Evaluation of Interferon-Gamma, Vitamin E, and Electrolytes (Sodium, Potassium, Chloride) Levels as Potential Biomarkers in Iraqi Breast Cancer Women

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Abstract: The primary objective of this study is to evaluate the potential of interferon-gamma, vitamin E, and electrolyte levels (sodium, potassium, and chloride) as biomarkers for breast cancer diagnosis. Patients and Methods: This study was conducted at the Oncology Teaching Hospital, Medical City, Baghdad, and included 130 female participants who ranged in age from 30 to 71 years. The blood samples were collected between May 13, 2024, and August 11, 2024.Methods: The levels of interferon-gamma, vitamin E, and electrolytes (sodium, potassium, chloride) were measured in the serum of the participants using appropriate laboratory techniques. The data obtained were then analyzed to identify any significant differences among the three groups. The results demonstrated that interferon-gamma levels were significantly elevated in both the newly diagnosed group (G1) and the chemotherapy-treated group (G2) when compared to the control group (C). Additionally, a decrease in vitamin E levels was observed in the newly diagnosed group (G1) compared to the treated group (G2) and the control group (C). The electrolyte analysis revealed a significant reduction in sodium and chloride levels in the newly diagnosed group (G1) compared to the other two groups, while potassium levels were significantly elevated in the newly diagnosed group (G1) compared to both the treated and control groups Furthermore, the ROC analysis showed that interferon-gamma (IFN-γ) demonstrated high sensitivity (93.33%) and specificity (62.50%), making it a strong marker for cancer detection. Sodium (Na) exhibited exceptional diagnostic performance with 100% sensitivity and specificity. Similarly, chloride (Cl) showed excellent results, with 100% sensitivity and 88.89% specificity. In contrast, vitamin E exhibited lower sensitivity (51.11%) but demonstrated high specificity (92.50%). The findings suggest that interferon-gamma, vitamin E, and electrolyte levels, specifically sodium, potassium, and chloride, could be significant biomarkers for differentiating between newly diagnosed breast cancer patients and healthy individuals.

1 INTRODUCTION

Cancer is a group of diseases that occur when cells lose control over their growth and division, leading to abnormal cell proliferation. Cancerous cells are characterized by their ability to invade adjacent tissues and destroy them, as well as their potential Cancer can spread to other parts of the body via the blood or lymphatic system, develops from the transformation of normal cells into malignant ones through a series of stages, typically progressing from a precancerous lesion to an invasive malignant tumor. These abilities are considered key characteristics of malignant tumors, while benign tumors are characterized by limited growth and an inability to invade surrounding tissues or spread to other body parts. However, in some cases, benign tumors can transform into malignant cancer [1]. In Iraq, breast cancer is the most prevalent type of cancer among women and one of the main causes of cancer-related mortality in the country. In recent years, the prevalence of breast cancer among women has significantly increased [2]. Early diagnosis and adherence to treatment are critical factors in reducing the risk of the disease progressing to advanced stages, which significantly contributes to lowering mortality rates. Moreover, adopting a

