International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 19s, 2025
https://theaspd.com/index.php

Management Of Chemotherapy In Suppressing Solid Tumors By SLC38A9, CLEC6A And Interleukin-42 As Novel Tumor Markers

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Abstract

Background: *Cancer remains one of the leading causes of morbidity and mortality worldwide, posing a significant challenge to healthcare systems and medical research. Broadly speaking, tumors can be classified into two main categories: solid tumors and hematologic (liquid) malignancies. While hematologic cancers-such as leukemia and lymphoma-primarily affect the blood and bone marrow, solid tumors are characterized by the abnormal growth of tissue in the form of a mass or lump within a specific organ or body site. Solid tumors encompass a wide range of cancers, including those of the breast, lung, prostate, colon, liver, brain, and many others. These malignancies account for a substantial portion of global cancer cases and deaths, highlighting the urgent need for continued research, early detection, and effective treatment strategies.* ***Patients and Healthy Control*** *a total of 60 individuals were enrolled in the current study, divided into two main groups:The first group (patients): included 30 patients diagnosed with various types of solid malignant tumors, ranging in age from 27 to 77 years. The second group (healthy controls): included 30 healthy individuals, serving as a control group, ranging in age from 26 to 66 years.* ***Kits and technique:*** *Sandwich-ELISA technique was applied to determine the level of SLC38A9, CLEC6A and Interleukin-42 in the serum samples of the study individuals.* ***Results:*** *The results of the current study showed no-significant differences (p=0.130) when comparing the level of SLC38A9 in the two cancerous patients groups together. Nevertheless, the study showed statistically significant differences when comparing the control group with the group of patients with solid tumors before treatment (p=0.010) and after chemotherapy (p=0.000), The study showed a significant decrease (p=0.000) in the levels of this parameter in the treated group before treatment (G1) compared to its levels in the treated group after treatment (G2). Similarly, the study demonstrated significant differences (p=0.001) when comparing the treated group with the control group. However, the results lacked statistical acceptability when comparing the group of solid tumor patients who received treatment with the control group (p=0.408). The study revealed statistically significant differences when comparing Interleukin-42 levels in the solid tumor group before receiving chemotherapy compared to the same samples after completing chemotherapy (p=0.008), as well as their counterparts in the control group (p=0.001). The study showed that the highest sensitivity (90%) was recorded for both CLEC6A and interleukin 42. All criteria demonstrated equally maximal sensitivity in this study, with each reaching 100%.While CLEC6A, they were less sensitivity to them 97% before Chemotherapy Treatment. In the group of solid tumor patients who received chemotherapy, the study showed that the highest sensitivity (93%) and highest specificity (90%) were recorded for SLC38A9. While the results showed that the combined sensitivity reached its maximum (97%) for SLC38A9 in combination with CLEC6A.* ***Conclusions:*** *SLC38A9, CLEC6A, and lnterleukin-42 are excellent tools for diagnosing malignant solid tumors. SLC38A9, CLEC6A, and lnterleukin-42 are an effective follow-up function for cancerous tumor detection.*

Key Words Solid Tumors, SLC38A9, CLEC6A and Interleukin-42

INTRODUCTION

Cancer remains one of the leading causes of morbidity and mortality worldwide, posing a significant challenge to healthcare systems and medical research[1] The tumors can be classified into two main categories: solid tumors and hematologic (liquid) malignancies[2], while hematologic cancers-such as leukemia and lymphoma-primarily affect the blood and bone marrow[3]. Solid tumors encompass a wide range of cancers, including those of the breast, lung, prostate, colon, liver, brain, and many others[4]. A tumor is an abnormal growth of tissue that results when cells divide and grow more than they should or do not die when they should. Tumors can form in any part of the body[5]. Solid tumors are abnormal masses of tissue that typically arise from the uncontrolled growth and division of cells within organs or tissues of the body solid tumors are localized and

form discrete lumps or masses. They can be benign (non-cancerous) or malignant (cancerous), but in the context of oncology, the term "solid tumors" usually refers to malignant neoplasms[6]. Malignant cells possess immunosuppressive properties, such as the expression of PD-L1 and the secretion of suppressive cytokines, which help them reduce their immunogenicity. The resistance mechanisms of malignant cells can be categorized into two main strategies: evading immune recognition and creating an immunosuppressive TME[7].

Tumorgenesis of solid tumors refers to the complex, multi-step process by which normal cells transform into malignant solid tumors[8]. There are several risk factors that increase the likelihood of developing solid tumors, e.g., tobacco use[9], infections[10], lifestyle factors[11], and environmental exposures[12].

