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Exploring the Impact of Serum Growth Factors in the Pathogenesis of Acute and Chronic Myeloid Leukemia

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Abstract

Objective: Leukemias comprise a class of life- threatening disorders that occur with abnormal elevation of the numbers of leukocytes in the blood and/or bone marrow. The aim of this study is to assess the potential association between the amounts of serum growth factors and the risk of developing acute and chronic myeloid leukemia.

Methods: The research comprised 168 participants, aged between 21 and 69 of these, 52 were diagnosed with acute myeloid leukemia, while 71 had chronic myeloid leukemia from Hiwa Hospital in Sulaymaniyah. Moreover, 45 healthy individuals, matched for age and gender, were also recruited to act as controls in the study. The levels of Basic fibroblast growth factor, Insulin-like growth factor I, Vascular endothelial growth factor, Hepatocyte growth factor, Platelet-Derived Growth Factor and Transforming growth factor-β in the serum were evaluated using the sandwich enzyme-linked immunosorbent assay (ELISA) method, employing kits produced by RayBiotech company. Between the patient groups and the healthy control group, the mean values for the study parameters were compared using a one-way ANOVA.

Results: The serum levels of all mentioned growth factors showed significantly elevation in patients comparing to controls.

Conclusion: Serum Basic fibroblast growth factor and other growth factors might be a potential complementary biomarker for acute myeloid leukemia and chronic myeloid leukemia.

Keywords: Leukemia, basic fibroblast growth factor, vascular endothelial growth factor, platelet-derived growth factor, white blood cells

Introduction

Leukemias are fatal diseases characterized by an abnormal increase in white blood cells in the bone marrow and/or blood.[1] First identified in the fourth century, leukemia was later classified into four main subtypes: chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), acute lymphocytic leukemia (ALL), and acute myeloid leukemia (AML).[2] AML, the most common adult leukemia, has a median diagnosis age of 68 years. It arises from the uncontrolled proliferation of clonal hematopoietic cells[3] and is influenced by genetic factors that dictate prognosis and progression. AML involves clonal expansion, somatic mutations in progenitor cells, and impaired hematopoiesis, leading to bone marrow failure. Common symptoms include shortness of breath, fatigue, increased bleeding risk, and infections due to neutropenia.[4] CML, a hematopoietic stem cell disorder, accounts for 15% of adult leukemia cases, with an incidence of 1–2 cases per 100,000 people.[5]

Cytokines, including growth factors, play a critical role in cell regulation, survival, and differentiation. Dysregulation of these factors can drive malignant transformation.[6] Among them, fibroblast growth factors (FGFs) are involved in processes such as wound healing, neurogenesis, migration, and proliferation. Basic fibroblast growth factor (bFGF or FGF-2), one of the 23 identified FGFs, was first isolated from the pituitary gland and brain.[7] Secreted primarily by macrophages and smooth muscle cells, bFGF is released through an unconventional mechanism. Angiogenesis, a key process in hematological malignancies like AML, is influenced by proangiogenic factors such as vascular endothelial growth factor (VEGF) and bFGF, which contribute to disease progression.[8]

Insulin-like growth factor-1 (IGF-1) is a mitogenic hormone that regulates metabolism, cell division, differentiation, and apoptosis inhibition. It acts as the primary mediator of growth hormone (GH) and is mainly secreted by the liver, functioning in both endocrine and paracrine manners. IGF-1 levels fluctuate throughout life, peaking during puberty, and alterations in its levels are linked to tumors, including acute lymphoblastic leukemia (ALL).[9] VEGF, a member of the Platelet-Derived Growth Factor (PDGF) family, is essential for cell survival, proliferation, and structural integrity. Overexpression of VEGF mRNA is a significant biomarker in various cancers, including hematological malignancies.[10] VEGF-A, located on chromosome 6, is associated with poor prognosis, chemotherapy resistance, and relapse in multiple myeloma, leukemia, and non-Hodgkin's lymphoma. It also plays a role in hematopoietic stem cell transplantation outcomes and bone marrow microvascular recovery.[11]

