

Research Article

The role of interleukin-19 in lung, colon and prostate cancer as a biomarker of metastasis

Raheem Abd Zaid AL-Abedi ¹¹Department of Pathological Analysis, Faculty of Science, University of Kufa, Iraq.*Corresponding author: raheema.alabedi@uokufa.edu.iq

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Abstract

Background: IL-19, a pro-inflammatory cytokine from IL-10 family, stimulates tumor proliferation, invasion and immune-evasion by activating IL-20R complex and induction of STAT3 signaling pathway. The levels of IL-19 in circulation in various solid cancers and correlation of these levels with metastasis and sensitivity to cytotoxic treatments have not been studied yet. We have attempted to evaluate serum IL-19 concentration in patients with lung, colorectal, and prostate cancer at different clinical stages, and its possible role in metastasis and response to treatment. **Methods:** Venous blood serum samples were obtained from 34 patients with clinically diagnosed lung (n=11), colorectal (n=11), or prostate cancer (n=12) at different clinical stages I – IV, and 6 healthy individuals of similar age. The IL-19 concentration in serum was quantified in duplicates via Quantitative Sandwich Enzyme Linked Immunosorbent Assay (ELISA) with four-parameter logistic (4-PL) curve fitting. Differences between groups in the distribution of IL-19 levels among different clinical stages, metastases, and systemic chemotherapy treatments were analyzed via non-parametric Mann Whitney U test and Kruskal Wallis test, respectively, with Holm-adjusted pairwise post-hoc analysis. **Results:** The serum IL-19 levels were significantly higher in cancer patients as compared with healthy controls (median 79.8 pg/mL vs. 29.8 pg/mL; $p=0.000202$). IL-19 levels were significantly different between the three cancer types ($p=0.00135$), with the maximum in lung cancer (median 108.5 pg/mL), median in colorectal (77.8 pg/mL), and minimum in prostate cancer patients (42.3 pg/mL). There was no significant difference in the levels of IL-19 in separate anatomical clinical stages I – IV ($p=0.587$). In contrast, there were significant differences in stage IV patients dependent on presence of systemic chemotherapy ($p < 0.005$): the serum IL-19 levels in the untreated stage IV cancer patients were significantly higher (median 349.16 pg/mL; IQR: 324.74 – 361.53 pg/mL), whereas the IL-19 levels in chemotherapy-treated stage IV cancer patients were significantly lower (median 49.68 pg/mL; IQR: 24.98 – 97.35 pg/mL). **Conclusions:** The IL-19 is involved in the systemic inflammation associated with cancer and exhibits distinct pattern of expression depending on the type of the tumor, with preferential expression in inflammatory thoracic tumors. Although the increase of IL-19 levels starts at the early stage of tumor development, the significant increase is seen in untreated advanced/metastatic cancers, which is drastically decreased in cytotoxic treatment.

1. Introduction

One of the major causes of morbidity and mortality throughout the world is cancer. As mentioned by the World Health Organization (WHO) [1], there are about 10 million cases of cancer deaths every year. There are four key features that characterize cancer, which include uncontrolled cell proliferation, evading growth suppressors, the resistance to apoptosis and invasive capability of cancer [2]. Cancers are usually classified in terms of the stage and the grade clinically. The stage of cancer involves the description of the size of primary tumor, involvement of the regional lymph nodes and the presence or absence of metastases, which is described with the help of well-known TNM staging system [3]. While the stage relates to the extent of disease, the grade involves the differentiation of the cancer cells which reflects the degree of malignancy of them [4]. Among the hallmarks of cancer, metastasis is the leading cause of mortality from cancer as it changes the localized disease into the systemic one which is very difficult to treat [5]. In order to form metastasis, several steps have to be followed, such as local invasion, intravasation into the blood or lymphatic vessel, survival during circulation, extravasation and colonization of distant organs [6].

2. Literature review

2.1. Mechanisms of Cancer Metastasis

Metastasis is the way in which tumor cells break away from their primary site, spread (through lymphatics or bloodstream), settle at distant sites, survive and form new tumors. This is the leading cause of death from cancer. The stages of the metastatic cascade include invasion, intrastation, survival in circulation, extravasation, dormancy/colonization and formation of macroscopic metastases, all of which present biological and physical hurdles [7].

2.2. Systems for grading and staging cancer

The process of tumor staging involves estimating the extent of spread of the disease within the body including tumor size, regional lymph nodes involvement and metastases of cancerous cells to distant organs. The TNM classification is one of the most popular approaches to staging developed by the American Joint Committee on Cancer (AJCC). The letter T refers to tumor size and extension, N refers to regional lymph nodes involvement and M refers to metastases [8]. Staging of cancer helps determine the extent of disease and the optimal treatment strategies. Staging is divided into clinical and pathological approaches. In contrast to clinical staging, which is determined by the data collected prior to the start of treatment (physical examination, imaging, biopsies), the pathological staging is performed after the tumor surgical excision and microscopic analysis [9]. Usually, staging is numerical: stage 0 corresponds to carcinoma in situ (localized non-invasive); stage I is associated with small localized tumors, stages II–III are locally advanced tumors possibly involving regional lymph nodes, and stage IV is defined by distant metastasis [10]. Tumor grading is an additional approach to the diagnosis of cancer besides staging. The grading involves microscopic estimation of the appearance of tumor cells and provides information about the difference between cancerous cells and normal cells and the rate of growth and spread. Well-differentiated tumors (Grade 1) are similar to the normal tissue and characterized by slow growing, whereas poorly differentiated or undifferentiated tumors (Grade 3) look abnormal tissues and are generally considered as aggressive [9]. As an example, lung adenocarcinoma is graded by the International Association for the Study of Lung Cancer (IASLC) grading system. The latter is based on the most common histologic pattern and percentage of high-grade patterns, and thus grades tumors into Grades 1–3 [11]. The Gleason score and Grade Group system are used for prostate cancer grading. These systems include combination of two most common histological patterns to give a score from 6 to 10, which is further subdivided into Grade Groups 1–5 [12]. Moreover, tumor proliferation is often estimated by measuring the percentage of dividing cells by the markers of proliferation like Ki-67 [13]. Cytokines play an essential role in regulation of immune and inflammatory reactions, and their contribution to tumor development and progression is increasingly recognized [14].

Among these cytokines, cytokines belonging to IL-10 family including IL-19 have received much attention owing to their roles in immune cell plasticity and cancer biology [15].

2.3. Role of Cytokines in Cancer with Emphasis on IL-19

The role of cytokines in oncogenesis and metastasis is dichotomous, with some cytokines acting as tumor suppressors and others as tumor promoters, angiogenic, immunosuppressive, and metastatic. One such cytokine of recent interest as a potential mediator of cancer growth and metastasis is interleukin-19 (IL-19), which belongs to the IL-10 family of cytokines. It is secreted from various immune and non-immune cells like macrophages and fibroblasts and acts through IL-20 receptors, leading to signaling through STAT3, MAPKs, and NF- κ B pathways [16]. It has been shown that expression of IL-19 is upregulated in many cancers, including breast, colon, and esophageal squamous cell carcinoma cancers and correlates with metastasis [17].

