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SOLUBLE CXCR4, SURVIVIN, AND EXOSOMAL BCL-2: PROMISING MARKERS FOR THE DIAGNOSIS OF LEUKEMIA AND EVALUATION THE INHIBITORY EFFICACY OF CHEMOTHERAPY

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ABSTRACT

Background: Malignant tumors are associated with cancer term due to their lack of a protective capsule and their invasive and metastatic properties. Maliglishing secondary tumors in distant parts of the body through metastasis. Metastasis is a crucial feature distinguishing malignant tumors from benign ones. During metastasis, cancer cells spread from a primary organ or tissue to a secondary site, promoting angiogenesis, the formation of new blood vessels. This process supports the growth and development of tumors by supplying the nutrients and oxygen necessary for their survival and expansion The term ‘’leukemia’’ is derived from an ancient Greek word leukos (white) and haima (blood) that means ‘’white blood’’ therefore it refers to a wide range of malignant disorders in hematopoietic stem cells (HSCs) in the bone marrow due to the accumulation of abnormal white blood cells (WBCs). The duration of this disease varies depending on the type of leukemia, therapeutic methods and patients’ response. Thus, leukemia is considered one of the most aggressive, dangerous hematologic disorder types of cancers all over the world. The current study aims to identify new prognostic markers for leukemias, distinguishing them from healthy individuals, and then monitor the effect of chemotherapy on suppressing carcinogenesis and achieving remission after receiving at least three consecutive chemotherapy doses. The study design was implemented practically by assessing the levels of Soluble C-X-C Motif Chemokine Receptor 4 "Soluble CXCR4", Survivin, and Exosomal BCL-2.

Patients and Healthy Control: During 7 months, a total of 60 individuals were enrolled in the current study, they are divided into two main groups: Leukemic patients group, that included 30 patients diagnosed with various types of leukemia, they ranging in age from 16 to 79 years, and Healthy Controls that included 30 healthy individuals, they ranging in age from 12 to 70 years. The samples of patients with leukemia were collected from the National Oncology and Hematology Hospital in Najaf Governorate, as well as Hematology and Oncology Hospital-Medical City of Al-Imam Al-Hussain in Karbala Governorate before chemotherapy and were followed up during the chemotherapy period. This group included 4different types of leukemia ALL, AML, CLL and CML. All patients with different types of leukemia were diagnosed by oncologists. Sandwich ELISA technique was applied to evaluate the studied criteria.

Results: The results showed a significant increase in soluble CXCR4 levels in the study patients before ($p=0.000$) and after receiving treatment together, as well as when comparing the study patients before receiving treatment with the control group. The study revealed significant differences when comparing Survivin levels in the leukemia group before receiving chemotherapy compared to the same samples after completing chemotherapy ($p=0.000$), as well as their counterparts in the control group ($p=0.000$). ANOVA test revealed a significant increase in Exosomal BCL-2 levels in leukemia patients before chemotherapy compared to healthy individuals ($p=0.000$), as well as compared to samples from the leukemia patient group after three consecutive doses of chemotherapy. The results of the correlation test between Soluble CXCR4 and both Survivin and Exosomal BCL-2; respectively, indicate statistically significant positive correlations in the group of patients with leukemia at diagnosis. On the other hand, the study showed a positively signigicant correlation only between Soluble CXCR4 and Exosomal BCL-2 ($r=0.648$ at $p=0.033$) in the control group. Despite the significant decrease in the levels of Soluble CXCR4, Survivin and Exosomal BCL-2 to nearly the levels of the control group after receiving at least 3 consecutive doses of chemotherapy, the relationship between Soluble CXCR4 and both Survivin and Exosomal BCL-2 remained positive and statistically acceptable.a significant positive correlation between Survivin to Exosomal BCL-2 in approximately 91 individuals of the leukemia patient group before treatment, while no such results were recorded in the control group. With the same manar, the outcomes indicate that the relationship between Survivin and Exosomal BCL-2 remained significantly positive in the leukemia patient group after receiving chemotherapy, despite the decrease in the level of these two parameters to levels similar to those recorded in the group of healthy individuals. The individual sensitivity and specificity of the evaluated criteria in the current study for diagnosting cancerous patients reached the highest level (100%). Post-treatment, the results showed that the highest sensitivity (100%) were published for Survivin and Exosonal BCL-2, while the highest specificity (100%) was recorded for Survivin.

Conclusions: The absolute sensitivity of the evaluated criteria provides them as three promising tools for diagnosting different leukemic cases, and verifying the effectiveness of chemotherapy in treating leukemia.