Hepatocyte growth factor (HGF), a multifunctional cytokine secreted by mesenchymal stem cells, regulates cell proliferation, survival, migration, and angiogenesis. The HGF gene, located on chromosome 7, is frequently altered in blood cancers. Elevated serum levels of HGF are associated with poor prognosis in CML, and HGF secreted by basophils can stimulate endothelial cell migration, suggesting its potential as a therapeutic target for CML.[12] Platelet-derived growth factor (PDGF), initially identified in platelets, regulates blood vessel development and pathology. It is secreted by various cells, including endothelial cells, neurons, fibroblasts, and macrophages, and functions through autocrine and paracrine signaling.[13]

Transforming growth factor-beta (TGF-β) is a multifunctional cytokine that modulates immune response, cell differentiation, proliferation, tissue homeostasis, and angiogenesis. Dysregulation of TGF-β is implicated in autoimmune diseases, fibrosis, and cancer. A deeper understanding

of TGF-β's role in normal and cancerous cells may reveal new therapeutic targets.[14] This study aims to explore the association between serum levels of growth factors (bFGF, IGF-1, VEGF, HGF, PDGF, and TGF-β) and the risk of developing AML and CML.

Materials and Methods

Clinical Data

The study included 168 participants, aged between 21 and 69. Of these, 52 were diagnosed with acute myeloid leukemia, while 71 had chronic myeloid leukemia from Hiwa Hospital in Sulaymaniyah. We also recruited 45 healthy individuals, matched for age and gender, to serve as controls in the study.

Blood Collection

For every patient, a 4–5 ml venous blood sample was obtained and put into Gold-top serum separator tubes. After being left at room temperature for 15 minutes, The samples were centrifuged for fifteen minutes at 4000 rpm. Immediately, serum samples were put into Eppendorf tubes that had already been labeled and coded. Any samples that were hemolyzed were thrown away, and the rest were kept at –20°C for later examination.

Biochemical Assay

BGFG, IGF-1, VEGF, HGF, PDGF, and TGF-β serum levels were measured using the sandwich enzyme-linked immunosorbent assay (ELISA) method with kits manufactured by RayBiotech.

Statistical Analysis

The data was statistically analyzed by using GraphPad Prism version 9. Mean ± SD was used to show the outcomes of statistical tests and bar graphs. The study parameters' mean values for the patients and healthy control groups were compared using a one-way ANOVA. *P*-values below 0.05 were considered statistically significant (P<0.05).

Results

Serum Levels of Growth Factors

Table 1 and Figures 1–5 and 6 shows that, in comparison to healthy controls, patients with acute myeloid leukemia (AML)

Table 1. **Protein growth factor mean ± SD values in serum samples from patient and healthy control groups**

Parameters	Control Group	AML	CML	*P*-Value
Basic fibroblast growth factor (BFGF) (pg/mL)	1.57 ± 0.14	8.61 ± 2.54	11.51 ± 3.02	0.0001
Insulin-like growth factor I (IGF-I) (ng/mL)	81.33 ± 31.8	175.1 ± 60.3	189.2 ± 53.3	0.001
Vascular endothelial growth factor (VEGF) (pg/mL)	152.11 ± 7.31	201.61 ± 66.02	233.04 ± 81.42	0.021
Hepatocyte growth factor (HGF)(ng/mL)	063.8 ± 0.173	0.901 ± 0.382	1.371 ± 0.59	0.017
Platelet-Derived Growth Factor (PDGF) (ng/mL)	2.29 ± 0.84	4.62 ± 1.60	7.62 ± 1.83	0.0131
Transforming growth factor-β (TGF-β1) (ng/mL)	31 ± 4.2	47 ± 15.6	65 ± 16.1	0.041

Value expressed in Mean ± SD. If the *P*-value of less than 0.05, is regarded as statistically significant.