Solute Carrier Family 38 Member 9 (SLC38A9) the amino acid transceptor, it belongs to the SLC38 cluster of the major facilitator superfamily (MFS). The SLC38 group includes eleven members some of which have been functionally characterized in cell systems an important aspect of SLC38A9 biology is its dual function as transporter and receptor for sensing nutrient sufficiency to regulate the mammalian target of rapamycin complex 1 (mTORC1) pathway[13]. SLC38A9, a lysosomal transmembrane protein, regulates the interaction of intracellular arginine sensors with the lysosomal membrane localized Rag GTPase. It acts as a scaffold, linking Rag GTPase with mTORC1 attached to the lysosome. SLC38A9 regulates essential amino acids' efflux from lysosomes in an arginine-regulated fashion. SLC38A9, however, responds to lysosomal arginine levels specifically SLC38A9 is a highly glycosylated trans membrane protein and consists of eleven trans membrane helices with a 120-residue N-terminal region towards the cytoplasm. Notably, SLC38A9 is crucial for the efflux of Lucien, Glutamine, Tyrosine, and Phenylalanine generated from lysosomal proteolysis, this efflux is necessary to activate mTORC1 through cytoplasmic sensors Thus, lysosomal sensors allow for the integration of lysosomal nutrient information into the regulation of mTORC1 activity. Collectively, amino acids are not only sources for energy and protein synthesis in tumor genesis, but also act on mTORC1 as signaling molecules[14]. Niemann-Pick disease, type C1 (NPC1) binds SLC38A9 at the lysosome membrane and inhibits mTORC1 signaling. NPC1 depletion leads to constitutive mTORC1 activation, suppressing autophagy. Additionally, NPC1 deficiency results in impaired autophagosome-lysosome fusion which has been linked to impaired lysosomal proteolysis. Others argue that the process is a proteolysis independent, but SNARE-dependent mechanism[15].

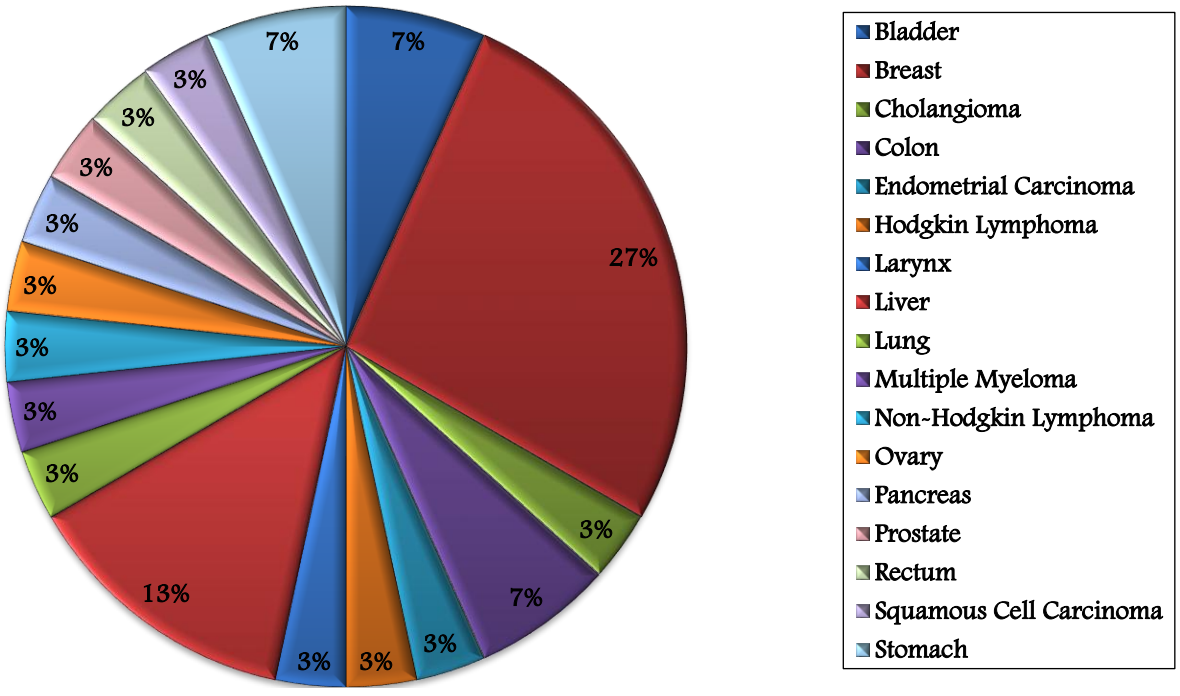
C-type lectin domain family 6, member A (CLEC6A), also known as dendritic cell-associated lectin-2 (Dectin-2), is a C-type lectin receptor best known for its role in pathogen recognition and induction of protective immune responses against fungi and other microbes[16, 17]. Previously, CLEC6A demonstrated an ability to agonism stimulates pro-inflammatory cytokine secretion and antigen presentation by TAMs, resulting in robust CD8+ T cell-mediated anti-tumor immunity differential gene expression of CLEC6A has been found in a wide range of solid tumor-associated macrophages compared to non-malignant[18]. CLEC6A plays a prominent role in regulating innate immunity and adaptive immunity[19]. Moreover; CLEC6A has shown great potential as a target for cancer immunotherapy, which can recognize high mannose structures[20].

Interleukins are a group of protein compounds belonging to a type of cytokines that are produced by numerous cells in the body, including immune cells[21]. They are involved in several important cellular processes, including proliferation, maturation, migration and adhesion, and also participate in the activation and differentiation of immune system cells[22]. Currently, the assessment of the levels of interleukins in the human body can be used as a diagnostic indicator of the development or progression of many diseases (heart disease, neurological disorders and cancers)[23]. Interleukins have numerous roles in immune modulation and inflammation, when they modify the communication pathways and cellular responses, specifically, they promote the growth of tumors and the breakdown of bone tissue[24]. Interleukins have an impact on the development of osteoclasts, the survival of tumor cells, and the development of novel blood vessels in the bone microenvironment[25]. Understanding the role of interleukins in the bone microenvironment is crucial for understanding the complex mechanisms that drive the progression of metastasis and for developing targeted therapies that interrupt interleukin-guided pathways to prevent bone metastasis. Identifying precise interleukins associated with the progression of cancer in the bone microenvironment could offer novel treatment strategies to prevent and control the spread of metastases in breast cancer and other malignant tumors. Interleukins have a critical role in cancer development, progression and control[26]. They can nurture