2.4. Biological Functions and Signaling of IL-19

Interleukin-19 belongs to the group of cytokines, which comprise IL-10 family, together with IL-10, IL-20 and IL-24. Members of IL-10 family possess similar structure and have an important function of controlling immune response. Recently, IL-19 became the object of research as it has been found that its biological activity depends on environmental factors that allow participating in inflammation processes both actively and passively [18]. Under physiological conditions, IL-19 is usually expressed in small quantities. However, under the condition of inflammation or cellular stress, the expression of this cytokine significantly rises. Macrophages, monocytes, and microglial cells are recognized as the key sources of IL-19 production. Endothelial cells and vascular smooth muscle cells (VSMCs) can also express IL-19, especially upon vascular damage or inflammation mediator exposure [19]. Regulation of the expression of IL-19 takes place in accordance with innate immune pathways. They include pathways associated with Toll-like receptors (TLRs), CGAS-STING signaling pathway, and stress kinases JNK [20]. IL-19 exerts its biological activity through interaction with IL-20 receptor complex, which contains two subunits:

IL-20R α and IL-20R β . The activation of intracellular signaling pathways, including JAK-STAT pathway results in STAT3 phosphorylation and modulation of gene transcription [21]. It was proposed that in the vascular tissues, IL-19 has a protective role. It inhibits proliferation of vascular smooth muscle cells, decreases oxidative stress through induction of heme oxygenase-1 and regulates mRNA decay of inflammatory genes [19].

2.5. IL-19 in Tumor Microenvironment and Metastasis

Interleukin-19 (IL-19) belongs to the cytokine group, namely the IL-10 cytokine family that is crucial for regulation of immune response and inflammation. Nevertheless, there are situations in which IL-19 causes the immune inflammatory responses. For example, in case of allergic diseases such as asthma, IL-19 stimulates T helper 2 (Th2) cytokine production – especially IL-4, IL-5, and IL-13. As a result, IL-19 contributes to airway hyperresponsiveness [22]. The importance of IL-19 has been identified in various disease models. For instance, in experimental autoimmune encephalomyelitis (EAE), which is a murine model of multiple sclerosis, IL-19 deficiency exacerbated the disease and increased the infiltration of T helper 17 (Th17) cells in the central nervous system, while recombinant IL-19 decreased disease severity. Importantly, in onco-immunology, IL-19 expression was discovered in the glioblastoma tissues, where it contributes to tumor invasion and immune evasion and can be used as a potential biomarker and target for therapy [23]. Interleukin-19 (IL-19) is a member of the IL-10 cytokine family that plays a pivotal role in the regulation of immune responses and inflammation. Recent studies have proven that IL-19 not only induces inflammatory processes but is also responsible for cancer cell dissemination and metastasis [24, 25]. IL-19 creates a pro-tumor microenvironment through activation of signaling pathways, such as STAT3 and NF- κ B, leading to the increase in the number of angiogenesis factors, such as VEGF, and causing tumor invasion and spread to other tissues and into the bloodstream [26]. Moreover, IL-19 has been shown to promote epithelial-mesenchymal transition (EMT), one of the crucial mechanisms of metastasis, providing cancer cells with mobility and ability to invade neighboring tissues [25]. These effects have been observed in various types of cancer – colon, lung, and prostate cancer – where high expression of IL-19 was correlated with high metastatic capacity and poor survival [25–27]. In addition, IL-19 regulates the microenvironment of the tumor by inhibiting the activity of anti-tumor immune cells – CD8+ T cells and natural killer cells, further promoting metastasis [28]. Thus, IL-19 acts both as a biomarker and a promoter of cancer metastasis, presenting a potential target for therapies aimed at cancer metastasis inhibition [24, 28]. Even though the growing amount of studies on the role of IL-19 in cancer metastasis and progression has been conducted, its clinical significance and connection with cancer development are not well studied yet. Therefore, additional research is necessary to determine whether IL-19 can be considered a biomarker. Thus, the aim of this study is to examine the role of IL-19 and the possibility of its correlation with cancer progression.

2.6. Study Aim and Rationale

Recent research indicates that there is an upregulation of interleukin-19 (IL-19) in a number of malignancies, including lung, colon, and prostate cancer. However, despite the fact that there has been a significant amount of evidence that indicates that IL-19 may play a role in cancer biology, its role in cancer metastasis as well as the relationship between IL-19 and the different stages of various cancers has yet to be fully determined.

3. Methods

3.1. Blood Collection

Venous blood samples from patients suffering from three forms of cancer—lung cancer, colon cancer, and prostate cancer—were used in the study. These patients were categorized in terms of the four clinical stages of their disease (Stage I, Stage II, Stage III, and Stage IV). Furthermore, the control group comprised healthy donors without any form of malignancy.

3.2. Serum Separation and Storage

About 5 mL of venous blood sample was obtained from all subjects in gel-containing tubes. These samples were allowed to clot at room temperature for 20 minutes. The next step involved centrifuging the clotted blood sample at 1500 $\times$ g for 10 minutes so that the clear serum could be obtained. These serum samples were then taken out using micropipette and placed into Eppendorf tubes so as to prevent cell contamination.

3.3. Enzyme Linked Immunosorbent Assay (ELISA)

3.3.1. Preparation of Reagents

The level of IL-19 cytokine in serum samples was determined using a human IL-19 ELISA Solarbio Life Sciences (SLS) SEKH-0030, kit based on the quantitative sandwich enzyme immunoassay technique. All reagents and samples were brought to room temperature for 30 minutes before use.

Preparation of Washing Buffer

The concentrated 20 $\times$ wash buffer was prepared from the double distilled water based on the volume needed for the experiment. It was incubated at 37°C until all crystals were dissolved in the wash buffer.

Preparation of standard

A lyophilized IL-19 standard solution of concentration 2000 pg/mL was prepared by dissolving it in 1 mL of SR1 Standard/Sample Diluent. It was allowed to dissolve in the medium for about 10-30 minutes while mixing gently.

The standard solutions of 2000, 1000, 500, 250, 125, 62.5, and 31.25 pg/mL were prepared through two-fold serial dilutions.

In order to make the dilutions, 500 μ L of Standard/Sample Diluent was first dispensed in 6 EP tubes. Then 500 μ L of the standard solution of 2000 pg/mL was dispensed in the first tube, mixed well to get a concentration of 1000 pg/mL. Then 500 μ L of this solution was dispensed in the second tube, mixed well and so forth in order to get the required concentrations. The Standard/Sample Diluent alone was used as the zero standard (0 pg/mL) as shown in Figure 1.

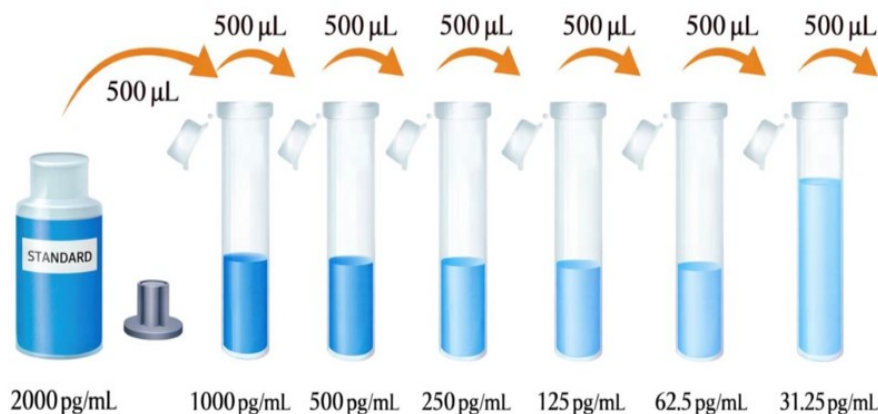


Figure 1: Standard Dilution Series

Biotin-Conjugated Anti-Human IL-19 Antibody

The stock solution of the biotin-conjugated antibody at a concentration of 100 times was diluted in a ratio of 1:100 with the SR2 Biotin-Conjugated Antibody Diluent.

