoni, to‘liq qon hisobi, gematologik ko‘rsatkichlar, tizimli yallig‘lanish, onkologik jarayonni bashorat qilish.

Relevance

Thyroid cancer (TC) is the most common malignant neoplasm of the endocrine system and ranks among the leading oncological diseases in terms of incidence growth rates. Despite a predominantly favorable prognosis for highly differentiated tumor forms, a significant proportion of patients present with regional lymphogenous metastases, extrathyroidal extension, disease recurrence, and, in certain cases, distant metastasis, which substantially compromises treatment outcomes and the patients' quality of life [1, 3, 4, 7].

Consequently, one of the pressing challenges in contemporary oncoendocrinology is the search for accessible, informative, and cost-effective biomarkers that enable the timely prediction of tumor aggressiveness at the initial diagnostic stage.

In recent years, particular attention has been directed toward the role of systemic inflammation in carcinogenesis, tumor progression, and the formation of metastatic potential. Chronic inflammation facilitates the activation of angiogenesis, remodeling of the tumor microenvironment, suppression of the antitumor immune response, potentiation of epithelial-mesenchymal transition, and the development of invasive growth. Quantitative alterations in peripheral blood cells reflect the severity of the host's systemic inflammatory response and can serve as surrogate markers of the tumor's biological activity [1, 2, 5, 11, 13].

In this regard, integral hematological indices of systemic inflammation calculated from a standard complete blood count—such as the Systemic Inflammation Response Index (SIRI), Aggregate Index of Systemic Inflammation (AISI), Derived Neutrophil-to-Lymphocyte Ratio (dNLR), as well as the Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), and Systemic Immune-Inflammation Index (SII)—are garnering increasing scientific and practical interest [2, 7, 12, 15]. These parameters comprehensively reflect the dynamic interplay among neutrophils, lymphocytes, monocytes, and platelets, characterizing the balance between pro-inflammatory mechanisms and antitumor immunity.

Numerous recent studies indicate that elevated values of SIRI, AISI, and dNLR are associated with adverse clinical and morphological characteristics of thyroid cancer, including larger tumor size, extrathyroidal extension, regional lymph node involvement, vascular invasion, advanced TNM stages, and an increased risk of recurrence. Furthermore, these indices demonstrate substantial potential as independent prognostic factors for both recurrence-free and overall survival [3, 8, 15, 17].

Of particular practical value is the fact that these hematological indices are derived from routine complete blood counts, do not require expensive laboratory assays, are readily available across all tiers of healthcare, and can be utilized repeatedly for dynamic patient monitoring. Integrating these indices into the preoperative diagnostic algorithm enhances the accuracy of risk stratification, facilitates the timely identification of patients likely to exhibit an aggressive disease course, optimizes the extent of surgical intervention (including the necessity for extended lymph node dissection), and personalizes postoperative surveillance and therapeutic strategies [14, 17, 20, 21].

Thus, investigating hematological indices of systemic inflammation in thyroid cancer represents a highly relevant avenue in modern clinical oncology. Exploring the diagnostic and prognostic significance of SIRI, AISI, dNLR, and other integral inflammatory indices will expand the capabilities for early prediction of clinical severity, metastasis, and recurrence risks, thereby advancing personalized management approaches for patients with thyroid cancer [6, 8, 14, 20].

The objective of this study is to investigate the principal hematological indices of systemic inflammation in patients with thyroid cancer.

Materials and methods

A total of 93 patients with various stages of thyroid cancer were enrolled and monitored from 2019 to 2026. Inclusion criteria: Adult patients (aged 18 and older) with morphologically confirmed TC.

Exclusion criteria: HIV/AIDS, malignancies of other localizations, exacerbations of autoimmune, allergic, and other infectious diseases (including viral hepatitis B and C), and pregnancy.

Based on hematological analyses, the following indices were investigated: SIRI, AISI, and dNLR.