an environment enabling and favoring cancer growth while simultaneously being essential for a productive tumor-directed immune response[27]. Systems interleukins facilitate cell-to-cell contact within the immune system A type of non-coding RNA known as lncRNAs mediates its actions by regulating miRNA-mRNA roles[28]. Because of their dual function in controlling the growth of tumors and altering the immune system's response to cancer cells, interleukins have been extensively studied concerning cancer. Understanding the complex relationships between interleukins, the immune system that impact the miRNA-mRNA axis, including Inc-RNAs, has advanced significantly in cancer research. Due to the significant and all-encompassing influence of interleukins on the immune system and the development and advancement of cancers[29].Interleukins with pro-inflammatory/anti-inflammatory functions, mainly secreted by antigen-presenting cells and T lymphocytes These secreted proteins execute their functions by binding to high-affinity receptors on the cell surface in an autocrine and paracrine manners. Various interleukins actively participate in intricate tumor regulatory networks,[30] impacting tumor progression via diverse mechanisms, such as tumor promoting inflammation, malignant transformation, growth, proliferation, angiogenesis, invasion, migration, and anti-tumor immunity[31]**.** Interleukin-42 is a new member of the interleukin family, and general information about it is virtually nonexistent. Therefore, the current study may be the first worldwide to evaluate interleukin-42 levels in patients with solid tumors, as no studies have been conducted to date to evaluate this type of interleukin in an illness state[32].

MATERIALS AND METHODS

The study population: Over a period of five months (from early October 2024 to the end of March 2025), a total of 60 individuals were enrolled in the current study, divided into two main groups: The first group (patients): included 30 patients diagnosed with various types of solid malignant tumors, ranging in age from 27 to 77 years. The second group (healthy controls): included 30 healthy individuals, serving as a control group, ranging in age from 26 to 66 years. The samples of patients with malignant solid tumors were collected from the National Oncology and Hematology Hospital before receiving chemotherapy and were followed up during the chemotherapy period. This group included 17 different types of cancerous solid tumors (Bladder, Breast, Cholangioma, Colon, Endometrial Carcinoma, Hodgkin Lymphoma, Larynx, Liver, Lung, Multiple Myeloma, Ovary, Pancreas, Prostate, Rectum, Squamous Cell Carcinoma, and Stomach).



All patients with different types of solid tumors were diagnosed by oncologists. Conversely, samples of the healthy control group were collected from the study community environment, such as nursing staff, laboratory workers, and statistical units at the National Oncology and Hematology Hospital, as well as from relatives and

the workers in Al-Manathira Specialized Laboratory. The current study required the exclusion of the following individuals:

- Cases with non-solid cancers, such as leukemia
- Cases who did not complete the planned course of chemotherapy
- Cases undergoing chemotherapy sessions due to relapse and recurrence of the cancer.
- Cases whose treatment program did not include chemotherapy doses.

Assessment of criteria concentration: Sandwich enzyme linked immune sorbent assay (Sandwich-ELISA) method was applied to determine the level of SLC38A9, CLEC6A and Interlukin-42 in the serum samples of the study individuals

The statistical analysis: The outcomes of the present study were analyzed through the statistical package for the social sciences (SPSS) version 26 software application statistical analysis system and excel (statistical package). The variables were illustrated by mean ± S.D, minimum, maximum, frequencies, and percentages. Graphics are presented using pie and bar charts. Inferential data analysis includes analysis of variance (ANOVA) test was applied to assess differences between the levels of the studied parameters. The probability of deflection than controls are considered statistically significant if p-value is below 0.05. Receiver operating characteristic (ROC) curve was applied to present the sensitivity of the evaluated parameters. Combined sensitivity and specificity percentages were calculated according to biomedical statistical.

RESULTS AND DISCUSSION

In order to study the effect of SLC38A9 on the incidence of cancer and the formation of solid tumors, levels of this protein were evaluated in samples of patients with solid tumors before and after chemotherapy, as well as in individuals serving as a control group. The results of the current study showed no-significant differences (p=0.130) when comparing the two groups with cancer (before and after chemotherapy) together. Nevertheless, the study showed statistically significant differences when comparing the control group with the group of patients with solid tumors before treatment (p=0.010) and after chemotherapy (p=0.000), as illustrated in **Table1.**

Table1: Levels of Solute Carrier Family 38 Member 9 in The Study Individuals

Subjects (n)	SLC38A9 (ng/mL) Mean ± S.D.	SLC38A9 (ng/mL) Min-Max	SLC38A9 (ng/mL) Range	p – value
G_1 (30)	41.410±3.711	33.658-50.706	17.048	0.130 for G_1 vs G_2
G_2 (30)	43.923±3.826	35.199-55.299	20.100	0.010 for G_1vs C
Controls (30)	37.080±9.645	11.946-53.069	41.123	0.000 for G_2vs C

G1: Solid Tumor Patients Pre-Treatment, G2: Solid Tumor Patients Post Chemotherapy Treatment. The Mean Difference is Significant at 0.05 Level