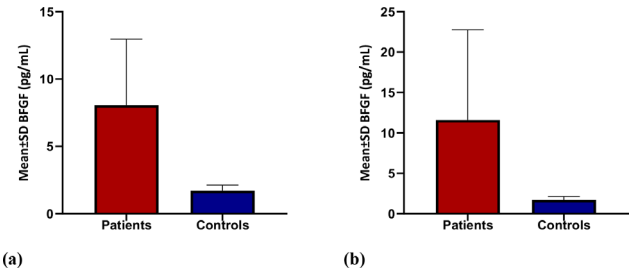

Fig. 1 **Comparison of BFGF concentration between sera samples of control and a (AML) and (b) CML patient groups.**

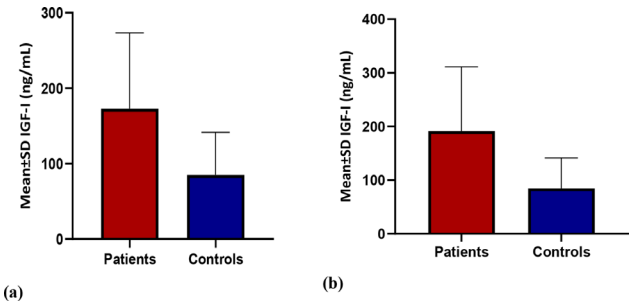

Fig. 2 **Comparison of IGF-I concentration between sera samples of control and (a) (AML) and (b) CML patient groups.**

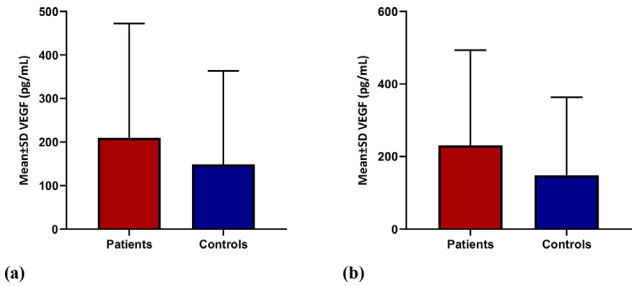

Fig. 3 **Comparison of VEGF concentration between sera samples of control and (a) (AML) and (b) CML patient groups.**

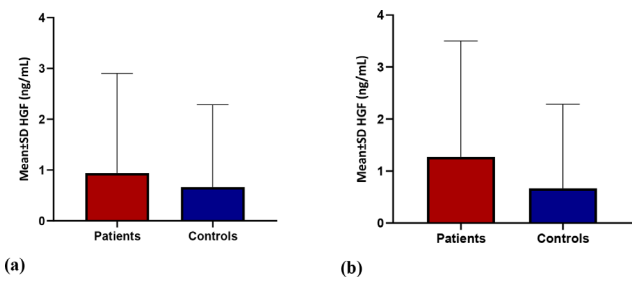

Fig. 4 **Comparison of HGF concentration between sera samples of control and (a) (AML) and (b) CML patient groups.**

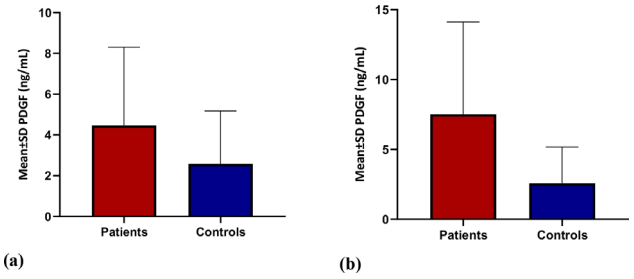

Fig. 5 **Comparison of PDGF concentration between sera samples of control and (a) (AML) and (b) CML patient groups.**

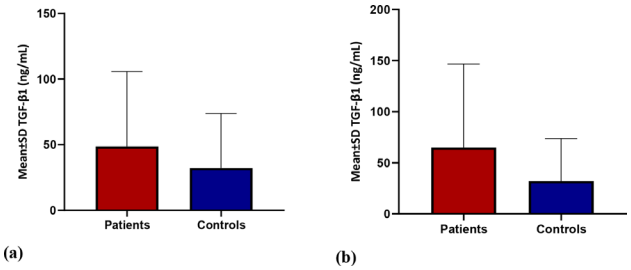

Fig. 6 **Comparison of TGF-β1 concentration between sera samples of control and (a) (AML) and (b) CML patient groups.**