SIRI (Systemic Inflammation Response Index): calculated as (Neutrophils × Monocytes) / Lymphocytes.AISI (Aggregate Index of Systemic Inflammation): calculated as (Neutrophils × Monocytes × Platelets) / Lymphocytes. dNLR (Derived Neutrophil-to-Lymphocyte Ratio): calculated

as Neutrophils / (White Blood Cells − Neutrophils). These indices reflect the severity of the systemic inflammatory response and the balance between innate and adaptive immunity, positioning them as promising diagnostic and prognostic biomarkers across various malignancies, including thyroid cancer.

Results and discussions

Despite significant strides in developing comprehensive diagnostic and therapeutic principles, the early diagnosis of thyroid cancer remains a critical priority. Elucidating the immunopathological mechanisms underlying TC pathogenesis will pave the way for novel diagnostic paradigms [1, 3, 9, 12].

Currently, significant emphasis in thyroid carcinogenesis is placed on immune reactions, the evaluation of which is vital for diagnosis, treatment, and prognosis. In clinical practice and research, there is a growing reliance on accessible laboratory diagnostics—utilizing not only standard complete blood count (CBC) parameters but also inflammatory indices to predict tumor aggressiveness, metastasis risk, recurrence, survival, and treatment response.

The following sections will present the primary values and systemic inflammation indices that hold significant prognostic value in TC. Table 1 presents the results of the evaluation of hematological systemic inflammation indices across all TC patients.

Table 1. Results of the principal hematological indices of systemic inflammation in thyroid cancer

GROUPS	SIRI (Systemic Inflammation Response Index)	AISI (Aggregate Index of Systemic Inflammation)	dNLR (Derived Neutrophil-to-Lymphocyte Ratio)
TC Patients	1.37 ± 0.85 *	595.92 ± 0.45 *	3.45 ± 1.45 *
Control (Norm)	0.33 ± 0.02	120.4 ± 9.40	0.55 ± 0.04

*Note: * - statistically significant differences compared to the control group (norm).*

An analysis of the principal hematological indices of systemic inflammation revealed that patients with thyroid cancer (TC) exhibit a statistically significant increase in all evaluated parameters compared to the cohort of practically healthy individuals. The most pronounced alterations were registered for the Aggregate Index of Systemic Inflammation (AISI). Its mean value in TC patients was 595.92 ± 0.45, whereas in the control group, this indicator was 120.4 ± 9.40. Consequently, AISI increased by 4.95 times (595.92 / 120.4 = 4.95; $p<0.05$), indicating a robust activation of the systemic inflammatory response accompanying the neoplastic process.

The Systemic Inflammation Response Index (SIRI) was also found to be significantly elevated in TC patients. Its mean value was 1.37 ± 0.85, compared to 0.33 ± 0.02 in healthy individuals. Thus, SIRI increased by 4.15 times relative to the control ($p<0.05$). The elevation of this index reflects a concurrent increase in the counts of neutrophils and monocytes against a backdrop of a relative decline in lymphocytes, characterizing a predominance of the pro-inflammatory response and an attenuation of antitumor immune surveillance.

A similar trend was identified when analyzing the derived Neutrophil-to-Lymphocyte Ratio (dNLR). In TC patients, its value reached 3.45 ± 1.45, while in the control group, it was only 0.55 ± 0.04. Therefore, the dNLR parameter was 6.27 times higher than in practically healthy individuals ($p<0.05$), representing the most pronounced relative increase among all the investigated indices.

The obtained results signify a profound activation of systemic inflammation in patients with thyroid cancer. The greatest relative increase was noted for dNLR (6.27-fold), followed by AISI (4.95-fold) and SIRI (4.15-fold).

These data corroborate the contemporary paradigm regarding the leading role of systemic inflammation in the pathogenesis and progression of thyroid cancer. The oncological process is accompanied by the activation of innate immunity, an increase in the levels of neutrophils, monocytes, and platelets, as well as a relative reduction in the lymphocyte count, which is reflected in the elevation of integral hematological inflammatory indices.

The 4.15-fold increase in SIRI indicates enhanced activity of the neutrophil-monocyte branch of the immune system. It is well established that neutrophils secrete pro-inflammatory cytokines (IL-1β, IL-6, TNF-α), reactive oxygen species, matrix metalloproteinases, and vascular endothelial growth factor

(VEGF), thereby facilitating tumor angiogenesis, invasion, and metastasis. Simultaneously, an elevated monocyte count reflects the accumulation of tumor-associated macrophages, which support tumor growth and the formation of an immunosuppressive microenvironment.