Overall, the study recorded a slight (non-statistically significant) increase in SLC38A9 levels when comparing the solid tumor group before and after treatment, indicating that chemotherapy does not affect the synthesis of this protein. The lowest (11.946 ng/mL) and highest (55.299 ng/mL) SLC38A9 levels were recorded in patients with solid tumors..SLC38A9 is a transport protein found on the surface of the lysosome. It acts as a transporter of amino acids, particularly glutamine and arginine. It is closely linked to the mTORC1 signaling pathway, which is important for regulating cell growth, survival, and nutrient response[33]. Solid tumors are highly dependent on growth signaling pathways such as mTORC1 and SLC38A9. Activation of this pathway is regulated by arginine sensing within the lysosome. Consequently, SLC38A9 expression is increased to support the continuity of signals that promote tumor growth and survival in a low-nutrient environment .Solid tumors suffer from nutritional and oxygen deprivation, which stimulates cancer cells to express high transport proteins such as SLC38A9 to secure the necessary amino acids[34]. SLC38A9 contributes to the stimulation of cellular metabolism and metabolism necessary for malignant cell growth and resistance to environmental stress. Most chemotherapies target cell division or DNA damage, not amino acid transporters. Therefore,

SLC38A9 is not a direct target for conventional chemotherapy, and therefore its expression remains high .Additionally, some studies suggest that elevated SLC38A9 may be associated with cancer cell resistance to therapy by promoting adaptive metabolism. Since it promotes metabolic adaptation, maintaining its expression may constitute a resistance mechanism that helps cells survive after treatment. Furthermore, even after tumor shrinkage or removal, low-nutrient environments may persist, maintaining the need for active SLC38A9 .Recent research suggests that inhibiting SLC38A9 may impair mTORC1 activity and reduce the ability of cancer cells to survive, especially in nutritionally stressed environments .It could be used as a biomarker of tumor status and potentially as a future therapeutic target. Recently, research has emerged on inhibiting the arginine–SLC38A9–mTORC1 pathway using lysosomal-loaded nano-inhibitors, which have proven preclinical efficacy and are now under investigation. The high tumor dependence on SLC38A9 makes it a potential target for reducing and inactivating mTORC1, which may improve the efficacy of chemotherapy in the future.

Levels of CLEC6A were evaluated in study samples to suggest it as a prognostic marker for solid tumors and to monitor patients' response to chemotherapy based on changes in CLEC6A levels. The study showed a significant decrease (p=0.000) in the levels of this parameter in the treated group before treatment (G1) compared to its levels in the treated group after treatment (G2). Similarly, the study demonstrated significant differences (p=0.001) when comparing the treated group with the control group. However, the results lacked statistical acceptability when comparing the group of solid tumor patients who received treatment with the control group (p=0.408), as revealed in**Table 2.**

Table2: Levels of C-Type Lectin Domain Family 6 Member A in The Study Individuals

Subjects (n)	CLEC6A (ng/mL) Mean ± S.D.	CLEC6A (ng/mL) Min-Max	CLEC6A (ng/mL) Range	p – value
G_1 (30)	3.545±.366	3.075-4.400	1.325	0.000 for G_1 vs G_2
G_2 (30)	4.302±.3443	3.474-5.035	1.561	0.001 for G_1vs C
Controls (30)	4.152±1.100	1.506-5.511	4.005	0.408 for G_2vs C

G1: Solid Tumor Patients Pre-Treatment, G2: Solid Tumor Patients Post Chemotherapy Treatment. The Mean Difference is Significant at 0.05 Level

When assessing CLEC6A levels during chemotherapy, a significant increase in this parameter was observed after receiving the doses specified in the chemotherapy regimen prescribed by the specialist (as illustrated inCLEC6A, also known as dendritic cell-associated lectin-2 (Dectin-2), which can recognize high mannose structures, is a recent discovered C-type lectin receptor with one CRD. CLEC6A is C-type lectin, is a trans membrane glycan-binding receptor widely studied in the context of infection. These glycan traits can be found in breast, colorectal and bile duct tumor cells, projecting CLEC6A expressing cells as interesting sensors to target high-mannose epitopes and trigger a pro-inflammatory and anti-tumoral response. In the case of autoimmune disorders, a glycan switch of host glycans towards mannose-enriched N-glycans was also found in the epithelial compartment of the kidneys of Lupus Nephritis patients.[35] CLEC6A plays a prominent role in regulating innate immunity and adaptive immunity. CLEC6A has shown great potential as a target for cancer immunotherapy .In Kimura Y' study, CLEC6A mediates phagocytosis of cancer cells by Kupffer cell and inhibits liver metastasis, CLEC6A is important for both adaptive and innate immunity, and is a potential target for immunotherapy. In Xiang T's study, CLEC6A coupled with BST1 and TLR7 from NETosis-related genes could significantly correlate with gastric cancer patients survival, and identify which patients were more sensitive to immunotherapy. However, the causative effect of CLEC6A on tumorgenesis and prognosis, immunotherapy of solid cancer remains not known. CLEC6A also mediates the phagocytosis of cancer cells by Kupffer cells, inhibiting liver metastasis, in a process dependent on the cell-surface transmembrane protein ERMAP and galectin-9[36]. CLEC6A has been extensively studied in the context of infection, where it has been shown to play a protective role. Due to its interaction with molecules with a high mannose content, this receptor has the potential to be used as a drug target in the development of new therapies, particularly against fungal pathogens[37]. The carbohydrate-binding MF was attributed to pattern recognition receptors that are