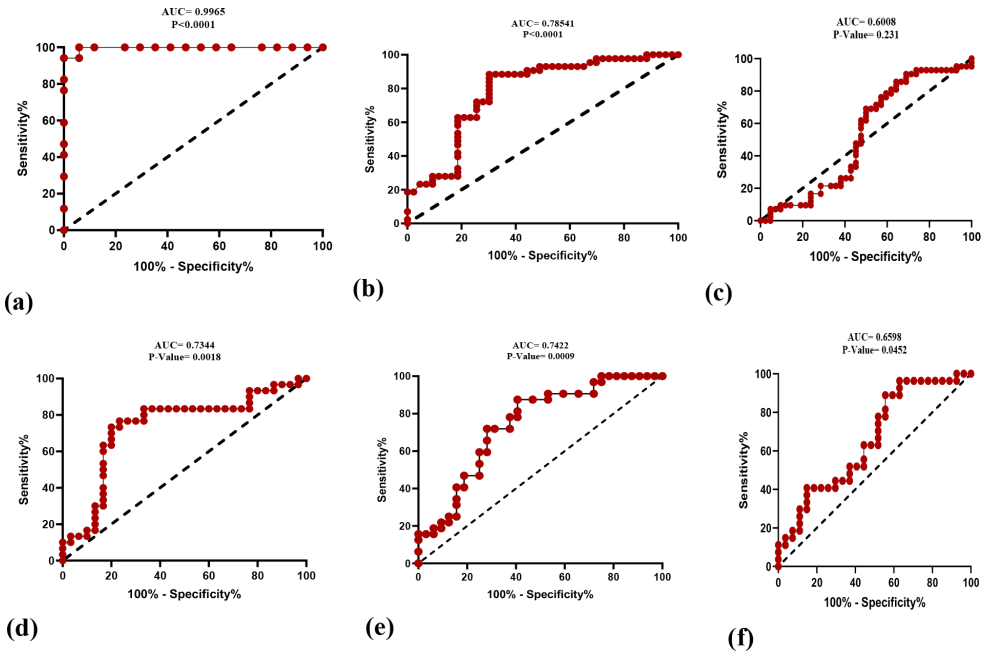

Fig. 7 **ROC curves of (a) BFGF, (b) IGF-I, (c) VEGF, (d) HGF, (e) PDGF and (f) TGF-β1.**

and chronic myeloid leukemia (CML) had significantly higher serum growth factor levels. For AML and CML, the levels of Basic Fibroblast Growth Factor (BFGF) rose from 1.57 ± 0.14 pg/mL to 8.61 ± 2.54 pg/mL and 11.51 ± 3.02 pg/mL, respectively (P = 0.0001). Insulin-Like Growth Factor I (IGF-I) increased from 81.33 ± 31.8 ng/mL in controls to 175.1 ± 60.3 ng/mL in AML and 189.2 ± 53.3 ng/mL in CML (P = 0.001). The levels of Vascular Endothelial Growth Factor (VEGF) rose from 152.11 ± 7.31 pg/mL in controls to 201.61 ± 66.02 pg/mL in AML and 233.04 ± 81.42 pg/mL in CML (P = 0.021). Hepatocyte Growth Factor (HGF) levels increased in AML and CML from 0.638 ± 0.173 ng/mL to 0.901 ± 0.382 ng/mL and 1.371 ± 0.59 ng/mL, respectively (P = 0.017). At AML, platelet-derived growth factor (PDGF) levels were 4.62 ± 1.60 ng/mL and in CML, 7.62 ± 1.83 ng/mL (P = 0.0131), compared to 2.29 ± 0.84 ng/mL in controls. AML and CML had higher levels (P = 0.041) of Transforming Growth Factor-β1 (TGF-β1) (47 ± 15.6 ng/mL and 65 ± 16.1 ng/mL, respectively) than controls (31 ± 4.2 ng/mL).

ROC Curve Analysis

The area under the curve (AUC) of (a) BFGF, (b) IGF-I, (c) VEGF, (d) HGF, (e) PDGF, and (f) TGF-β1 were (0.9965), (0.78541), (0.6008), (0.7344), (0.7422), and (0.6598), respectively, as shown in Figure 7.