The nearly five-fold increase in AISI (4.95 times) demonstrates the pronounced activation of three cellular components of systemic inflammation simultaneously: neutrophils, monocytes, and platelets. Platelets actively interact with circulating tumor cells, shielding them from immune surveillance, promoting the formation of micrometastases, and stimulating neoangiogenesis. Consequently, a high AISI is regarded as one of the most promising integral markers of an aggressive tumor course.

The most substantial increase in dNLR (6.27-fold) reflects a marked disruption in the neutrophil-to-lymphocyte ratio. Lymphocytes serve as the primary effector cells of antitumor immunity, whereas elevated neutrophils promote the development of chronic inflammation and immunosuppression. In numerous studies, high dNLR values are associated with a greater likelihood of regional metastasis, extrathyroidal extension, advanced disease stages, and diminished recurrence-free survival.

Thus, the acquired results are in full accordance with modern understandings that chronic systemic inflammation is a critical component of tumor progression in thyroid cancer. The determination of SIRI, AISI, and dNLR allows for an objective assessment of the degree of inflammatory activity, reflecting the biological aggressiveness of the tumor.

Interim Conclusions: A statistically significant increase in all investigated hematological indices of systemic inflammation was detected in TC patients compared to the healthy control group ($p<0.05$). The SIRI index increased from 0.33 ± 0.02 to 1.37 ± 0.85, corresponding to a 4.15-fold elevation. The AISI index rose from 120.4 ± 9.40 to 595.92 ± 0.45, increasing by 4.95 times. The most pronounced changes were recorded for dNLR, which surged from 0.55 ± 0.04 to 3.45 ± 1.45 (a 6.27-fold increase).

The substantial elevation of SIRI, AISI, and dNLR reflects the marked activation of the systemic inflammatory response accompanying the development of thyroid cancer and validates the prospect of utilizing these indices as accessible laboratory markers for diagnosis, evaluation of tumor biological aggressiveness, and prediction of clinical severity.

Table 2 illustrates the values of the indices of an adverse TC course at early and advanced stages. Based on these data, it is evident that characteristic alterations occur at these disease stages, as detailed below.

Table 2. Results of the principal hematological indices of systemic inflammation in thyroid cancer by stage

GROUPS	SIRI (Systemic Inflammation Response Index)	AISI (Aggregate Index of Systemic Inflammation)	dNLR (Derived Neutrophil-to-Lymphocyte Ratio)
TC Patients (Early Stages)	0.94 ± 0.15 *	335.8 ± 5.38 *	1.85 ± 0.35 *
TC Patients (Advanced Stages)	2.35 ± 0.96 *^	784.9 ± 9.44 *^	5.12 ± 0.66 *^
Control (Norm)	0.33 ± 0.02	120.4 ± 9.40	0.55 ± 0.04

*Note: * - statistically significant differences compared to the norm; ^ - statistically significant differences between the studied TC groups (early vs. advanced).*

The analysis of the principal hematological indices of systemic inflammation demonstrated that even at the early stages of the disease, patients with thyroid cancer (TC) exhibit a statistically significant elevation in all studied parameters compared to the cohort of practically healthy individuals. As the tumor process progresses and transitions to advanced stages, the index values increase even more significantly. This is confirmed by statistically significant differences not only relative to the control group but also between the early and advanced stages of the disease ($p<0.05$).

Investigation of the Systemic Inflammation Response Index (SIRI) revealed that in TC patients at early stages, its value was 0.94 ± 0.15, significantly exceeding the control group's parameter (0.33 ± 0.02) by 2.85 times ($p<0.05$). In patients with advanced stages of the disease, SIRI increased to 2.35 ± 0.96, which was 7.12 times higher than the norm ($p<0.05$) and 2.50 times higher than the early-stage parameter

($p<0.05$). The obtained results point to a progressive activation of the systemic inflammatory response correlative with the dissemination of the tumor process.