Streptavidin-HRP Working Solution

Working solution of streptavidin-HRP 100 $\times$ concentrated was made by diluting with SR3 streptavidin-HRP diluent at a ratio of 1:100. The diluted solution was stirred and used within 30 minutes.

3.3.2. B Assay Procedure

The diagram below shows the complete ELISA procedure

All reagents and samples were pre-warmed to room temperature before beginning the test. The plate was washed two times with 300 μ L 1 $\times$ wash buffer in each well and then dried with absorbent paper. 100 μ L of serially diluted standards was added to the corresponding standard wells. 100 μ L of Standard/Sample Diluent was added to the blank wells, while 100 μ L of serum samples was added to the corresponding sample wells. The plate was sealed and incubated at 37°C for 90 min.

The solution was discarded and washed four times with 300 μ L of wash buffer in each well to remove residual solution in the process of washing. Then, 100 μ L of Biotin-Conjugated antibody working solution was added to each well. The plate was sealed and incubated at 37°C for 60 min. Discard the solution and wash four times. 100 μ L of Streptavidin-HRP working solution was added to each well, and incubated at 37°C for 30 min. Wells were washed five times with wash buffer.

Then, 100 μ L of TMB substrate solution was added to each well and incubated at 37°C for 15 min in the dark.

Finally, 50 μ L of Stop Solution was added to each well in the order same with that of substrate solution. Solution changed from blue to yellow. The measurement of the optical density (O.D.) was performed within 5 min in PARA MEDICAL microplate reader at 450 nm with a reference wavelength of 630 nm. The optical density (O.D.) was obtained by subtracting the absorbance at 450 nm.

The concentrations of IL-19 in the samples were determined by calculating the standard curve of the concentration versus O.D. values according to a four-parameter logistic (4-PL) curve fitting approach.

3.4. Statistical Analysis

All statistical analysis was performed using GraphPad Prism (version 10.0; GraphPad Software, San Diego, CA, USA). The non-normality of the distribution of data (Shapiro-Wilk test) necessitated the use of non-parametric tests in all comparisons. The data are shown as median $\pm$ IQR.

Two independent groups comparison (e.g., control group and cancer patients) was done using the Mann-Whitney U test. Comparing three or more independent groups (e.g., cancer stage, cancer type, metastatic status including control group) was done by Kruskal-Wallis test. If there was a difference between the groups, the post-hoc pairwise comparison was performed by Mann-Whitney U test with Holm correction as shown in Figure 2.

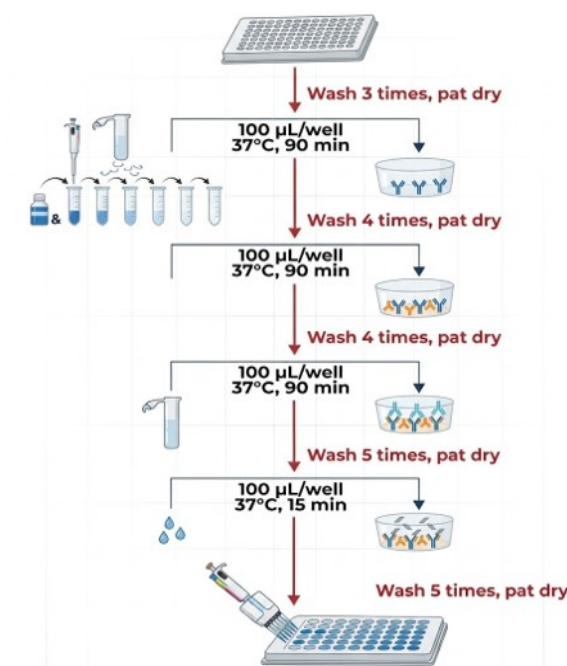


Figure 2: ELISA procedure

In the case of sub-groups analysis (e.g., metastasis, chemo time and treatment time), outliers were defined and excluded from analysis according to the interquartile range (IQR) criterion (values that were smaller than $Q1 - 1.5 \times IQR$ and larger than $Q3 + 1.5 \times IQR$ were eliminated). Only the sub-groups with the number of participants equal or higher than three were included into analysis ($n \geq 3$).

P-value less than 0.05 was considered statistically significant. Significance is shown as * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$.

4. Results

4.1. Interleukin-19 level in healthy and cancer patients

IL-19 levels were determined among both control samples and those of patients suffering from cancer through averaging of three replicate per sample. The level of IL-19 was significantly higher in the patients' group ($n=34$) as compared to the control group ($n=6$) (Mann-Whitney U test, $p=0.000202$). Despite the fact that the results of the patient group exhibited more variance and some high results, the general distribution was still biased upwards as shown in Figure 3.

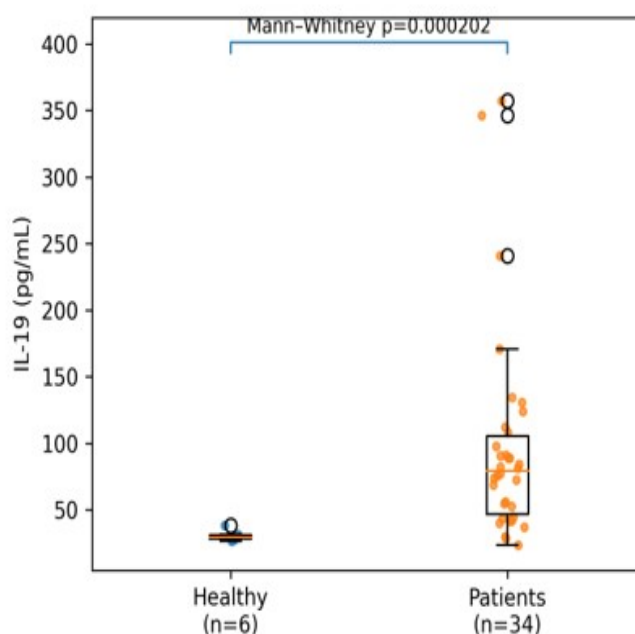


Figure 3: Interleukin-19 (IL-19) levels in healthy controls ($n=6$) and cancer patients ($n=34$). Boxplots show median and IQR with individual data points; Mann-Whitney U test $p=0.000202$

4.2. Interleukin 19 level crosse cancer stage

Comparison of IL-19 levels for various stages of the disease (from I to IV) was done by taking an average value of IL-19 for two samples per one sample. IL-19 levels are shown as medians with interquartile ranges for different stages of the disease (Stage 1, N=4; Stage 2, N=6; Stage 3, N=11; Stage 4, N=13). Though IL-19 levels differed for the various stages of the disease, there was no statistically significant difference between the stages ($p=0.587$ Kruskal-Wallis test) as shown in Figure 4.