KEYWORDS: Leukemia, Chemotherapy , Soluble CXCR4, Survivin, Exosomal BCL-2

INRTODUCTION

Malignant tumors are associated with cancer term due to their lack of a protective capsule and their invasive and metastatic properties. Metastasis is a crucial feature distinguishing malignant tumors from benign ones. During metastasis, cancer cells spread from a primary organ or tissue to a secondary site, promoting angiogenesis, the formation of new blood vessels. This process supports the growth and development of tumors by supplying the nutrients and oxygen necessary for their survival and expansion [Saghezi et al., 2025]. In general, cancer is a type of tumor that demonstrates abnormal cell growth with the potential to invade or spread from its originating organ ("site") to other parts of the body tumors gain their potential to invade or spread by acquiring multiple malignant phenotypes through genetic and epigenetic alterations that disrupt key cellular pathways such as DNA damage and repair, control of proliferation, and avoiding immune destruction [Schwartz, 2024]. According to the National Cancer Institute (NCI) and the Centers for Disease Control and Prevention (CDC), cancer represents a significant global health problem, encompassing over 100 different types that may originate in specific tissues and spread throughout the body. It is among the leading causes of morbidity and death worldwide [Erasha et al., 2025]. Cancers are broadly classified into solid tumors and hematological malignancies. Solid tumors arise in organs and form localized masses, whereas hematological malignancies, including leukemia, lymphoma, and multiple myeloma, originate in blood-forming tissues and typically do not form solid masses [Ma et al., 2024]. Blood malignancies rank fifth among all cancer forms in developed countries. Although intense treatment can cure some blood cancers, only 40% of them have the potential to be cured, and 60% of those can be fatal Early diagnosis is difficult due to the gradual onset of symptoms, which often appear as signs of other illnesses [Warnakulasuriya and Tiwari, 2026]. In recent decades, the incidence and mortality rates of cancer have been increasing in the world Grasping the intricacies of carcinogenesis is essential for the formulation of effective prevention and treatment strategies. Over the past half century, therapies that target tumor cells have significantly prolonged the survival of cancer patients and greatly improved their prognosis [Zhou et al., 2025]. Scientists developed a variety of cancer therapies, such as chemotherapy, radiotherapy, surgical therapy, and immunotherapy, which are currently available. These treatments can harm healthy cells and may cause other adverse effects. Consequently, scientists are investigating innovative approaches to target and eliminate tumor cells while selectively minimizing side effects [Erasha et al., 2025]. Leukemia is 13th in cancer cases and 10th in cancer associated deaths based on reported information from the International Agency for Research on Cancer (IARC). Leukemia is most common in people aged over 60, also, it is the most affected cancer in children and youngsters under the age of 20, marking it as one of the three cancer cases identified [Aby et al., 2024]. In Iraq, leukemia is the 4th most common cancer among both men and women. Recent epidemiological studies show that its incidence is steadily increasing, particularly among children and young adults. Iraq ranks 26th globally in leukemia mortality rates, with an age adjusted death rate of 4.79 per 100,000 population. In 2020, leukemia deaths accounted for approximately 0.90% of all deaths in the country. The incidence is higher among males than females, with a male-to-female ratio of ~1.4:1 in some governorates, such as Karbala. The prevalence of different types of leukemia in Iraq varies, but acute leukemia remains the most common. ALL is the most prevalent type, especially among children, accounting for ~41% to 48% of all leukemia cases. AML is the second most common, representing 19% to 25% of all blood cancer cases. CML accounts for ~8% to 24% of cases, while CLL is the least common and typically affects older adults, accounting for about 15%. Leukemia represents ~25% to 40% of all childhood cancers in Iraq. In Mosul, leukemia is the most common childhood cancer, with an annual incidence rate of 5.45 per 100,000 children. The average age at diagnosis in Iraq (around 30 years) is significantly lower than in Western countries (65 years in the US), which is attributed to Iraq's young population. Baghdad has recorded the highest distribution of leukemia cases of all types compared to other governorates. Studies in Muthanna Governorate have also observed a significant increase in cases over the last decade (2014-2023) [Mjali et al., 2019].

MATERIAL AND METHODS

The cohort study model was applied in the current work. The current study aims to identify new prognostic markers for leukemias, distinguishing them from healthy individuals, and then monitor the effect of chemotherapy on suppressing carcinogenesis and achieving remission after receiving at least three consecutive chemotherapy doses. The study design was implemented practically by assessing the levels of a group of proteins (Soluble C-X-C Motif Chemokine Receptor 4 "Soluble CXCR4", Survivin, and Exosomal BCL-2); they had not previously been studied in leukemias that included in the current work. During 7 months, a total of 60 individuals were enrolled in the current study, divided into two main groups: Leukemic patients group, that included 30 patients diagnosed with various types of leukemia, they ranging in age from 16 to 79 years, and Healthy Controls that included 30 healthy individuals, they ranging in age from 12 to 70 years. The samples of patients with leukemia were collected from the National Oncology and Hematology Hospital in Najaf Governorate, as well as Hematology and Oncology Hospital-Medical City of Al-Imam Al-Hussain in Karbala Governorate before chemotherapy and were followed up during the chemotherapy period. This group included 4different types of leukemia "AcuteLymphoblastic Leukemia (ALL), Acute Myeloid Leukemia (AML), Chronic Lymphocytic Leukemia (CLL) and Chronic Myeloid Leukemia (CML)". All patients with different types of leukemia 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.

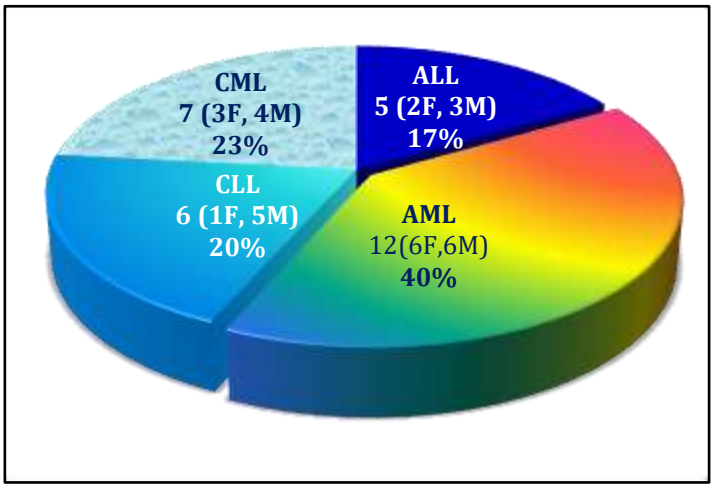

Figure 1: Sex and Percentage of Various Leukemia Patients Types Participating in the Study

The current study required the exclusion of the following cases: patients with secondary leukemia, patients with solid cancers, patients who did not complete the planned course of chemotherapy, cases undergoing chemotherapy sessions due to relapse and recurrence of leukemia and cases whose treatment program did not include chemotherapy doses.
Samples for this study were obtained from individuals by drawing 5 mL sample of venous blood was collected from all study participants, including patients with various leukemia types and healthy individuals using sterile intravenous. The gel tube was placed at room temperature for one minute to allow the blood to clot, serum was then separated from the blood samples by centrifugation at 5000×g for 5 minutes. Serum samples were subsequently divided into three aliquots and stored in Eppendorf tubes at -20 °C until used for assessing the study parameters. Sandwich enzyme linked immune sorbent assay (Sandwich ELISA) method was applied to evaluate the studied criteria, the ELISA apparatus was supplied by Genex Laboratories, USA.
The outcomes of the present work 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 included independent student's t-test and analysis of variance (ANOVA) test to assess differences among the levels of the studied parameters in the patients and healthy individuals groups. Pearson's correlation was applied to determine the relation among the parameters of the present study. 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 DISCUSION