A similar pattern was identified upon examining the Aggregate Index of Systemic Inflammation (AISI). In the early stages of TC, its mean value was 335.8 ± 5.38, surpassing the parameter of healthy individuals (120.4 ± 9.40) by 2.79 times ($p<0.05$). At advanced stages, AISI escalated to 784.9 ± 9.44, representing a 6.52-fold increase over the control value ($p<0.05$) and a 2.34-fold increase over the early-stage value ($p<0.05$). Such a marked elevation in AISI reflects the intensification of the inflammatory reaction involving neutrophils, monocytes, and platelets as the tumor advances.

The most striking alterations were detected during the analysis of the derived Neutrophil-to-Lymphocyte Ratio (dNLR). In patients with early-stage TC, its value was 1.85 ± 0.35, exceeding the healthy cohort's parameter (0.55 ± 0.04) by 3.36 times ($p<0.05$). At advanced stages, dNLR reached 5.12 ± 0.66, exceeding the norm by 9.31 times ($p<0.05$) and the early-stage parameter by 2.77 times ($p<0.05$). It was dNLR that demonstrated the most pronounced dependency on the stage of the tumor process.

Consequently, all investigated hematological indices of systemic inflammation consistently escalated as the disease progressed. The maximal degree of elevation relative to the norm was characteristic for dNLR (9.31-fold), followed by SIRI (7.12-fold) and AISI (6.52-fold).

The acquired results provide evidence of a close interrelationship between the severity of the systemic inflammatory response and the stage of thyroid cancer. Although a significant activation of inflammatory mechanisms is noted even at the early stages of the disease, the intensity of inflammation increases substantially with tumor progression.

Virtually identical dynamics were observed for AISI, which increased from 335.8 ± 5.38 to 784.9 ± 9.44 (a 2.34-fold increase between early and advanced stages). Because this index aggregates the counts of neutrophils, monocytes, and platelets, its substantial increase reflects a complex activation of systemic inflammation accompanying tumor progression. High AISI values may indicate an increased probability of vascular invasion, lymphogenous metastasis, and an unfavorable prognosis.

The most pronounced stage-dependency was noted for dNLR, which surged from 1.85 ± 0.35 to 5.12 ± 0.66 (a 2.77-fold increase). Compared to the control group, this parameter increased by more than 9 times, pointing to a profound imbalance between innate and adaptive immunity. It is well-documented that an increase in neutrophils is accompanied by enhanced production of pro-inflammatory cytokines (IL-6, IL-1β, TNF-α), angiogenic factors, and metalloproteinases, whereas a reduction in the relative lymphocyte count reflects the suppression of the antitumor immune response. It is for this reason that dNLR is considered one of the most informative laboratory predictors of an aggressive course and adverse prognosis across various solid tumors.

The statistically significant disparities between early and advanced disease stages across all investigated indices ($p<0.05$) testify to the high sensitivity of SIRI, AISI, and dNLR to tumor progression. This confirms their viability as supplementary laboratory criteria for assessing the clinical severity of thyroid cancer.

Conclusion

1. In patients with TC, a statistically significant increase in all investigated hematological indices of systemic inflammation was detected even at the early stages of the disease compared to practically healthy individuals. In early-stage TC, the SIRI index increased by 2.85 times, AISI by 2.79 times, and dNLR by 3.36 times relative to the control group.
2. At advanced stages of the disease, the index values escalated even more significantly: SIRI exceeded the norm by 7.12 times, AISI by 6.52 times, and dNLR by 9.31 times.
3. Statistically significant differences were established between the early and advanced stages of the disease: SIRI increased by 2.50 times, AISI by 2.34 times, and dNLR by 2.77 times as the disease progressed.
4. The dNLR demonstrated the most pronounced association with tumor progression, allowing it to be classified as the most sensitive hematological marker of clinical severity in thyroid cancer.
5. The obtained results validate the high diagnostic and prognostic utility of SIRI, AISI, and dNLR. Their determination—based on a standard complete blood count—can be utilized for the early assessment of a tumor's biological aggressiveness, prediction of clinical severity and metastasis risk, and the personalization of therapeutic strategies in patients with thyroid cancer.

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