Discussion

Basic fibroblast growth factor (bFGF) has been extensively studied for its role as a key inducer of angiogenesis. Recent research highlights its involvement in regulating signaling pathways and its critical function in promoting angiogenesis.[15] As a pro-angiogenic factor, bFGF is associated with tissue injury, chronic inflammation, and cancer progression.[16] In diseases like cancer, angiogenesis and inflammation are closely linked, with inflammatory cells enhancing bFGF-mediated angiogenesis by increasing the release of other pro-angiogenic factors, such as VEGF and angiopoietin-2 (Ang2).[17] Additionally, bFGF promotes angiogenesis by upregulating HK2, which maintains glycolysis in vascular endothelial cells.[18]

The FGF/FGFR signaling pathway activates the PLCγ/IP3/Ca2+ cascade, a key regulator of angiogenesis[16] (Zahra et al., 2021). Recent studies show that bFGF alters VEGFR1 splicing toward soluble VEGFR1 (sVEGFR1), increasing the expression of splice kinase SRPK1 and splice factors SRSF1 and SRSF3 in endothelial cells.[19] This mechanism has been linked to bFGF and sVEGFR1 expression in squamous lung cancer.[15] Elevated levels of bFGF and VEGF are associated with lower survival rates in non-small cell lung cancer, hepatocellular carcinoma, and non-Hodgkin lymphoma.[20] In hematological malignancies, bFGF has shown conflicting results.

While some studies report elevated circulating bFGF levels in AML and CML patients compared to healthy controls,[21] others found lower levels in AML patients.[22] These discrepancies may stem from differences in sample size, sample type, and regional variations, underscoring the need for multi-region studies to clarify bFGF's role in leukemia. As a heparin-binding polypeptide, bFGF activates tyrosine kinase, enhancing cell migration, proliferation, and differentiation.[23] It also influences the survival of myeloid progenitors and hematopoietic stem cells[24] (Shah et al., 2013). Due to its proangiogenic properties, bFGF inhibitors are being explored as potential tumor treatments.[20] Elevated serum bFGF levels are linked to poor prognosis in AML and lymphoma, suggesting its potential as a prognostic biomarker.

Chemotherapy has been shown to reduce circulating bFGF levels and improve AML prognosis, though its role in AML angiogenesis remains debated. Despite some studies finding no difference in bFGF levels between AML patients and healthy individuals, the significant increase in circulating bFGF in AML and CML patients highlights its potential as a biomarker and therapeutic target. Serum bFGF levels are closely associated with AML and CML, playing a critical role in leukemogenesis. Higher bFGF levels correlate with aggressive disease and poor prognosis in AML, making it a reliable prognostic marker. While its role in CML is less clear, emerging evidence suggests its involvement in disease pathophysiology, warranting further investigation.

Higher levels of IGF-1 have been linked to an increased risk of colorectal, prostate, and breast cancers. IGF-1, a potent mitogen, plays a critical role in antiapoptotic and metastatic processes in many malignancies. Dysregulation of IGF-1 expression can lead to uncontrolled cell division and proliferation, contributing to cancer development[25] (Qin et al., 2019). The IGF-1 gene consists of six exons, with exons 3 and 4 encoding the mature IGF-1 polypeptide.[26] IGF-1 is primarily produced by the liver in response to growth hormone stimulation and acts through autocrine and paracrine mechanisms. It promotes cell division by binding to the IGF-1 receptor, activating the RAS–mitogen-activated protein kinase signaling cascade.[27] Additionally, IGF-1 exhibits antiapoptotic effects by activating the phosphatidylinositol 3-kinase-AKT pathway, further implicating it in cancer progression. Overexpression of IGF-1R, a key promoter of tumor progression, is frequently observed in various cancers. Reduced blood levels of IGF-1 are associated with malignant lymphoblast proliferation, as IGF-1R overexpression in bone marrow sequesters serum IGF-1.[28] Disruptions in the GH–IGF axis, such as increased IGFBP-3 proteolysis in acute leukemia, impair IGF production and binding protein stability.[9] Elevated IGF-1 levels are also linked to acromegaly and increased cancer risk, particularly in colorectal, breast, and prostate cancers.[29] IGFBP3, which inhibits proliferation and promotes apoptosis, is associated with reduced cancer risk when present in higher levels.[30]

Recent studies are exploring the role of IGF-I in acute myeloid leukemia (AML) and chronic myeloid leukemia (CML). High IGF-I levels may contribute to AML pathophysiology, worsening prognosis and disease progression. However, the relationship between IGF-I and CML remains unclear, necessitating further research to uncover potential therapeutic targets for these hematologic cancers.