essential for pathogen identification. These receptors included genes encoding C-type lectin domain family proteins, such as CLEC10A, CLEC12A, CLEC12B, CLEC1B, CLEC4D, CLEC4E, CLEC5A, and CLEC6A. The BPs related to cell migration highlighted enrichment of humoral immune response processes associated with chemo tax[38].CLEC6A, for example, regulates Th17 responses to histoplasmosis and coccidioidomycosis and plays a protective role in streptococcal immunity. CLEC6A additionally regulates ROS production and NADPH oxidase-independent NETosis in Candida infection. CLEC6A represents pattern recognition receptors, CLEC6A can also regulate Th2 immunity through the generation of cysteinylleukotrienes. CLEC6A is a gene of human innate immunity, it can directly mediate intracellular signaling, recognize a variety of endogenous and exogenous ligands, and drive both innate and adaptive immunity. Chen et al., indicated that breast cancer patients in the CLEC6A high expression group had a better prognosis compared to those in the low expression group. Additionally, were identified to construct a NET-related gene signature for predicting prognosis in SKCM This gene could be a promising therapeutic target[39].Analysis of CLEC6A levels in solid tumor patients showed a significant decrease in gene expression of this protein before the start of chemotherapy, while a significant increase in its levels was observed after treatment. It is believed that this change may reflect an immune response resulting from the immunomodulatory effect of chemotherapy, or a result of improved immune cell function that may have been suppressed by the tumor before treatment. This expression pattern suggests the potential use of CLEC6A as a biomarker for monitoring chemotherapy response, and perhaps as a prognostic indicator associated with clinical improvement. However, these findings require further studies to confirm their clinical significance and their association with long-term survival and response outcomes.

Interleukin-42 levels were evaluated in serum samples from the solid tumor group and the control group. The study revealed statistically significant differences when comparing interleukin-42 levels in the solid tumor group before receiving chemotherapy compared to the same samples after completing chemotherapy (p=0.008), as well as their counterparts in the control group (p=0.001). In contrast, statistical processing revealed no significant differences in interleukin-42 levels when comparing the solid tumor group who received chemotherapy with healthy individuals (p=0.462), as shown in **Table 3**.

Table 3: Levels of Interleukin-42 in The Study Individuals

Subjects (n)	Interleukin-42 (pg/mL) Mean±S.D.	Interleukin-42 (pg/mL) Min-Max	Interleukin-42 (pg/mL) Range	p – value
G_1 (30)	8.484±.966	6.571-10.573	4.002	0.008 for G_1vs G_2
G_2 (30)	7.480±1.305	3.128-9.556	6.428	0.001 for G_1 vs C
Controls (30)	7.209±1.849	3.289-10.844	7.555	0.462 for G_2 vs C

G1: Solid Tumor Patients Pre-Treatment, G2: Solid Tumor Patients Post Chemotherapy Treatment. The Mean Difference is Significant at 0.05 Level

Interleukin-42 levels were compared in the two groups of patients with solid tumors before and after receiving chemotherapy. The results of the study showed a significant decrease in the concentration of interleukin-42 after receiving the third dose, such that the levels of this parameter approached what was recorded in the control group. Interleukins are a group of protein compounds belonging to a class of cytokines produced by many cells in the body, including immune cells. These interleukins are involved in many important cellular processes, including proliferation, maturation, migration, and adhesion, and they also participate in the activation and differentiation of immune system cells. According to published research, approximately 40 types of interleukins have been characterized, and their number is constantly increasing (at the end of the 20th century, this group consisted of 30 types). Furthermore, interleukins, as a component of the cytokine network, have been shown to affect the entire human body, including metabolic activity, the cardiovascular system, and the neuroendocrine system, allowing for the maintenance of homeostasis[40].Interleukins are a means of communication for innate and adaptive immune cells, as well as non-immune cells and tissues. Thus, interleukins play a crucial role in the development and control of cancer. Interleukins can create an environment that enables and encourages cancer growth, while simultaneously being essential for a productive

tumor-directed immune response. These properties of interleukins can be exploited to improve immunotherapies to enhance their efficacy and reduce side effects[41].It is widely accepted that immune dysfunction, including abnormally expressed cytokines, is closely associated with the development of colorectal cancer. In recent years, interleukins have attracted significant attention due to their distinct roles in the onset and progression of many cancers by promoting tumor formation, growth, angiogenesis, and tumor cell invasion and dissemination. Interleukins play a pivotal role in modulating the development of bone metastases by regulating the complex interactions between malignant cells and bone cells within the local tumor microenvironment. Investigating the molecular mechanisms controlling the actions of interleukins in relation to bone metastases is essential for developing personalized therapeutic regimens and improving the prognosis of patients with advanced cancer[42]. Interleukin-42 is the most recently studied interleukin, and no previous studies have been conducted on it. Therefore, the interpretation of its levels in the current body of work is based on hypotheses that converge with general knowledge about various cytokines. The high levels of Interleukin-42 in patients with solid tumors before chemotherapy, followed by a significant decline after treatment, may be explained by understanding the role of this cytokine in the tumor environment and response to therapy. Although Interleukin-42 is not a widely known cytokine (such as IL-6 or IL-10), we hypothesize that it represents an inflammatory cytokine with similar function, or that it is a newly discovered cytokine being studied in the context of cancer. Solid tumors often stimulate inflammatory responses in the body. Interleukin-42 may be produced by immune cells (such as macrophages or T cells) or even by cancer cells within the tumor microenvironment. This elevation may reflect the body's attempt to fight the tumor or may result from inflammation that promotes tumor growth.Some inflammatory cytokines contribute to the formation of new blood vessels (angiogenesis) or suppress the anti-tumor immune response, helping the tumor grow. Interleukin-42 may have a similar role in promoting a favorable tumor environment. A possible explanation for the decrease in Interleukin-42 levels after chemotherapy is a reduction in tumor mass. Chemotherapy kills cancer cells, shrinking the tumor and reducing the factors that stimulate Interleukin-42 production. As the tumor shrinks, the need for the associated inflammatory response decreases, and thus, the stimulation of Interleukin-42 production by immune cells decreases. In addition, some chemotherapy drugs lead to a general suppression of immune system activity, which may lead to a decrease in the production of Interleukin-42 and other cytokines.