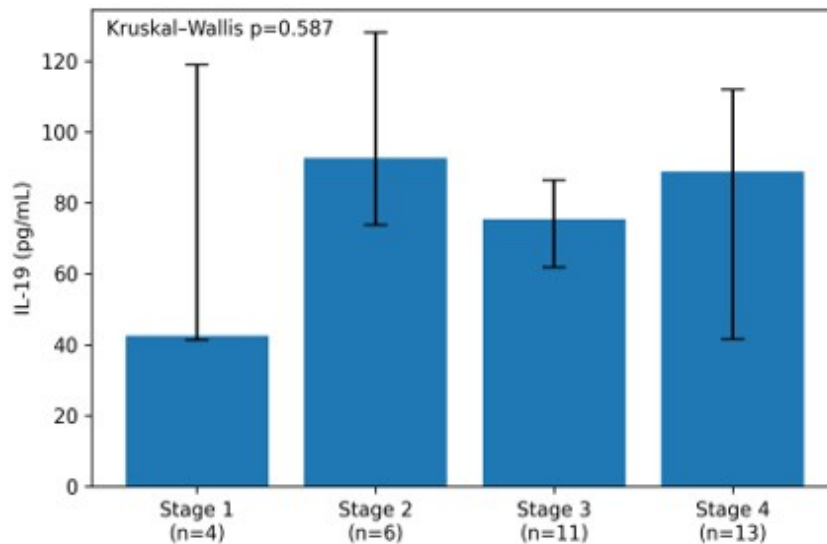


Figure 4: Interleukin-19 (IL-19) levels across cancer stages (I–IV). Bars represent the median IL-19 concentration (pg/mL) and error bars represent the interquartile range (IQR). Numbers under each stage indicate sample size (n). Overall comparison was performed using the Kruskal–Wallis test ($p=0.587$)

4.3. Interleukin-19 level by cancer type

The levels of IL-19 between different cancers (colon, lung, and prostate cancers) were compared using the means calculated per sample from duplicated samples. There were significant differences in the levels of IL-19 between different cancers (Kruskal-Wallis test, $p=0.00135$). The lung cancers exhibited higher levels of IL-19, while colon and prostate cancers were intermediate and low respectively as shown in Figure 5.

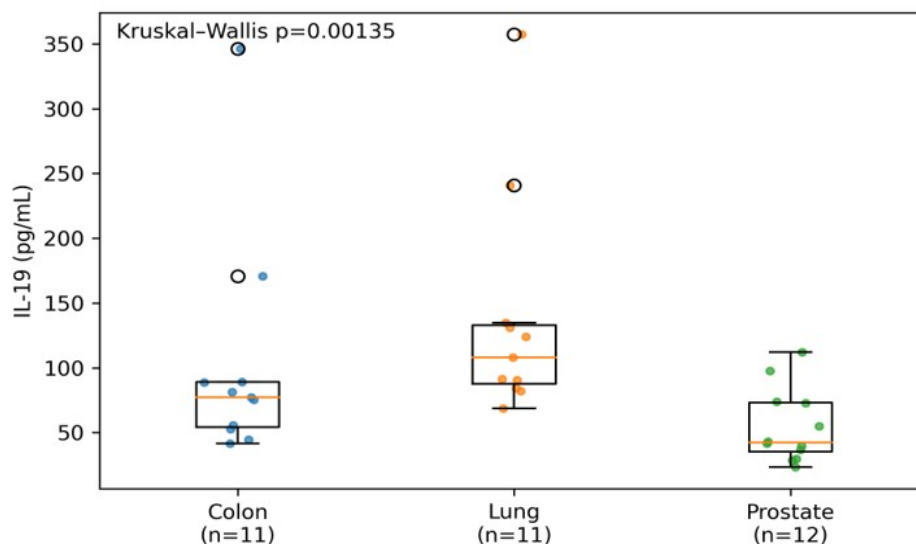


Figure 5: Interleukin-19 (IL-19) concentrations by cancer type. Boxplots show the median and interquartile range (IQR), with individual patient values overlaid as points. Sample sizes are shown beneath each cancer type. Overall group differences were assessed using the Kruskal–Wallis test ($p=0.00135$)

4.4. IL-19 across stages by cancer type

The median levels of IL-19 in different cancer stages for each type of cancer were considered to analyze stage-specific patterns in order to minimize the effect of skewness on the results. In order not to obtain unstable values, subgroups of stage-cancer with at least three patients

were used for plotting patterns ($n \geq 3$). There were stage-specific differences in median levels of IL-19 in different types of cancer, with median IL-19 being elevated in lung cancer in comparison with colon and prostate cancers as shown in Figure 6.

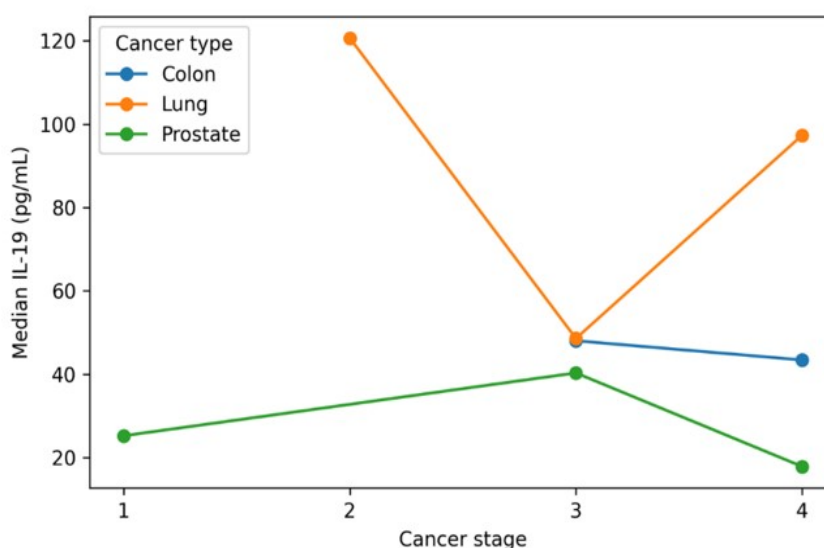


Figure 6: Pattern plot of median interleukin-19 (IL-19) concentrations across cancer stages stratified by cancer type. Lines connect the median IL-19 values (pg/mL) across stages for each cancer type. Only stage–type subgroups with $n \geq 3$ were plotted to reduce bias from very small sample sizes; groups with $n < 3$ were not shown

4.5. Interleukin-19 level in metastasis versus non metastasis cancer

For assessment of the differences in IL-19 expression between groups that were either non-metastatic (Stages 1–2) or metastatic (Stages 3–4), outliers were identified within each group by an IQR method. The median levels of IL-19 were greater in the metastatic group than in the non-metastatic group; however, there was still some overlap in the distributions as shown in Figure 7.

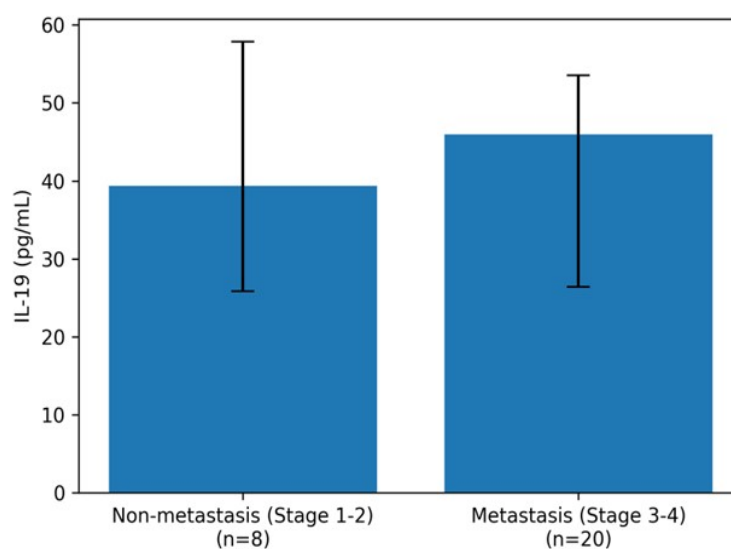


Figure 7: Interleukin-19 (IL-19) levels in non-metastatic versus metastatic cancer. Patients were classified as non-metastasis (Stage 1–2) or metastasis (Stage 3–4). Bars represent the median IL-19 concentration (pg/mL) and error bars represent the interquartile range (IQR). Sample sizes are shown below group labels. Outliers were removed within groups using an IQR-based method prior to plotting

4.6. Interleukin level among healthy non-metastasis and metastasis cancer

IL-19 levels were analyzed in healthy controls, non-metastatic cancer (Stages 1–2) and metastatic cancer (Stages 3–4) based on the average level for each sample obtained from triplicates. Using the IQR-based approach, within group outliers were identified and excluded, and a significant difference in IL-19 levels between the three groups was seen (Kruskal-Wallis $p=0.0126$). Pairwise comparisons (Mann-Whitney U test after Holm correction) showed that IL-19 levels were significantly higher in non-metastatic and metastatic cancers, but not between non-metastatic and metastatic cancers as shown in Figure 8.