The current study was designed to evaluate Soluble C-X-C Motif Chemokine Receptor 4 (Soluble CXCR4), Survivin, and Exosomal BCL-2 as prognostic markers for leukemias, firstly, and to assess patients' response to chemotherapy after three sequances cgemotherapy doese, secondly. Essentially, the study included two groups (leukemic patients and controls). The current study included 60 participants divided into two groups. The first group comprised 30 patients diagnosed with various types of leukemia, ranging in age from 16 to 79 years. This group consisted of 18 males (69%) and 12 females (40%). The second group comprised 30 individuals with no family history of cancer, selected according to specific criteria as described in section 2.3.3. They were further divided into two subgroups: 14 males (47%) and 16 females (53%), ranging in age from 12 to 70 years. The patients group was initially diagnosed (Group G1) and then followed throughout their chemotherapy treatment, during which time blood samples were collected (Group G2). The study indicated that 18 patients were city residents (8 females and 10 males), while the remaining patients were from rural areas (4 females and 8females). Nineteen of the leukemic patients were educated (7 females and 12 males), while the 11 uneducated patients consisted of 7 females and 4 males. Educational level and place of residence may influence leukemia susceptibility indirectly through their association with socioeconomic conditions, environmental exposures, occupational hazards, and healthcare accessibility [Fritschi et al., 2014; Castaño-Vinyals, et al., 2015]. Lower educational attainment and residence in rural agricultural regions have been linked to increased leukemia risk in several epidemiological studies, although findings remain heterogeneous across populations [Schüz and Erdmann, 2016]. Consequently, these variables are best regarded as surrogate markers of exposure and social determinants of health rather than direct etiological factors in leukemogenesis [Leon et al., 2019].
The epidemiological studies have demonstrated significant gender-related differences in leukemia incidence. In general, males exhibit a higher incidence rate than females for most types of leukemia, including ALL, AML, and CLL. The underlying mechanisms are not fully understood but may involve genetic factors, hormonal influences, differences in immune responses, and environmental exposures. Therefore, sex is considered an important demographic variable in the leukemia research and is often included in statistical analyses to evaluate its potential impact on disease occurrence and clinical outcomes [Siegel et al., 2025]. Several studies have reported significant sex-related differences in the incidence of leukemia. In general, males exhibit a higher risk of developing most leukemia subtypes than females. A recent review

by Mostafa et al., highlighted that the major leukemia subtypes, including AML, ALL, CML, and CLL, demonstrate marked sex-based variations in the incidence and mortality rates, with males consistently showing higher incidence rates than females [Mostafa et al., 2026]. Age is one of the most important risk factors associated with the development of leukemia. The incidence of leukemia varies considerably among different age groups and according to the leukemia subtype. ALL is the most common leukemia in children, whereas AML, CLL, and CML are predominantly diagnosed in adults and elderly individuals. The increased risk of leukemia with advancing age may be attributed to the accumulation of genetic alterations, age related impairment of immune function, and prolonged exposure to environmental carcinogens. Consequently, age is considered a critical demographic factor affecting leukemia incidence, disease progression, treatment response, and prognosis [Shallis et al., 2019].

The levels of soluble CXCR-4 were measured in serum samples from the study groups, and the results showed a significant increase in soluble CXCR-4 levels in the study patients before (p=0.000) and after receiving treatment together, as well as when comparing the study patients before receiving treatment with the control group, as shown in **Table 1.** In contrast, the results of the current study indicate no statistically significant changes (p=0.854) in soluble CXCR-4 levels in leukemia patients after completing the chemotherapy doses prescribed by the specialists when compared to the control group.

Table 1: Levels of Soluble CXCR-4 in The Study Individuals

Subjects (n)	Soluble CXCR-4 (ng/mL) Mean ± S.D.	bluble CXCR-4 (ng/mL) Min-Max	Soluble CXCR-4 (ng/mL) Range	p–value
G_1 (30)	7.560±1.199	5.412-8.252	2.840	0.000 for G_1 vs G_2
G_2 (30)	3.633±1.069	3.032-5.616	2.584	0.000 for G_1 vs C
Controls (30)	3.305±1.338	2.977-4.516	1.539	0.854 for G_2 vs C

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

The markedly elevated levels of soluble CXCR4 observed in leukemia patients before chemotherapy may reflect the high leukemic burden and the intense interaction between leukemic cells and the bone marrow microenvironment. The CXCL12/CXCR4 signaling axis plays a central role in leukemia pathogenesis by promoting leukemic cell survival, proliferation, migration, homing, and resistance to apoptosis. Leukemic blasts frequently overexpress CXCR4, which enhances their retention within protective bone marrow niches and facilitates disease progression. High CXCR4 expression has been consistently associated with poor prognosis, increased relapse risk, and reduced response to therapy in acute leukemias [Burger and Peled, 2009]. From an immunological and molecular perspective, elevated circulating soluble CXCR4 may result from increased shedding or release of the receptor from leukemic cells due to their high turnover rate and extensive interaction with stromal cells. The increased number of malignant cells in circulation and bone marrow provides a substantial source of CXCR4-containing membrane fragments, microvesicles, and soluble receptor molecules. Furthermore, activation of the CXCL12/CXCR4 pathway contributes to leukemic cell survival and protection from immune-mediated elimination, thereby sustaining elevated CXCR4 levels during active disease [Uy, et al., 2012]. The significant decline in soluble CXCR4 levels after completion of chemotherapy is likely attributable to the marked reduction in leukemic cell burden. Successful chemotherapy eliminates a large proportion of CXCR4-expressing leukemic blasts, thereby decreasing the major source of soluble receptor release. In addition, the disruption of leukemia–stroma interactions and the restoration of normal hematopoiesis may reduce activation of the CXCL12/CXCR4 signaling pathway. Consequently, circulating sCXCR4 concentrations decline and may approach normal levels in patients who respond favorably to treatment [Bae, et al., 2015]. Another possible mechanism is that chemotherapy diminishes the inflammatory and tumor-supportive bone marrow microenvironment, reducing chemokine-mediated signaling and cellular trafficking. Since CXCR4 is critically involved in leukemic cell homing and chemoresistance, reduction of disease activity is expected to be accompanied by lower soluble CXCR4 levels. Studies have demonstrated that CXCR4 expression is strongly linked to leukemia cell survival and microenvironment-mediated resistance, and that targeting CXCR4 can enhance chemosensitivity and improve treatment responses [Sison, et al., 2013]. Tumor Immunology studies have demonstrated that CXCR4-mediated interactions between leukemic cells and bone marrow stromal cells contribute to disease progression, chemoresistance, and immune escape. The measurement of soluble CXCR4 in serum may provide a less invasive assessment of CXCR4 pathway activity and leukemic burden compared with cellular expression analysis, highlighting its potential value as a prognostic and treatment-monitoring biomarker in leukemia patients.