Efficiency of the evaluated parameters in detection of different solid tumors

Sensitivity is known as the true positive rate or the probability of detection, it measures the proportion of positives that are correctly identified.Specificity is known as the true negative rate; it measures the proportion of negatives that are correctly identified.The calculation of sensitivity and specificity is used for assessing the efficiency of the tested parameters to suggest them as diagnostic markers. The diagnostic efficiency of the included criteria in this work were evaluated by applying the receiver operating characteristic (ROC) as demonstrated in**in Figurers 4, 5,** and **6** for SLC38A9, CLEC10A, and Interleukin-42; respectively. **Table 4** shows the area under the curve and threshold values for the parameters evaluated in patients with solid tumors before receiving chemotherapy. The study showed that the highest sensitivity (90%) was recorded for both CLEC6A and interleukin 42.

Table 4: Receiver Operating Characteristic Analysis of the Evaluated Criteria as Diagnostic Markers for Solid Tumors

Criteria	AUC	SE	p-value	Cutoff value	Sensitivity%	Specificity%	CI (95%)
SLC38A9	0.606	0.042	0.016	38.907	87	84	0.459-0.752
CLEC6A	0.218	0.039	0.000	3.427	90	90	0.083-0.353
Interleukin-42	0.702	0.070	0.007	7.601	90	84	0.554-0.839

AUC: Area Under Curve, SE: Standard Error

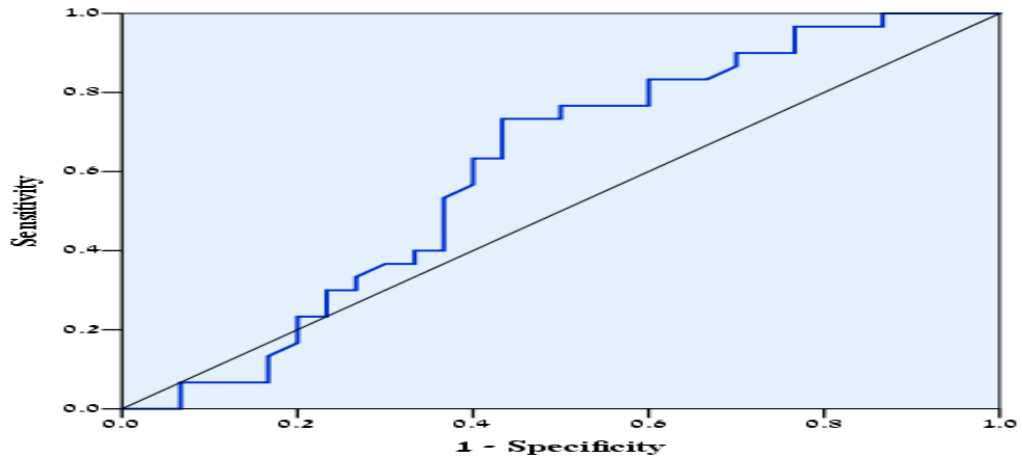


Figure 4: Receiver Operating Characteristic Curve of SLC38A9 in Solid Malignant Tumors Patients Before Chemotherapy

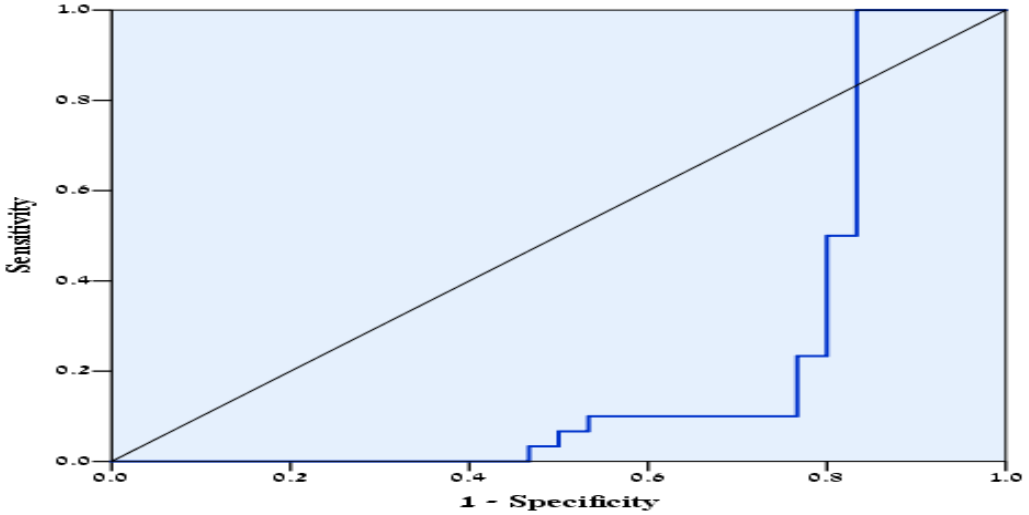


Figure 5: Receiver Operating Characteristic Curve of CLEC6A in Solid Malignant Tumors Patients Before Chemotherapy