The findings align with a recent study showing that acute myeloid leukemia (AML) patients have elevated VEGF levels at diagnosis and relapse, with lower levels observed post-treatment or in remission compared to healthy controls.[31] This suggests that reducing VEGF levels may improve disease outcomes. VEGF and its receptors are promising therapeutic targets in AML, though debates persist due to conflicting results, likely from small sample sizes and methodological differences.[8] VEGF, the most potent angiogenesis-stimulating factor, enhances vascular permeability and promotes endothelial cell migration and proliferation.[32] While normal tissues produce minimal VEGF for endodermal cell regulation, cancerous cells overexpress VEGF, driving vascular damage, invasion, and metastasis, often accompanied by platelet activation.[33] VEGF also upregulates urokinase plasminogen activator (uPA), tissue plasminogen activator (tPA), and plasminogen activator inhibitor 1 (PAI-1), altering endothelial gene activation and promoting vascular formation.[34]

Elevated VEGF levels are observed in AML and chronic myeloid leukemia (CML), suggesting its potential as a biomarker. In AML, high VEGF correlates with poor prognosis, increased angiogenesis, and disease aggressiveness, highlighting its role as a prognostic marker and therapeutic target. While VEGF is also elevated in CML, its significance remains unclear. Further research is needed to clarify VEGF's mechanisms in leukemia, which could lead to novel therapies targeting angiogenesis pathways.

HGF serum levels have been shown to predict melanoma prognosis.[35] HGF, a multipurpose cytokine, is linked to tumorigenesis, tissue regeneration, and organogenesis. It activates the c-MET receptor, triggering signaling pathways like Akt/PKB and ERK/MAP-Kinase, which are critical in cancer development and spread.[36] In the tumor microenvironment, stromal cells release HGF, binding to the c-MET receptor and initiating the HGF/c-MET signaling cascade. This pathway, essential for wound healing and embryonic development, is rarely active in adults outside of cancer. It's inappropriate activation, caused by excess HGF, MET mutations, or c-MET overexpression, promotes angiogenesis, invasion, migration, metastasis, and cell survival.[37] HGF and its receptor MET significantly influence oncogenesis, cancer metastasis, and treatment resistance.[38] Inflammation and cancer are closely linked, with elevated inflammatory markers like neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein (CRP) associated with poor prognosis in cancers such as pancreatobiliary cancer.[39] Chronic inflammation, such as in pancreatitis, increases HGF and c-MET expression, highlighting the connection between inflammation and HGF/c-MET signaling.[37]

The HGF/c-MET pathway is critical for metastatic disease, regulating cell survival, proliferation, and invasion through pathways like PI3K/Akt and MAPK/ERK.[36] In the tumor microenvironment, cancer-associated fibroblasts produce HGF, which directly promotes angiogenesis by binding to endothelial cell receptors and indirectly stimulates it by inducing pro-angiogenic proteins like VEGF.[38] Elevated HGF levels in pancreatic cancer patients with metastases further underscore its role in cancer progression.[37] In leukemia, HGF levels are linked to AML and CML, suggesting a role in leukemogenesis and disease progression. Elevated HGF in AML correlates with aggressive disease and poor prognosis, making it a potential prognostic marker and therapeutic target. In CML, HGF may support leukemic cell survival, though its mechanisms remain unclear. Further research into HGF's role in AML and CML could inform targeted therapies.