The study revealed statistically significant differences when comparing Survivin levels in the leukemia group before receiving chemotherapy compared to the same samples after completing chemotherapy (p=0.000), as well as their counterparts in the control group (p=0.000). Dissimilarity, statistical processing revealed no significant differences in Survivin levels when comparing the leukemia group who received chemotherapy with healthy individuals (p=0.481), as shown in **Table 2.**

Table 2: Levels of Survivin in The Study Individuals

Subjects (n)	Survivin (ng/mL) Mean±S.D.	Survivin (ng/mL) Min-Max	Survivin (ng/mL) Range	p – value
G_1 (30)	8.042±1.966	7.715-9.323	1.608	0.000 for G1 vs G2 0.000 for G1 vs C 0.481 for G2 vs C
G_2 (30)	4.122±1.305	3.824-5.506	1.682	
Controls (30)	3.693±1.852	3.093-5.112	2.019	

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

Survivin is a member of the Inhibitor of Apoptosis Protein (IAP) family and plays a crucial role in regulating cell division, inhibiting apoptosis, and promoting tumor cell survival. Under normal physiological conditions, Survivin expression is either absent or very low in most differentiated adult tissues; however, it is markedly overexpressed in a wide range of hematological and solid malignancies [Xie et al., 2026]. The significantly elevated serum Survivin levels observed in leukemia patients before chemotherapy may reflect the increased leukemic burden and enhanced resistance of malignant cells to programmed cell death. Leukemic blasts frequently overexpress Survivin as a survival mechanism, enabling them to evade apoptosis despite the accumulation of genetic abnormalities. Increased Survivin expression has been associated with aggressive disease behavior, increased proliferation, poor prognosis, and resistance to chemotherapy in both acute and chronic leukemias [Ghorbani et al., 2025]. From a molecular perspective, Survivin contributes to leukemogenesis by inhibiting caspase-dependent apoptotic pathways and supporting mitotic progression. Furthermore, rapidly proliferating leukemic cells may release Survivin into the circulation through cellular turnover, apoptosis-resistant cell populations, extracellular vesicles, and exosomes, resulting in elevated serum concentrations [Ghorbani et al., 2025]. Also, the leukemic microenvironment promotes Survivin expression through activation of several oncogenic signaling pathways, including PI3K/Akt, STAT3, NF-κB, and Wnt/β-catenin pathways. These pathways enhance leukemic cell survival and contribute to the maintenance of high Survivin levels during active disease [McCubrey et al., 2014]. Following chemotherapy, the marked reduction in serum Survivin levels is likely attributable to the substantial elimination of Survivin-expressing leukemic cells. Effective chemotherapy induces apoptosis in malignant cells, decreases tumor burden, and suppresses the signaling pathways responsible for Survivin overexpression. Consequently, the release of Survivin into the circulation is significantly reduced [Peng et al., 2013]. Moreover, successful treatment may partially restore normal hematopoiesis and reduce tumor-associated inflammatory signaling, leading to further down-regulation of Survivin production. Therefore, the post-treatment decline in serum Survivin levels may serve as an indicator of therapeutic efficacy and disease remission [Mahmoud et al., 2022]. According to alteration in the levels of Survivin pre- and post-treatment, therefore, serum Survivin may represent a useful biomarker for disease activity and treatment response in leukemia patients. Similar findings have been reported in leukemia as well as several solid tumors, supporting the role of Survivin as a biomarker of tumor activity and therapeutic response, i.e., increased Survivin expression has been reported in AML and was associated with enhanced blast survival and poor clinical outcome. Elevated Survivin levels have been linked to resistance to chemotherapy in ALL [Tanaka K et al., 2000]. Studies in breast cancer, colorectal cancer, lung cancer, and gastric cancer have demonstrated significantly higher Survivin levels in patients before treatment, followed by reductions after successful chemotherapy or surgical tumor removal. Meta-analyses have consistently identified Survivin as a marker of tumor aggressiveness and poor prognosis across multiple cancer types [Li, 2005; Jaiswal et al., 2015].

Statistical analysis using ANOVA revealed a significant increase in extracellular BCL-2 protein levels in leukemia patients before chemotherapy compared to healthy individuals (p=0.000), as well as compared to samples from the leukemia patient group after three consecutive doses of chemotherapy. The results indicated that the levels of this protein decreased significantly after chemotherapy, to levels close to those in the control group. When comparing the chemotherapy-treated group with the control group, no statistically significant differences were observed between the two groups (p=0.493), as shown in **Table 3**.

Table 3: Levels of Exosomal BCL-2 in The Study Individuals

Subjects (n)	Exosomal BCL-2 (ng/mL) Mean±S.D.	Exosomal BCL-2 (ng/mL) Min-Max	Exosomal BCL-2 (ng/mL) Range	p - value
G1 (30)	151.328±22.712	123.225-161.373	38.148	0.000 for G1 vs G2 0.000 for G1 vs C 0.493 for G2 vs C
G2 (30)	69.882±16.601	34.764-78.629	43.765	
Controls (30)	67.183±27.111	42.369-70.282	27.913	