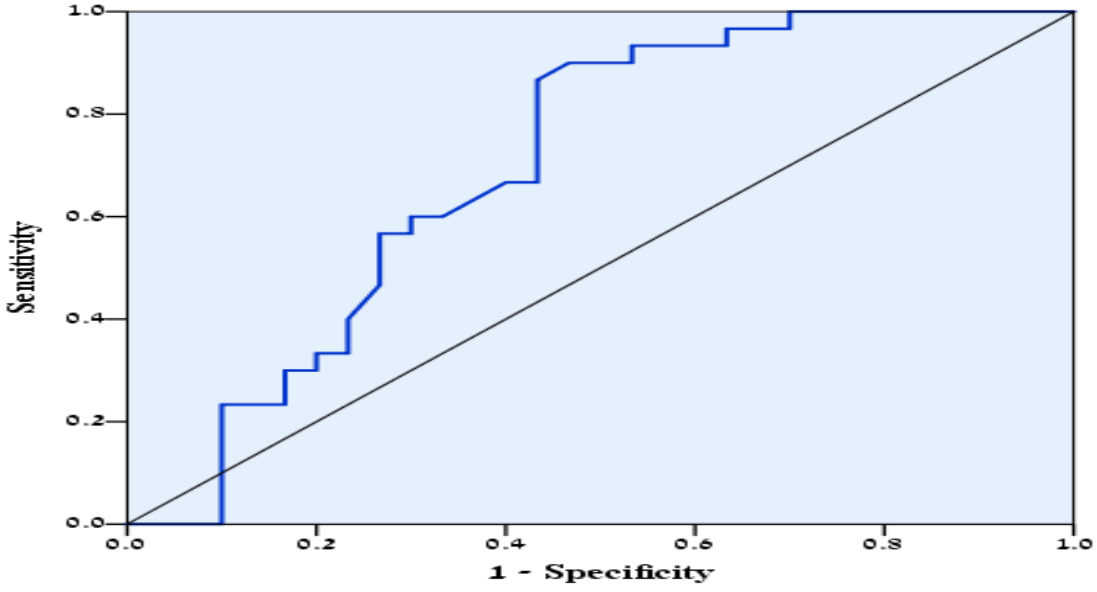


Figure 6: Receiver Operating Characteristic Curve of Interleukin-42 in Solid Malignant Tumors Patients Before Chemotherapy

The combined sensitivity of the criteria, SLC38A9, CLEC6A, and Interleukin-42 in solid tumors was evaluated before chemotherapy treatment, as illustrated in **Table 5**. All criteria demonstrated equally maximal sensitivity in this study, with each reaching 100%.While CLEC6A, they were less sensitivity to them 97% before Chemotherapy Treatment.

Table 5: The Combined Sensitivity of the Evaluated Parameters before Chemotherapy Treatment

Parameters	SLC38A9	CLEC6A	Interleukin-42
SLC38A9	-	100	100
CLEC6A		-	100
Interleukin-42			-

Table 6 shows the area under the curve and threshold values for the criteria evaluated in the group of solid tumor patients who received chemotherapy. The study showed that the highest sensitivity (93%) and highest specificity (90%) were recorded for SLC38A9.

Table6: Receiver Operating Characteristic Analysis of Evaluated Parameters as Predictive Markers of Response to Chemotherapy

Criteria	AUC	SE	p-value	Cutoff value	Sensitivity%	Specificity%	CI (95%)
SLC38A9	0.733	0.053	0.002	39.112	93	90	0.599-0.867
CLEC6A	0.448	0.079	0.492	3.552	76	70	0.294-0.603
Interleukin-42	0.512	0.076	0.877	7.011	70	70	0.362-0.661