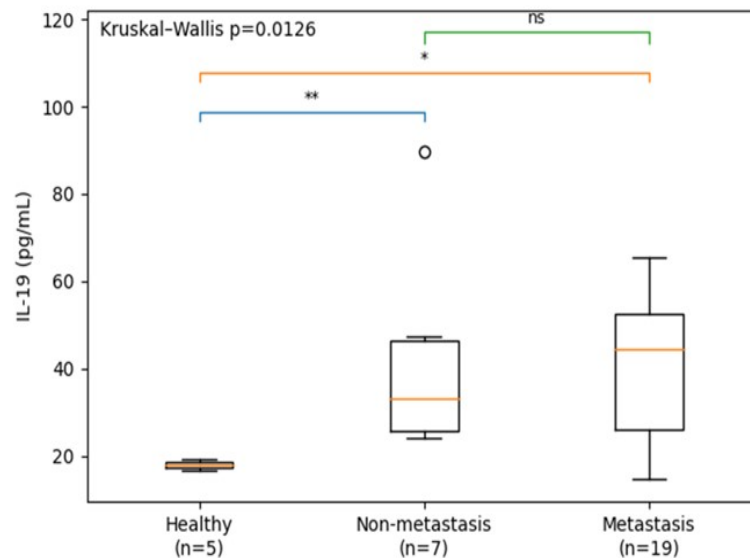


Figure 8: IL-19 concentrations in healthy individuals and cancer patients depending on metastases. The patients were categorized into either non-metastasis (Stage 1-2) or metastasis (Stage 3-4) categories. Box plots show the median and interquartile range (IQR), while the whiskers show the variability and outliers. The number of samples in each category is given under each sample. The overall analysis was conducted by applying Kruskal-Wallis test, and post-hoc pairwise analysis was conducted using Mann-Whitney U test with Holm correction; significance is marked as ns, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. The outliers were eliminated in each category based on IQR criteria before statistical analysis and presentation

4.7. IL-19 levels before and after chemotherapy

In order to examine whether treatment with chemotherapy impacts the levels of IL-19 in each stage of cancer, patients were divided into categories according to stage (I–IV) and treatment status: Chemo (treated with chemotherapy) or No Chemo (not receiving chemotherapy). Small numbers of patients in subcategories can generate unstable distribution estimations; therefore, box plots were shown for subcategories having $n \geq 3$. In general, there was a great deal of overlap in the IL-19 distributions of treated and untreated patients in the stages when both subgroups had sufficient number of patients as shown in Figure 9.

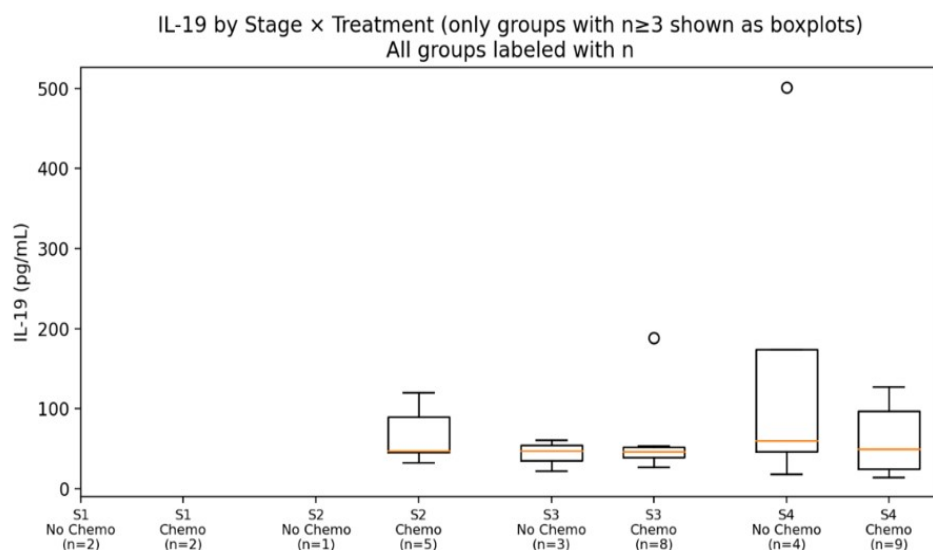


Figure 9: IL-19 Levels by Cancer Stage according to Chemotherapy. The subjects were divided by their cancer stage (1-4) and whether “No Chemo” or “Chemo” therapy was administered to them. Box plots indicate the median value (line in the center), interquartile range (boxes) and the outliers (points). The numbers of observations (n) for each combination of stages and treatment are shown below each group title. Box plots are provided only if at least three observations ($n \geq 3$) are present in both treatment groups of a particular stage

4.8. Treatment duration is associated with IL-19 levels

To examine the relation of the duration of treatment to IL-19 level among various cancer stages, the chemotherapy patients were classified as “short” and “long” according to the median of chemotherapy duration (Short ≤ 90 days; Long > 90 days). Median and IQR of IL-19 levels by stage were calculated. In order to prevent unstable estimate due to very few numbers of each stage-duration groups, the groups which had more than three subjects were represented using bars, otherwise the groups were labeled without representing them on bar graphs. The

results suggest that there was great variation in IL-19 level within stages and overlap among duration groups as shown in Figure 10.

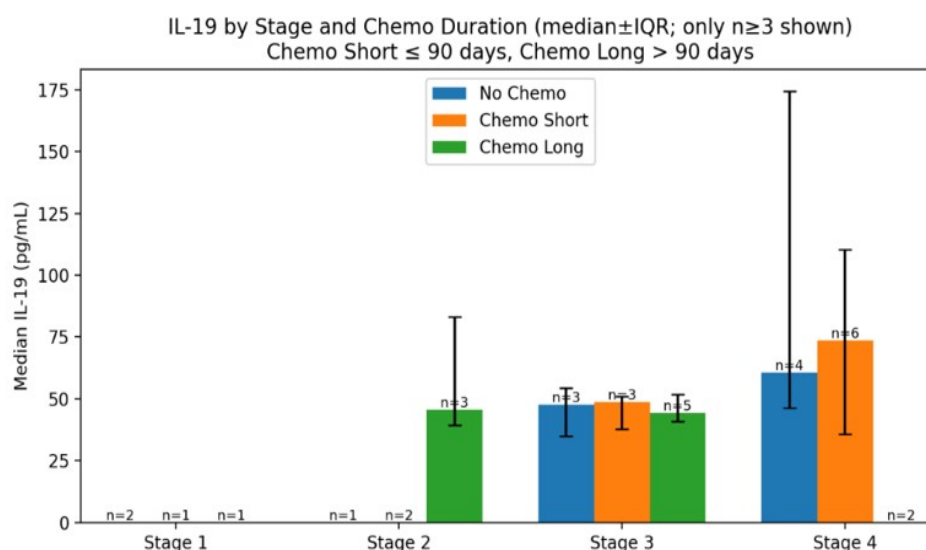


Figure 10: Interleukin-19 (IL-19) levels with respect to cancer stage and based on chemotherapy duration. Subjects were divided into groups based on their cancer stages (from 1 to 4) and were classified as either “No Chemo”, “Chemo Short” (≤ 90 days), or “Chemo Long” (> 90 days). Bars indicate the median IL-19 level (pg/mL) and error bars represent interquartile range (IQR). The sample size (n) is indicated for each group. To minimize bias introduced due to small sample sizes, plots are done only for $n \geq 3$, while others are labeled but not plotted