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

Exosomal BCL-2 is increasingly recognized as a marker of tumor survival, resistance to apoptosis, and intercellular communication within the tumor microenvironment. The significantly elevated levels of exosomal BCL-2 observed in leukemia patients before chemotherapy may reflect the increased leukemic burden and the enhanced anti-apoptotic activity of malignant cells. BCL-2 is a key anti-apoptotic protein that inhibits the mitochondrial pathway of apoptosis by preventing mitochondrial membrane permeabilization and caspase activation. Leukemic cells frequently overexpress BCL-2 to evade programmed cell death and maintain uncontrolled proliferation. Consequently, exosomes released from leukemic blasts may contain elevated amounts of BCL-2 protein and other apoptosis-regulating molecules. These exosomes can transfer survival signals to neighboring malignant cells and contribute to disease progression, immune evasion, and chemotherapy resistance [Rehman et al., 2027]. From a biological perspective, the increased release of BCL-2-containing exosomes may represent a mechanism by which leukemia cells modify the bone marrow microenvironment. Exosomes can transport proteins, RNAs, and signaling molecules that promote cell survival and suppress apoptosis. Studies in AML have demonstrated that exosomes derived from apoptosis-resistant leukemic blasts are enriched with proteins involved in anti-apoptotic pathways, including members of the BCL-2 family [Rejili et al., 2026]. Furthermore, exosome-mediated communication has been implicated in the development of chemoresistance in leukemia. Bone marrow stromal cell-derived exosomes can protect leukemic cells from chemotherapy-induced apoptosis by maintaining elevated BCL-2 activity and suppressing pro-apoptotic signaling pathways [Ansarian et al., 2025]. The marked reduction in exosomal BCL-2 levels after completion of chemotherapy is likely attributable to the elimination of a substantial proportion of BCL-2-overexpressing leukemic cells. Successful chemotherapy decreases tumor burden, restores apoptotic signaling, and reduces the production and release of tumor-derived exosomes. Consequently, circulating exosomal BCL-2 levels decline and may approach those observed in healthy individuals. Similar post-treatment normalization of exosomal biomarkers has been reported in leukemia and other malignancies, supporting their utility as indicators of therapeutic response (Rehman et al., 2027]. Additionally, chemotherapy may disrupt the protective interactions between leukemic cells and the bone marrow microenvironment, thereby reducing the need for exosome-mediated survival signaling. The decline in exosomal BCL-2 may therefore reflect both a reduction in leukemic cell mass and a restoration of normal apoptotic homeostasis [Bao et al., 2026]. The significantly elevated exosomal BCL-2 levels observed in leukemia patients before chemotherapy may be attributed to increased leukemic burden, enhanced anti-apoptotic activity, and intensified exosome-mediated communication within the bone marrow microenvironment. Overexpression of BCL-2 enables leukemic cells to evade apoptosis and contributes to disease progression and treatment resistance. Following chemotherapy, exosomal BCL-2 levels decreased markedly, likely due to the reduction of leukemic cell mass, restoration of apoptotic mechanisms, and decreased release of tumor-derived exosomes. These findings suggest that exosomal BCL-2 may serve as a promising biomarker for monitoring disease activity and therapeutic response in leukemia patients. Kucharzewska and subsequent exosome studies in hematologic malignancies demonstrated that tumor-derived exosomes carry survival-promoting proteins and participate in tumor progression and treatment resistance [Kucharzewska et al., 2013]. Szczepanski reported that exosomes released by apoptosis-resistant AML blasts contain regulatory proteins involved in apoptosis antagonism, including BCL-2-associated pathways [Szczepanski et al., 2016]. Zhang demonstrated that bone marrow stromal cell-derived exosomes protect leukemic cells from etoposide-induced apoptosis through modulation of BCL-2/BAX signaling [Zhang et al., 2017]. Studies in breast cancer have shown that BCL-2 is highly expressed in tumor cells and that exosome-based targeting of BCL-2 can restore apoptosis and reduce tumor survival, highlighting the biological importance of exosomal BCL-2-related pathways across different cancer types [Kaban et al., 2021].

The results of the correlation test between Soluble CXCR4 and both Survivin and Exosomal BCL-2; respectively, indicate statistically significant positive correlations in the group of patients with leukemia at diagnosis (before receiving chemotherapy). On the other hand, the study showed a positively signigicant correlation only between Soluble CXCR4 and Exosomal BCL-2 (r=0.648 at p=0.033) in the control group**.** Despite the significant decrease in the levels of Soluble CXCR4, Survivin and Exosomal BCL-2 to nearly the levels of the control group after receiving at least 3 consecutive doses of chemotherapy, the relationship between Soluble CXCR4 and both Survivin and Exosomal BCL-2 remained positive and statistically acceptable, as shown in **Table 4.**

Table 4: Correlation of Soluble CXCR4 to the Evaluated Parameters in Leukemic Patients and Healthy Control Groups

Evaluated Parameters	Pre-treatment Leukimic Patients		Post-treatment Leukimic Patients		Healthy Individuals	
	r	p	r	p	r	p
Survivin	**0.830****	0.000	0.451*	0.013	0.226	0.056
Exosomal BCL-2	0.709**	0.000	**0.598****	0.001	0.420*	0.033

***Correlation is significant at the 0.05 level, **Correlation is significant at the 0.01 level**

The significant positive correlation between Soluble CXCR4 and both Survivin and Exosomal BCL-2 in leukemia patients prior to chemotherapy may reflect the coordinated activation of molecular pathways that promote leukemic cell survival, proliferation, and resistance to apoptosis [Mousavi et al., 2025]. CXCR4 is a chemokine receptor that plays a pivotal role in leukemic cell homing, retention within the bone marrow niche, and disease progression. Upon binding to its ligand CXCL12 (SDF-1), CXCR4 activates several downstream signaling pathways, including PI3K/Akt, MAPK/ERK, and NF-κB. These pathways are known to induce the expression of anti-apoptotic and pro-survival proteins, including Survivin [Su et al., 2021]. Survivin suppresses caspase activation and promotes cell cycle progression.

Increased CXCR4 signaling has been associated with enhanced Survivin expression in several hematological malignancies, thereby facilitating leukemic cell survival and resistance to programmed cell death. Consequently, patients exhibiting elevated Soluble CXCR4 levels are likely to demonstrate increased Survivin expression, resulting in the observed positive correlation [Bellemrrabet et al., 2026]. Activation of the CXCL12/CXCR4 axis has been shown to upregulate BCL-2 expression through PI3K/Akt- and NF-κB-dependent mechanisms, thereby enhancing cell survival. Furthermore, leukemic cells actively release extracellular vesicles, particularly exosomes, which carry proteins, mRNAs, and microRNAs involved in tumor progression. Elevated Exosomal BCL-2 levels may reflect increased anti-apoptotic signaling and intercellular communication within the leukemic microenvironment. Since CXCR4 signaling promotes both cellular survival and interaction with the bone marrow niche, higher Soluble CXCR4 levels may coincide with enhanced exosomal release of BCL-2 related cargo. Therefore, the positive association between soluble CXCR4 and Exosomal BCL-2 likely represents a shared biological mechanism aimed at protecting leukemic cells from apoptosis [Kalluri and LeBleu, 2020]. These findings indicate that elevated CXCR4 activity is closely linked to enhanced apoptotic resistance and leukemic cell persistence, thereby contributing to disease progression and poor prognosis before therapeutic intervention.