AUC: Area Under Curve, SE: Standard Error

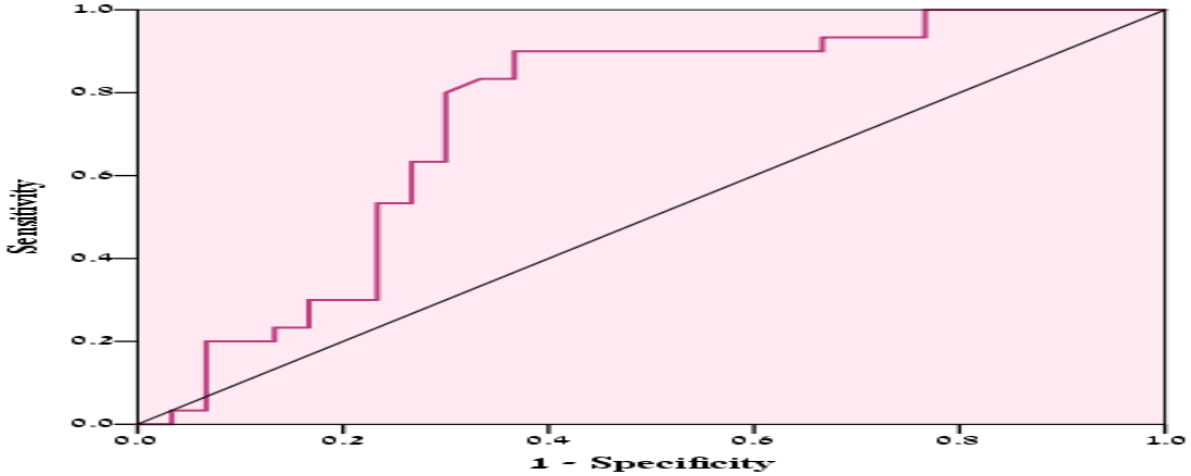


Figure 7: Receiver Operating Characteristic Curve of SLC38A9 in Solid Malignant Tumors Patients After Chemotherapy

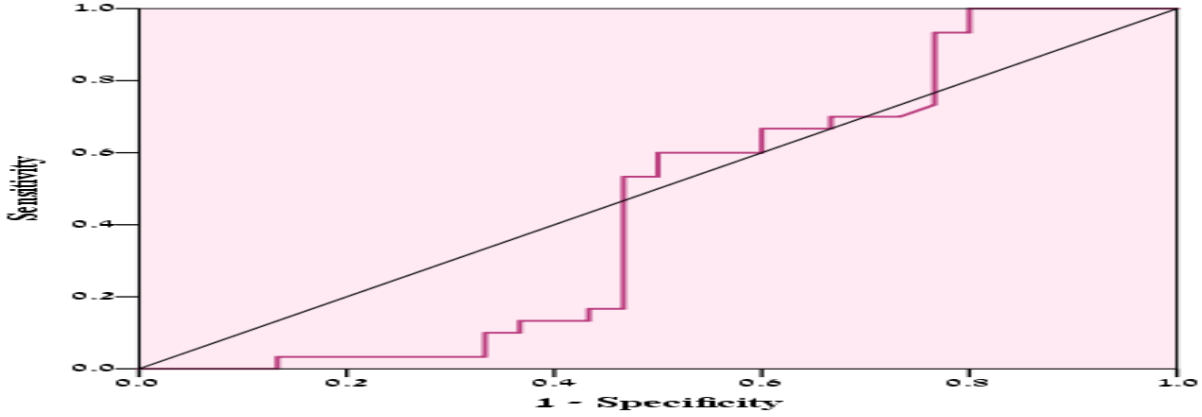


Figure8:Receiver Operating Characteristic Curve of CLEC6A in Solid Malignant Tumors Patients After Chemotherapy

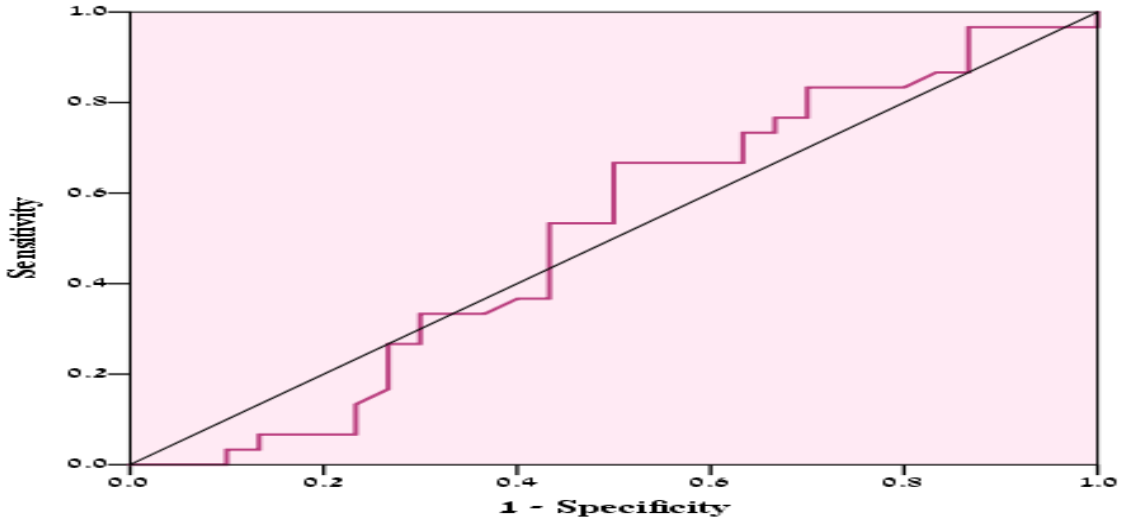


Figure9: Receiver Operating Characteristic Curve of Interleukin-42 in Solid Malignant Tumors Patients After Chemotherapy

While the combined sensitivity of the criteria SLC38A9, CLEC6A, Interleukin-42, was evaluated for solid tumors after chemotherapy, as shown in **Table7**. The results showed that the combined sensitivity reached its maximum (97%) for SLC38A9 in combination with CLEC6A.

Table7: The Combined Sensitivity of the Evaluated Parameters after Chemotherapy Treatment

Parameters	SLC38A9	CLEC6A	Interleukin-42
SLC38A9	-	97	93
CLEC6A		-	90
Interleukin-42			-

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