4.9. Interleukin level in stage 4

Figure 11. presents the distribution of serum levels of IL-19 in healthy control individuals, stage IV cancer patients under chemotherapy, and stage IV cancer patients without undergoing any chemotherapy. The values are displayed as the median level with interquartile range (IQR), where the individual values are depicted as overlapped dots. Healthy controls had the lowest levels of IL-19, having a median level of 18.14 pg/mL (IQR: 17.24 – 19.33). Stage IV patients undergoing chemotherapy had a higher level of IL-19 compared to healthy control individuals, with a median level of 49.68 pg/mL (IQR: 24.98 – 97.35). The highest IL-19 level was reported in the group of stage IV patients who did not receive any chemotherapy, with a median level of 349.16 pg/mL (IQR: 324.74 – 361.53).

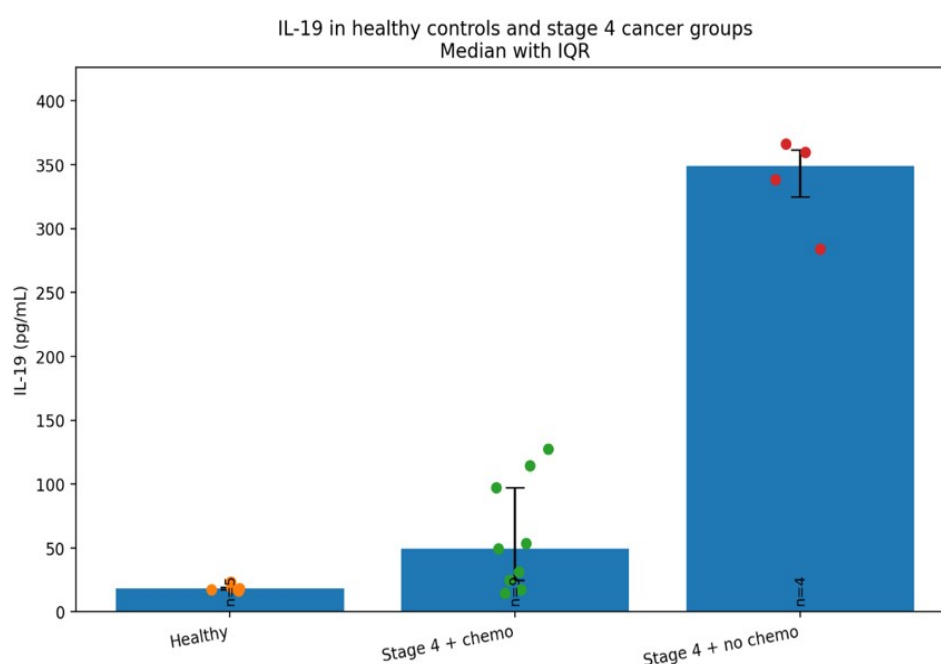


Figure 11: Levels of interleukin-19 (IL-19) in serum samples from healthy subjects and from stage IV cancer patients receiving and not receiving chemotherapy. Bars show median serum IL-19 levels (pg/mL) while error bars represent IQR. Data points represent values for individual subjects. Number of healthy controls was 5, number of stage IV patients receiving chemotherapy was 9, and number of stage IV patients not receiving chemotherapy was 4. Median IL-19 levels were 18.14 pg/mL (IQR: 17.24 – 19.33) in healthy subjects, 49.68 pg/mL (IQR: 24.98 – 97.35) in stage IV patients receiving chemotherapy, and 349.16 pg/mL (IQR: 324.74 – 361.53) in stage IV patients not receiving chemotherapy. $p < 0.005$.

5. Discussion

This investigation aimed to determine the levels of serum interleukin-19 (IL-19) in cancer patients and healthy individuals. It evaluated the association of IL-19 levels with the administration of chemotherapy, cancer type, and the stage of the disease. The results revealed that IL-19 levels are markedly higher in cancer patients than healthy individuals and that their levels depend on the cancer type.

5.1. Increased IL-19 in Cancer Patients

The level of IL-19 was significantly higher in cancer patients compared to the control group ($p = 0.000202$). This result is consistent with the growing body of evidence suggesting that IL-19 promotes tumor progression by activating STAT3 signaling pathways [29, 30]. IL-19 can promote the development of cancer cells, increase their motility, avoid the immune system, and create a favorable tumor microenvironment [31].

Recently, it was reported that IL-19 can stimulate the secretion of various inflammatory mediators as well as angiogenesis; these processes can contribute to the development and maintenance of tumors [29]. Moreover, cytokines from the IL-10 family are being recognized more and more often as modulators of inflammatory and immune response in relation to cancer [32]. Hence, the increased level of IL-19 in this study population might suggest its potential role as a biomarker for malignancy-related inflammation.

5.2. IL-19 Across Cancer Stages

Even though there were differences in the levels of IL-19 in stages I–IV, no statistically significant result was obtained ($p = 0.587$). The lack of difference between stages suggests that the increase in IL-19 occurs early in tumor development and continues consistently through all the following stages.

Inflammation plays a key role in cancer, and the disturbance of inflammatory cytokines occurs even at early stages of disease [33]. The chronic activation of STAT3 pathway, which can be induced by various cytokines such as IL-19 and other members of IL-19 family, results in chronic inflammation irrespective of tumor stage [30]. Hence, IL-19 can reflect inflammation activation rather than the tumor load itself.

Moreover, the smaller sample size in early stages may have reduced statistical power.

5.3. Differences by Cancer Type

The levels of IL-19 were significant in colon, lung, and prostate cancer ($p = 0.00135$), wherein lung cancer exhibited the highest levels.

Such finding correlates with the literature suggesting significant inflammation in lung cancer cases due to the activation of STAT3 via cytokines [29, 30]. Inflammation usually takes place in the case of lung cancer, resulting in cytokine overproduction [33].

On the other hand, prostate cancer is often defined as relatively less inflamed (“immune-cold”) tumor when compared to lung or colorectal cancer [31].

5.4. IL-19 and Metastatic Status

The median levels of IL-19 were higher in patients with metastases compared to those of non-metastatic patients, but the difference between them failed to achieve statistical significance. Overall difference between the groups of healthy individuals, non-metastatic and metastatic patients was significant ($p = 0.0126$).

Based on the previous studies, IL-19 can contribute to tumor progression and its dissemination. It is supposed to be mediated by its action on the polarization of tumor-associated macrophages and activation of STAT3 pathway [34]. Tumor-associated macrophages are believed to be essential for tumor dissemination process, whereas cytokines from the IL-10 family are responsible for creating immune suppressive microenvironment of tumors [32, 35].

That is why increased IL-19 in metastatic patients could be biologically reasonable despite the lack of statistical significance in this particular case.

5.5. IL-19 and Chemotherapy

From the data, one can note a clear trend: IL-19 concentration was very high in the group of Stage IV cancer patients without chemotherapy, while in the case of patients with Stage IV cancer and with chemotherapy, IL-19 levels were significantly lower, but still higher than in control samples. The median IL-19 levels for control, chemotherapy, and no-chemotherapy samples were 18.14 pg/mL, 49.68 pg/mL, and 349.16 pg/mL, respectively. This means that in advanced cancer, chemotherapy can be linked to low IL-19 levels, probably through reduction of tumor burden, inflammatory signaling modulation, or tumor microenvironment change. However, it should be noted cautiously due to the small number of samples in each of the subgroups, particularly for untreated Stage IV patients. Regardless of this, the new data suggest that it cannot be argued anymore that the impact of chemotherapy on IL-19 levels is completely inconsistent.