Chemotherapy primarily reduces the overall leukemic burden and suppresses the expression of molecules associated with tumor survival and proliferation. Consequently, the circulating levels of soluble CXCR4, Survivin, and exosomal BCL-2 decline markedly following treatment. The persistence of positive correlations between soluble CXCR4, Survivin, and Exosomal BCL-2 following chemotherapy, despite the significant decline in their circulating concentrations, suggests that these biomarkers remain under coordinated biological regulation after treatment [Nehrbas et al., 2020]. Although chemotherapy effectively reduced the leukemic burden and normalized the levels of these markers toward those observed in healthy individuals, the underlying molecular interactions linking CXCR4-mediated signaling with anti-apoptotic pathways appear to be preserved. Since CXCR4 activation can regulate downstream PI3K/Akt and NF-κB pathways, which in turn modulate Survivin and BCL-2 expression, patients exhibiting relatively higher residual CXCR4 activity may also maintain relatively higher levels of Survivin and exosomal BCL-2 [Huang et al., 2026]. Therefore, the observed post-treatment correlations likely reflect the persistence of a common survival network within residual leukemic cells and/or recovering hematopoietic cells rather than ongoing high-level expression of these biomarkers. This finding indicates that chemotherapy reduced the magnitude of biomarker expression without completely disrupting the biological associations among them [Nowroozi, 2026]. The maintenance of these positive correlations after chemotherapy may indicate that soluble CXCR4, Survivin, and exosomal BCL-2 are components of the same adaptive survival axis. While chemotherapy successfully diminished the overall expression of these biomarkers, individual differences in residual disease burden, minimal residual disease (MRD), bone marrow niche interactions, or hematopoietic regeneration may continue to drive their coordinated expression. Thus, the preserved correlations support the concept that CXCR4-dependent survival signaling remains biologically relevant even after apparent therapeutic response and may contribute to disease persistence or future relapse in a subset of patients [Khan et al., 2025; Zhou et al., 2026].

Another plausible explanation involves immune and hematopoietic recovery after chemotherapy. During bone marrow reconstitution, physiological signaling pathways involved in cell survival, trafficking, and tissue repair may contribute to the coordinated expression of CXCR4-related and anti-apoptotic molecules. Thus, the maintained correlations may not solely reflect residual malignancy but may also indicate shared regulatory mechanisms involved in post-treatment hematopoietic recovery [Demir et al., 2026].

Table 5 indicates a significant positive correlation between Survivin to Exosomal BCL-2 in approximately 91 individuals of the leukemia patient group before treatment, while no such results were recorded in the control group. With the same manar, the outcomes indicate that the relationship between Survivin and Exosomal BCL-2 remained significantly positive in the leukemia patient group after receiving chemotherapy, despite the decrease in the level of these two parameters to levels similar to those recorded in the group of healthy individuals.

Table 5: Correlation of Survivin to Exosomal BCL-2 in Leukemic Patints and Healthy Control Groups

Evaluated Parameters	Pre-treatment Leukimic Patients		Post-treatment Leukimic Patients		Healthy Individuals	
	r	p	r	p	R	p
Exosomal BCL-2	**0.811****	**0.000**	**0.536****	0.001	**0.120**	**0.082**

***Correlation is significant at the 0.05 level, **Correlation is significant at the 0.01 level**

The significant positive correlation observed between Survivin and Exosomal BCL-2 in leukemia patients prior to chemotherapy may reflect the coordinated activation of anti-apoptotic pathways that promote leukemic cell survival, proliferation, and resistance to programmed cell death. Survivin, a member of the inhibitor of apoptosis protein (IAP) family, suppresses caspase activation and regulates mitotic progression, thereby enhancing cell viability and proliferation. Likewise, BCL-2 is a key anti-apoptotic protein that prevents mitochondrial outer membrane permeabilization and inhibits the intrinsic apoptotic pathway. Elevated levels of BCL-2 packaged within exosomes may indicate active intercellular transfer of survival signals within the leukemic microenvironment [Ghorbani et al., 2025]. The positive association between these two biomarkers suggests that leukemic cells simultaneously upregulate multiple survival mechanisms to evade apoptosis. Cells expressing higher levels of Survivin are likely to exhibit increased BCL-2 expression and secretion through exosomes, resulting in a stronger anti-apoptotic phenotype. This coordinated expression may be driven by common oncogenic signaling pathways such as PI3K/AKT, NF-κB, STAT3, and MAPK, which are frequently

activated in hematological malignancies and are known to induce both Survivin and BCL-2 expression [Laein et al., 2026; Sharma et al., 2026]. Furthermore, exosome-mediated delivery of BCL-2 may enhance the survival capacity of neighboring leukemic cells and modify the bone marrow microenvironment, thereby supporting disease progression. The correlation therefore reflects not only intracellular apoptosis resistance but also exosome-dependent communication that contributes to leukemic cell persistence [Hrdinova and Kupcova, 2026]. The concurrent elevation of Survivin and Exosomal BCL-2 indicates a highly apoptosis-resistant leukemic phenotype, which may be associated with increased tumor burden, aggressive disease behavior, and reduced sensitivity to chemotherapy [Kakkat et al., 2024]. Several studies have reported functional cooperation between Survivin and BCL-2 in cancer cells, i.e., Adida et al., (1998) demonstrated that Survivin expression is associated with enhanced cell survival and resistance to apoptosis in malignant cells. Asanuma et al., (2005) reported that BCL-2 and Survivin cooperate to protect tumor cells from apoptotic stimuli, suggesting complementary anti-apoptotic functions, while; Carter et al., (2012) showed that Survivin expression positively correlates with BCL-2 family proteins in hematologic malignancies and contributes to chemoresistance [Laein et al., 2026; Sharma et al., 2026; Hrdinova and Kupcova, 2026; Kakkat et al., 2024]. Exosomal transfer of anti-apoptotic molecules, including BCL-2-related proteins, has been increasingly recognized as an important mechanism by which leukemia cells support survival and disease progression [Moqbel et al., 2026]. The persistence of a positive correlation between Survivin and Exosomal BCL-2 after chemotherapy, despite normalization of their circulating levels, suggests that chemotherapy attenuates the magnitude of anti-apoptotic signaling rather than abolishing the intrinsic biological linkage between these molecules. This finding may reflect continued co-regulation through shared survival pathways, the presence of minimal residual leukemic cells, and/or coordinated expression during hematopoietic recovery. Therefore, the correlation likely represents preservation of the underlying apoptosis-regulatory network despite successful therapeutic reduction of leukemic burden [Kim, 2026].

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 **Figures 2, 5, 3, 6,** and **4, 7** for **Soluble CXCR4, Survivin,** and **Exosomal BCL-2**; respectively.

Table 6 shows the area under the curve and threshold values for the parameters evaluated in patients with leukemia before receiving chemotherapy. The individual efficiency (sensitivity) and specificity of the evaluated criteria in the current study for diagnosting cancerous patients reached the highest level (100%).

Table 6: Receiver Operating Characteristic Analysis of the Evaluated Criteria as Diagnostic Markers for Leukemia

Criteria	AUC	SE	p-value	Cutoff value	Sensitivity%	Specificity%	CI (95%)
Siluble CXCR4	0.988	0.001	0.000	6.065	100	100	0.956-1.000
Survivin	1.000	0.000	0.000	6.223	100	100	1.000-1.000
Exosonal BCL-2	1.000	0.000	0.000	99.162	100	100	1.000-1.000

AUC: Area Under Curve, SE: Standard Error.