PDGF is a critical mitogen for many cell types, including connective tissue cells. It forms homodimers and heterodimers of A- and B-polypeptide chains, which bind to and activate receptor-α and receptor-β, two protein tyrosine kinase receptors (PDGF-RTK).[40] PDGF-D promotes tumor growth, angiogenesis, and metastasis through pathways like Notch, NF-κB, PI3K/Akt, ERK, mTOR, and MAPK. In pancreatic carcinomas, PDGF-D regulates Notch-1 and NF-κB activation, driving angiogenesis and malignant invasion.[41] PDGF-D overexpression in prostate and renal cell carcinomas accelerates tumor formation, angiogenesis, and metastasis, suggesting its carcinogenic potential.[42,43] These findings support the role of PDGF overexpression in cancer progression. PDGF-D is also linked to the epithelial-to-mesenchymal transition (EMT), a key mechanism in tumor metastasis, through pathways like NF-κB and Notch. High PDGF-D expression correlates with EMT activation in prostate cancer.[44] While PDGF may accelerate AML and CML progression, further research is needed to confirm this.

The outcomes of this study are consistent with researches, which demonstrated that TGFB1 serum levels were significantly elevated in acute leukemia patients, returned to normal in those who achieved total remission, and declined again during recurrence.[45] This suggests that TGFB1 levels may serve as a dynamic biomarker for disease progression and treatment response in leukemia. However, contrasting findings were reported by Al-Mowallad et al.,[46] who observed no significant difference in TGFB1 plasma levels between 60 children diagnosed with ALL and healthy controls. These discrepancies may stem from differences in study populations, sample types, or methodologies, highlighting the need for further research to clarify TGFB1's role in leukemia. It is well established that malignant cells often evade regulatory mechanisms that inhibit normal cell proliferation, facilitating malignant transformation. The downregulation of TGFB1 expression observed in ALL patient plasma could lead to uncontrolled growth of cancerous cells, exacerbating bone marrow hyperplasia and peripheral blood invasion by leukemic clones.[45] TGFB1 is known to play a dual role in cancer, acting as a tumor suppressor in early stages and promoting tumor progression in advanced stages. In leukemia, TGFB1's role appears complex, with its levels fluctuating based on disease phase and treatment outcomes. This dual functionality underscores the importance of understanding TGFB1's mechanisms in leukemia to develop targeted therapies. The study's findings also suggest that TGFB1 may be a potential prognostic marker for leukemia. Elevated TGFB1 levels in acute leukemia patients could indicate aggressive disease, while normalization during remission may reflect treatment efficacy. Conversely, the downregulation of TGFB1 in ALL patients may contribute to disease progression by enabling leukemic cells to bypass growth-inhibitory signals. Further research is needed to explore TGFB1's role in different leukemia subtypes and its potential as a therapeutic target. By elucidating TGFB1's mechanisms, researchers may uncover novel strategies to improve leukemia treatment and patient outcomes.

To confirm the six growth factors' real function as diagnostic biomarkers. To ascertain each one's diagnostic performance, ROC curves were created and AUC values were examined. A greater diagnostic performance is indicated by a higher area under the curve (AUC). Figure 7a illustrates that the serum levels of BFGF exhibited a significant AUC of 0.9965 ($P < 0.0001$). The ROC curve results showed that 8 BFGF had the best AUC to evaluate the potential usefulness of biomarkers in diagnosing AML and CML (AUC = 0.9965, $P < 0.0001$), followed by IGF-I (AUC = 0.78541, $P < 0.0001$), PDGF (AUC = 0.7422, $P = 0.009$), HGF (AUC = 0.7344, $P = 0.0018$), TGF-β1 (AUC = 0.6598, $P = 0.0452$), and VEG AUC = 0.6008, $P = 0.231$) (Figure 7). Therefore, serum growth factors, including BFGF, may be a supplementary biomarker for AML and CML.

Conclusions

The current study's findings show that CML and AML patients had higher circulating growth factors levels, therefore their serum estimation may be a potential biomarker in the early detection and diagnosis of CML and AML as well as targeted therapy and poor prognosis.

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Conflict of Interest

The author has revealed no conflicts of interest throughout this study.

Ethical Approval

The project was approved by the presidency of Erbil Polytechnic University. Issue Number (4306), Date: 19/5/2024.

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