5.6. Overall Interpretation

From all of the results obtained above, it can be said that there is increased IL-19 in cancer patients, which correlates with inflammatory process related to tumors. The biomarker successfully distinguished cancer patients from controls, as well as different cancer groups among each other. Although previously, there was no correlation found between IL-19 concentration in different disease stages, the new results on Stage IV patients suggest that IL-19 in advanced cancers depends greatly on the state of chemotherapy treatment. The patients who did not have chemotherapy treatment had higher concentrations of IL-19, while chemotherapy treatment decreased the levels of this biomarker, indicating that therapy can affect IL-19-induced inflammation process.

6. Conclusion

This study showed that the level of IL-19 is higher in cancer patients as compared to healthy subjects which indicates the involvement of IL-19 in cancer-induced inflammation. In addition, IL-19 varies depending on the type of cancer, which further proves that the level of IL-19 expression is affected by the specific biological nature of each tumor. While there was no significant variation observed in cancer stages with regard to IL-19 in the overall population, the new analysis of the stage IV patients showed an interesting pattern in that the patients who do not get chemotherapy had significantly higher levels of IL-19 than the patients who got the therapy, although the levels were higher than healthy subjects for both of them. Thus, in advanced cancer, IL-19 is related not only to the inflammation caused by the disease but also the kind of therapy received by patients.

Recommendations

Given the above analysis, along with the newly included Stage IV data, we can recommend the following steps for future research:

1. Increase sample size of advanced-stage patients: To confirm the difference in IL-19 between untreated and chemotherapy-treated advanced-stage patients, future research should include larger samples of such patients.
2. Study longitudinal dynamics of IL-19 in response to chemotherapy: Given that the new data demonstrate the possible influence of chemotherapy on IL-19 in advanced cancer, IL-19 should be studied prior to, during, and after chemotherapy to identify its possible role as a predictor of treatment response.
3. Consider treatment status in analyzing IL-19: Future research should not only consider IL-19 in terms of stages/metastases of cancer, but should also stratify patients with regard to whether they had received chemotherapy, since treatment affects IL-19 dynamics in advanced cancer.
4. Balance the subgroups of patients across cancer types/stages: This would help to identify whether differences in IL-19 are caused by cancer type, disease stage, presence of metastasis, or treatment.
5. Investigate mechanism behind chemotherapy-induced decrease in IL-19: Experimentally it is necessary to investigate what underlying mechanisms lie behind decreased levels of IL-19 after chemotherapy: it may reflect decreased tumor burden or reduced activity of the tumor microenvironment or other phenomena.

Limitations of the Work

1. The study used cross-sectional approach in which data was collected from one point in time.
2. Low sample size, particularly for control group and early stages.
3. Lack of biological sample testing (serum test only).
4. Possible uncontrolled confounding factors (age, smoking, other health issues).
5. Further studies could be conducted to assess the effect of IL-19 along with other cytokines on multi-marker tests.

Future Work

1. Multi-center studies using large cohorts.
2. Longitudinal studies to assess IL-19 expression.
3. Tissue-based studies (IHC of IL-19 and receptors).
4. Mechanistic studies on EMT, angiogenesis, and immune evasion.
5. Evaluating IL-19 as a target for therapy.
6. IL-19 in combination with other cytokines as biomarkers.

Article Information

Ethical Approval: The study was approved by the HUMAN RESEARCH ETHICS COMMITTEE/ University of Kufa, Faculty of Science/ Medical pathological analyses under approval number 25, DATE/ 12/08/2025.

Informed Consent: Written informed consent was obtained from all participants before their inclusion in the study.

Consent for Publication: Not applicable.

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Clinical Trial Registration: Not applicable.

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References

- [1] World Health Organization. Global cancer burden growing, amidst mounting need for services, 2024. URL <https://www.who.int/news/item/01-02-2024-global-cancer-burden-growing--amidst-mounting-need-for-services>.
- [2] D. Hanahan and R. A. Weinberg. Hallmarks of cancer: the next generation. *Cell*, 144(5):646–674, 2011. URL <https://doi.org/10.1016/j.cell.2011.02.013>.
- [3] J. D. Brierley, M. Giuliani, B. O'Sullivan, B. Rous, and E. V. Eycken. *TNM classification of malignant tumours*. John Wiley & Sons, 2025.
- [4] M. B. Amin, F. L. Greene, S. B. Edge, C. C. Compton, J. E. Gershenwald, R. K. Brookland, L. Meyer, D. M. Gress, D. R. Byrd, and D. P. Winchester. The eighth edition AJCC cancer staging manual: continuing to build a bridge from a population-based to a more “personalized” approach to cancer staging. *CA Cancer J Clin*, 67(2):93–99, 2017. URL <https://doi.org/10.3322/caac.21388>.
- [5] A. W. Lambert, D. R. Pattabiraman, and R. A. Weinberg. Emerging Biological Principles of Metastasis. *Cell*, 168(4):670–691, 2017. URL <https://doi.org/10.1016/j.cell.2016.11.037>.
- [6] S. Valastyan and R. A. Weinberg. Tumor metastasis: molecular insights and evolving paradigms. *Cell*, 147(2):275–292, 2011. URL <https://doi.org/10.1016/j.cell.2011.09.024>.
- [7] J. Fares, M. Y. Fares, H. H. Khachfe, H. A. Salhab, and Y. Fares. Molecular principles of metastasis: a hallmark of cancer revisited. *Signal Transduct Target Ther*, 5(1):28, 2020. URL <https://doi.org/10.1038/s41392-020-0134-x>.
- [8] M. B. Amin, S. Edge, and F. Greene. *Cancer Staging Manual*. Springer, New York, 2017. Pages 1-30.
- [9] C. H. Hsing, H. C. Cheng, Y. H. Hsu, C. H. Chan, C. H. Yeh, C. F. Li, and M. S. Chang. Upregulated IL-19 in breast cancer promotes tumor progression and affects clinical outcome. *Clin Cancer Res*, 18(3):713–725, 2012. URL <https://doi.org/10.1158/1078-0432.ccr-11-1532>.
- [10] G. Cserni, E. Chmielik, B. Cserni, and T. Tot. The new TNM-based staging of breast cancer. *Virchows Arch*, 472(5):697–703, 2018. URL <https://doi.org/10.1007/s00428-018-2301-9>. PMID: 29380126.
- [11] K. S. Tan, A. Reiner, K. Emoto, T. Eguchi, Y. Takahashi, R. G. Aly, N. Rekhtman, P. S. Adusumilli, and W. D. Travis. Novel Insights Into the International Association for the Study of Lung Cancer Grading System for Pulmonary Adenocarcinoma. *Modern Pathology*, 37(5):1001–1012, 2024. URL <https://doi.org/10.1016/j.modpat.2024.100520>.
- [12] J. I. Epstein, L. Egevad, and M. B. Amin. The 2014 ISUP Gleason Grading System: Update and Recommendations for Prostate Cancer Reporting. *European Urology*, 69(4):613–620, 2016.
- [13] M. Dowsett, T. O. Nielsen, and R. A'Hern. Assessment of Ki67 in Breast Cancer: Recommendations from the International Ki67 in Breast Cancer Working Group. *Journal of the National Cancer Institute*, 103(22):1656–1664, 2011. URL <https://doi.org/10.1093/jnci/djr393>.
- [14] J. J. O'Shea, M. Gadina, and R. M. Siegel. Cytokines and cytokine receptors. In A. K. Abbas, A. H. Lichtman, and S. Pillai, editors, *Cellular and Molecular Immunology*, pages 267–301. Elsevier, Philadelphia, 9th edition, 2018.
- [15] S. Rutz, X. Wang, and W. Ouyang. The IL-20 subfamily of cytokines—from host defence to tissue homeostasis. *Nature Reviews Immunology*, 14(12):783–795, 2014. URL <https://doi.org/10.1038/nri3766>.
- [16] G. Gallagher. Interleukin-19: multiple roles in immune regulation and disease. *Cytokine Growth Factor Rev*, 21(5):345–352, 2010. URL <https://doi.org/10.1016/j.cytogfr.2010.08.005>.
- [17] C. H. Hsing, H. C. Cheng, Y. H. Hsu, C. H. Chan, C. H. Yeh, C. F. Li, and M. S. Chang. Upregulated IL-19 in breast cancer promotes tumor progression and affects clinical outcome. *Clin Cancer Res*, 18(3):713–725, 2012. URL <https://doi.org/10.1158/1078-0432.ccr-11-1532>.
- [18] R. Sabat. IL-10 family of cytokines. *Cytokine & Growth Factor Reviews*, 21(5):315–324, 2018. URL <https://doi.org/10.1016/j.cytogfr.2010.11.001>.
- [19] Michael V Autieri. IL-19 and Other IL-20 Family Member Cytokines in Vascular Inflammatory Diseases. *Frontiers in Immunology*, 9:700, 2018. URL <https://doi.org/10.3389/fimmu.2018.00700>.
- [20] S. H. Small, E. J. Tang, R. L. Ragland, Y. Ruzankina, D. W. Schoppy, R. S. Mandal, M. R. Glineburg, Z. Ustelenca, D. J. Powell, F. Simpkins, F. B. Johnson, and E. J. Brown. Induction of IL19 expression through JNK and cGAS-STING modulates DNA damage-induced cytokine production. *Science Signaling*, 14:eaba2611, 2021. URL <https://doi.org/10.1126/scisignal.aba2611>.
- [21] H. Horiuchi, B. Parajuli, H. Komiya, Y. Ogawa, S. Jin, K. Takahashi, Y. T. Azuma, F. Tanaka, A. Suzumura, and H. Takeuchi. Interleukin-19 Abrogates Experimental Autoimmune Encephalomyelitis by Attenuating Antigen-Presenting Cell Activation. *Frontiers in Immunology*, 12:615898, 2021. URL <https://doi.org/10.3389/fimmu.2021.615898>.