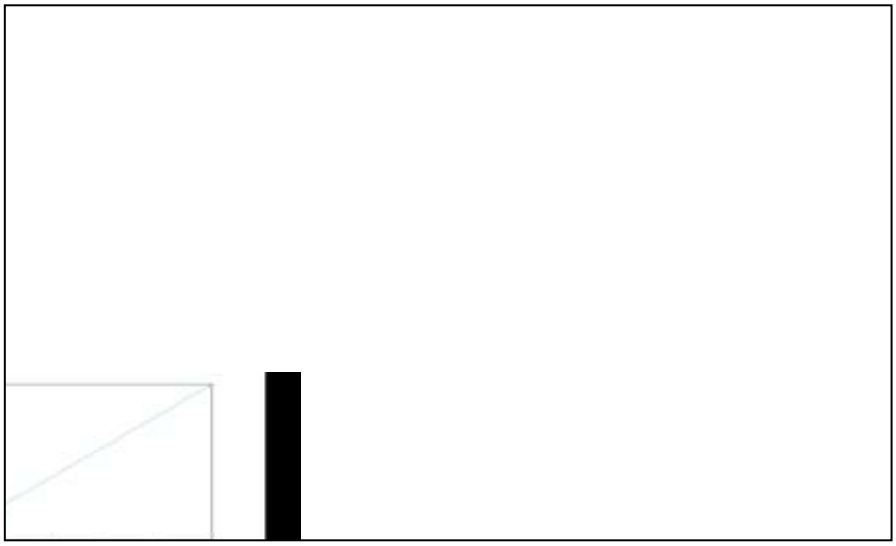

Figure 2: Receiver Operating Characteristic Curve for Soluble CXCR4 Pre-Treatment

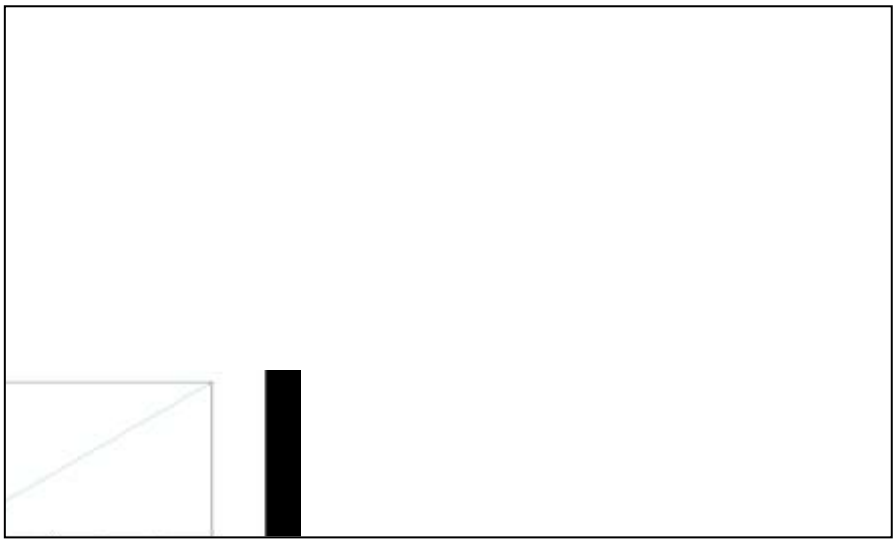

Figure 3: Receiver Operating Characteristic Curve for Survivin Pre-Treatment

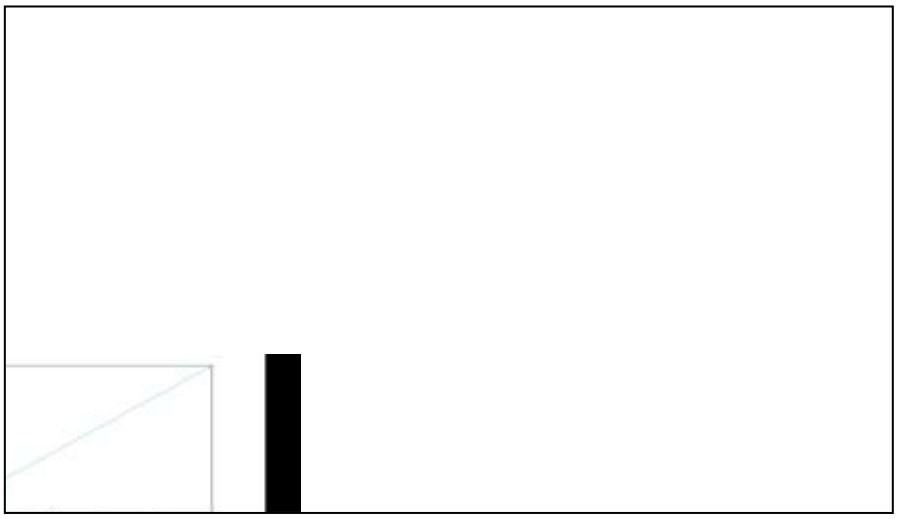

Figure 4: Receiver Operating Characteristic Curve for Exosomal BCL-2 Pre-Treatment

The combined sensitivity of the criteria (**Soluble CXCR4**, **Survivin**, and **Exosomal BCL-2**) were examined in the leukemic cases, as shown in **Table 7**. All criteria in this study showed a similar maximum sensitivity for each parameters (100%).

Table 7: The Combined Sensitivity of the Evaluated Parameters before Chemotherapy Treatment

Criteria	Soluble CXCR4	Survivin	Exosomal BCL-2
Soluble CXCR4	100	100	100
Survivin		100	100
Exosomal BCL-2			100

The absolute sensitivity of the criteria evaluated in the current work provides them as tools to diagnosise different leukemic cases.

Table 8 shows the area under the curve and threshold values for the evaluated criteria in the group of leukemic patients who received chemotherapy. The study showed that the highest sensitivity (100%) were published for Survivin and Exosonal BCL-2, while the highest specificity (100%) was recorded for Survivin.