- [22] Y. H. Weng, W. Y. Chen, Y. L. Lin, J. Y. Wang, and M. S. Chang. Blocking IL-19 Signaling Ameliorates Allergen-Induced Airway Inflammation. *Front Immunol*, 10:968, 2019. URL <https://doi.org/10.3389/fimmu.2019.00968>. PMID: 31114590, PMCID: PMC6503049.
- [23] W. Chiu, J. B. Hsu, Y. W. Chang, L. C. Hsieh, Y. T. Li, Y. C. Wu, C. Y. Chu, Y. H. Chiang, W. Y. Guo, C. C. Wu, L. W. Chen, H. W. Kao, W. L. Lin, L. W. Tseng, T. W. Weng, D. P. Kuo, S. J. Cheng, Y. C. Chen, Huang S. W., H. J. Kung, and C. Y. Chen. IL-19 as a promising theranostic target to reprogram the glioblastoma immunosuppressive microenvironment. *Journal of Biomedical Science*, 32: 1126, 2025. URL <https://doi.org/10.1186/s12929-025-01126-w>.
- [24] G. Gallagher. Interleukin-19 promotes tumor progression and metastasis through STAT3 signaling in human cancers. *Cancer Immunology Research*, 6(4):424–435, 2018.
- [25] X. Wang. IL-19 facilitates epithelial-mesenchymal transition and metastasis in colorectal cancer. *OncoTargets and Therapy*, 12: 1121–1132, 2019.
- [26] H. Zhang. Interleukin-19 enhances angiogenesis and metastasis in prostate cancer via NF- κ B/VEGF pathway. *Frontiers in Oncology*, 11:678912, 2021.
- [27] Y. Li. The role of IL-19 in modulating tumor microenvironment and promoting metastasis in lung cancer. *Journal of Translational Medicine*, 18(1):256, 2020.
- [28] J. Chen. IL-19 as a novel mediator of immune evasion and metastasis in solid tumors. *Cytokine*, 150:155767, 2022.
- [29] Y. Chen, M. F. Chen, and M. S. Lu. Interleukin-19 promotes tumor progression and immune evasion through STAT3 signaling in lung cancer. *Frontiers in Oncology*, 11:641191, 2021.
- [30] H. Park, S. Lee, J. Lee, H. Moon, and S. W. Ro. Exploring the JAK/STAT Signaling Pathway in Hepatocellular Carcinoma: Unraveling Signaling Complexity and Therapeutic Implications. *International Journal of Molecular Sciences*, 24(18):13764, 2023. URL <https://doi.org/10.3390/ijms241813764>.
- [31] C. Ding, H. Gao, L. Zhang, Z. Lu, B. Zhang, D. Li, and F. Sun. The signature based on interleukin family and receptors identified IL19 and IL20RA in promoting nephroblastoma progression through STAT3 pathway. *Scientific Reports*, 15(1):11639, 2025. URL <https://doi.org/10.1038/s41598-025-96094-4>. PMID: 40185911, PMCID: PMC11971410.
- [32] G. Gallagher and J. Eskdale. Interleukin-10 family cytokines and their receptors: Emerging roles in tumor immunology. *Cytokine & Growth Factor Reviews*, 45:1–10, 2019.
- [33] M. S. Millat, M. M. Hasan, M. S. Uddin, M. A. Salam, M. A. Aziz, I. Akhter, M. S. Hussain, N. Mohammad, F. A. Tanjum, M. S. Mostaq, M. A. Mahmud, M. N. Amin, and M. S. Islam. Inflammatory cytokines and specific factors influencing lung cancer progression. *Cancer Pathogenesis and Therapy*, 3(6):484–500, 2025. URL <https://doi.org/10.1016/j.cpt.2025.04.002>. PMID: 41179937, PMCID: PMC12573595.
- [34] G. A. Lee, J. B. Hsu, Y. W. Chang, L. C. Hsieh, Y. T. Li, Y. C. Wu, C. Y. Chu, Y. H. Chiang, W. Y. Guo, C. C. Wu, L. W. Chen, H. W. Kao, W. L. Lin, L. W. Tseng, T. W. Weng, D. P. Kuo, S. J. Cheng, Y. C. Chen, S. W. Huang, H. J. Kung, and C. Y. Chen. IL-19 as a promising theranostic target to reprogram the glioblastoma immunosuppressive microenvironment. *Journal of Biomedical Science*, 32 (1):34, 2025. URL <https://doi.org/10.1186/s12929-025-01126-w>. PMID: 40057744, PMCID: PMC11889942.
- [35] Y. Yang, S. Li, K. K. W. To, S. Zhu, F. Wang, and L. Fu. Tumor-associated macrophages remodel the suppressive tumor immune microenvironment and targeted therapy for immunotherapy. *Journal of Experimental and Clinical Cancer Research*, 44(1):145, 2025. URL <https://doi.org/10.1186/s13046-025-03377-9>. PMID: 40380196, PMCID: PMC12083052.