Table 8: Receiver Operating Characteristic Analysis of Evaluated Criteria as Predictive Markers of Response to Chemotherapy

Criteria	AUC	SE	p-value	Cutoff value	Sensitivity%	Specificity%	CI (95%)
Soluble CXCR4	0.857	0.042	0.000	5.893	97	90	0.771-0.966
Survivin	1.000	0.000	0.000	6.445	100	100	1.000-1.000
Exosonal BCL-2	0.978	0.007	0.000	81.955	100	93	0.959-1.000

AUC: Area Under Curve, SE: Standard Error

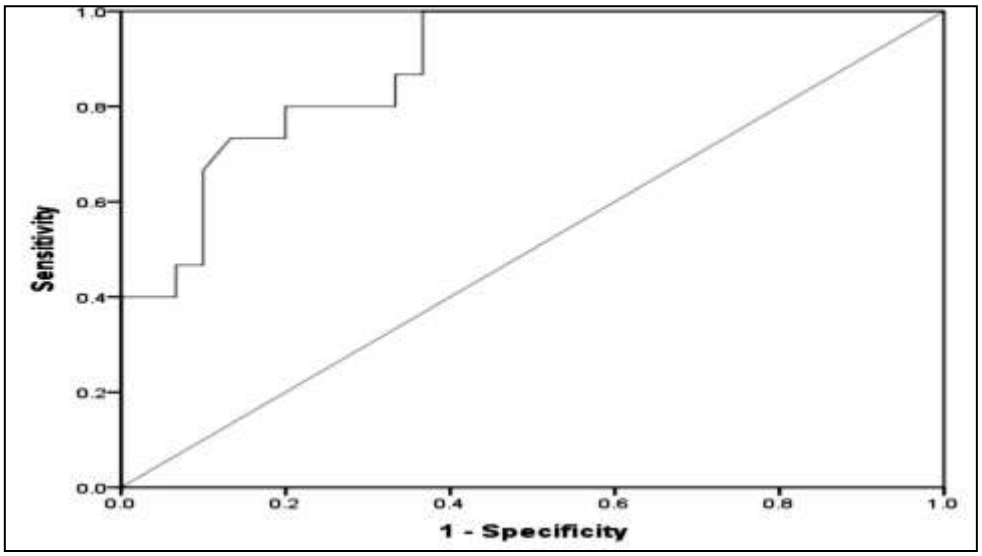

Figure 5: Receiver Operating Characteristic Curve for Soluble CXCR4 Post-Chemothetapy Treatment

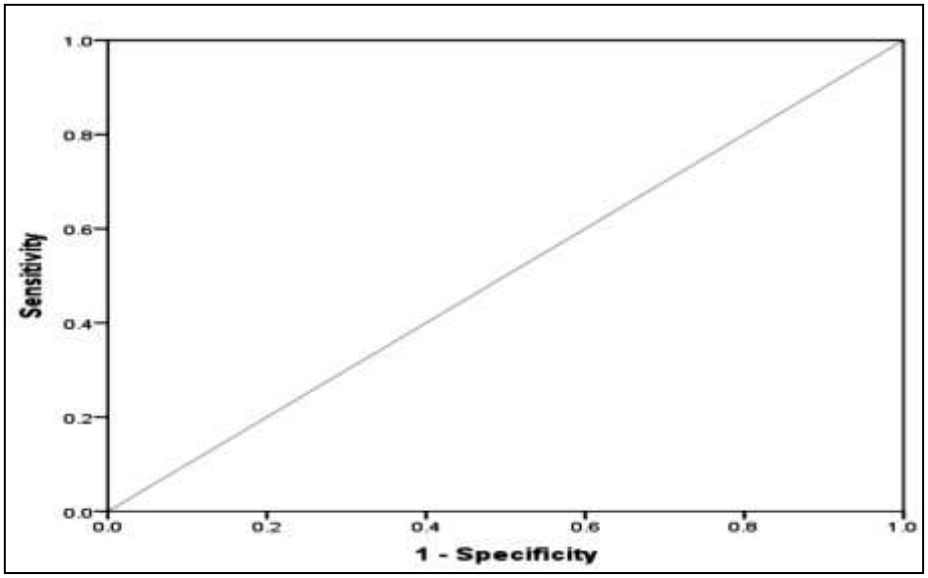

Figure 6: Receiver Operating Characteristic Curve for Survivin Post-Chemothetapy Treatment

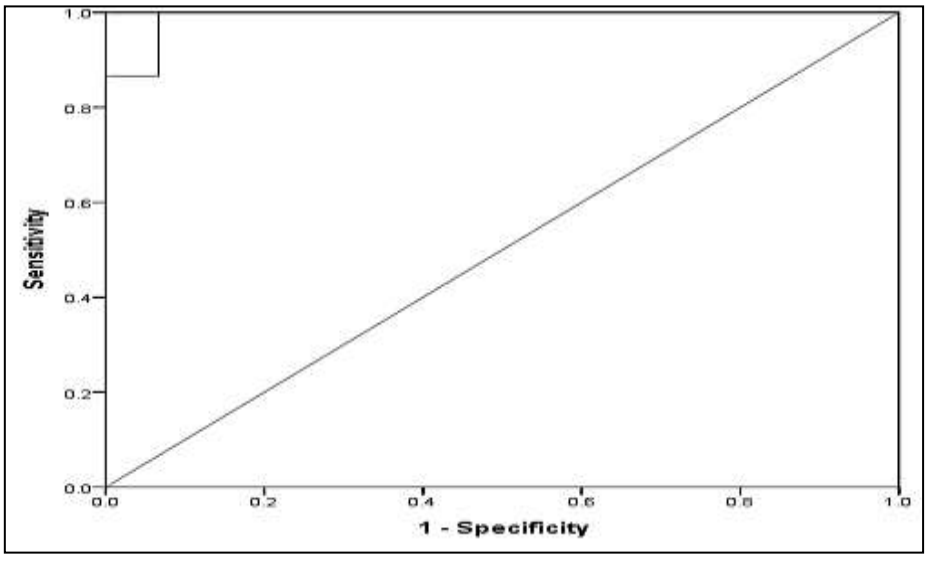

Figure 7: Receiver Operating Characteristic Curve for Exosomal BCL-2 Post-Chemothetapy Treatment

The combined sensitivity of the studied criteria (**Soluble CXCR4**, **Survivin**, and **Exosomal BCL-2**) were examined in the leukemic cases, as shown in **Table 9**. The results showed that measuring the criteria together raises the sensitivity

of the criteria to its maximum level (100%), therefore, the current study provides three promising tools for verifying the effectiveness of chemotherapy in treating leukemia.

Table 9: The Combined Sensitivity of the Evaluated Ctiteria Post-Chemotherapy Treatment

Criteria	Soluble CXCR4	Survivin	Exosomal BCL-2
Soluble CXCR4	90	100	100
Survivin		100	100
Exosomal BCL-2			93

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