healthy lifestyle and modifying daily habits are essential elements in the prevention of diseases such as cancer [3]. Vitamin E is a fat-soluble antioxidant that plays an important role in protecting unsaturated fatty acids from oxidative stress. The most active form of this vitamin is alpha-tocopherol. Due to its role as an antioxidant, low levels of Vitamin E have been linked to an increased risk of cancer [4]. Vitamin E is one of the major fat-soluble antioxidants found in plasma and red blood cells in humans. Tocopherols are found in lipoproteins and cellular membranes, where they have the ability to scavenge free radicals such as oxygen (O) and hydroxyl (HO) radicals. However, its primary biological role is in interacting with peroxide radicals (ROO) to form tocopherol radicals, which contributes to preventing lipid peroxidation resulting from oxidative stress. Oxidized Vitamin E can be regenerated primarily by Vitamin C, along with other compounds such as glutathione (GSH) and Vitamin A [5]. Natural killer (NK) cells, T lymphocytes, macrophages, and epithelial cells all produce the soluble cytokine interferon-gamma (IFN-γ) [6]. IFN-γ is essential for cellular immunity activation and anti-tumor immunological stimulation responses through its ability to induce programmed cell death. It is considered beneficial in immunotherapy for various types of cancer. Additionally, IFN-γ inhibits angiogenesis in tumor tissues and stimulates the death of regulatory T cells [7]. About 60 years ago, IFN-γ was identified to be the sole member of the type II interferon family. White blood cells produce this substance, which was first identified as a viral inhibitor. The IFN-γ gene encodes IFN-γ, which is made up of two polypeptide chains that are not covalently bound. IFN-γ is found in human blood in three different molecular forms with different molecular weights. Of them, one is the free active form of IFN-γ, while the other two are the cytokine's mature forms [6,8]. Sodium is a naturally occurring element found in soil, water, and plants. It is essential for human health and enters the body through food and water. Sodium is abundant in foods, with the most common form being sodium chloride (table salt). Sodium is also found in water, although its concentration varies depending on the water source. Hyponatremia is a common electrolyte disturbance seen in various diseases, including cancer. It is frequently observed in patients with malignancies, including early-stage cancer, particularly breast cancer [9,10]. Potassium is the primary intracellular cation, with more than 95-98% of potassium residing inside cells. It is necessary for the digestive system, muscles, neurons, kidneys, and heart to all operate properly. Potassium is a component of key minerals required for proper daily physiological functions, playing a critical role in muscle and tissue health throughout the body. Maintaining optimal potassium levels is crucial for overall health [11]. Chloride represents two-thirds of the negatively charged ions (extracellular anions) in the serum. It plays an essential role in maintaining acid-base balance and works alongside sodium to regulate the osmotic balance of body fluids. Chloride levels in the blood increase in conditions such as increasedrespiratory rate, severe fever, aspirin poisoning, anxiety, and dehydration. Conversely, chloride levels decrease in conditions such as slow respiratory rate (e.g., in morphine poisoning, severe vomiting, chronic diarrhea, untreated diabetes mellitus, hyponatremia, and mercury diuretic use). Chemotherapy and radiation treatments can cause vomiting, leading to a loss of chloride from gastric secretions. Repeated vomiting may result in hypochloremia. Chloride levels are often related to sodium levels in the blood, and hypochloremia is common in cancer patients with hyponatremia due to kidney damage from chemotherapy or interference with AVP secretion by cancer cells [12,13].

2 MATERIALS AND METHODS

Study Design: this research was carried out at Medical City's Oncology Hospital in Baghdad, where a total of 130 blood samples were collected and categorized into three groups: 40 healthy controls (C), 45 individuals with newly diagnosed breast cancer (G1, prior to the initiation of treatment), and 45 patients who had undergone chemotherapy (G2). All blood samples were allowed to coagulate before being processed for serum separation. Inclusion Criteria: for the control group, blood samples were obtained from individuals who had no history of breast cancer, as confirmed by comprehensive medical evaluations. For the breast cancer group, blood samples were collected from individuals after confirmation of the diagnosis through standard procedures, including mammography and biopsies, such as Fine Needle Aspiration (FNA) or Core Needle Biopsy (CNB). The chemotherapy group consisted of patients who had undergone chemotherapy, with blood samples collected 4-6 weeks after the completion of chemotherapy. Exclusion Criteria: exclusion criteria included individuals with a history of benign tumors, rheumatoid arthritis (RA), type 2 diabetes mellitus

(DMII), kidney failure, liver failure, cardiovascular diseases, autoimmune disorders, or any other chronic systemic conditions that could interfere with the study results. Sample Collection and Preparation: serum was taken from samples of venous blood., which were collected from participants. After allowing the blood to coagulate, the samples were immediately subjected to centrifugation at 2300×g within 10 minutes of collection. The separated serum was then stored at -85°C until analysis. Biomarker Measurements: the serum concentrations of interferon-gamma (IFN-γ) and Vitamin E were quantified using enzyme-linked immunosorbent assay (ELISA) kits provided by Elk Biotechnology, USA, following the manufacturer's instructions. Duplicate measurements were performed for each sample, and the results were compared with a reference curve. Additionally, the levels of electrolytes (sodium, potassium, and chloride) were measured using a fully automated GE300 Genrui Electrolyte Analyzer. Ethical approval: this study adhered to the ethical principles established in accordance with the Declaration of Helsinki, the procedure was carried out following the patient's verbal and informed consent prior to sample collection. The study protocol, along with the subject information and consent form, received approval from the local ethics committee of the Baghdad Health Directorate Ministry of Health, as documented under number 4081, dated 29/1/2024.

3 STATISTICS

Statistical analysis for this study was performed using SPSS software (version 26). Data were assessed using Group means were compared using the Duncan Multiple Range Test at a significance level of ($p < 0.01$), and Analysis of Variance (ANOVA) was used to find significant differences. Additionally, MedCalc software was used to perform Receiver Operating Characteristic (ROC) curve analysis to evaluate the diagnostic performance of the assessed parameters, including sensitivity, specificity, and diagnostic The normality of the data distribution was verified using the Shapiro-Wilk test, and the data were found to follow a normal distribution.

4 RESULTS

4.1 Statistical Analysis and Findings

The findings indicated that the level of IFN-γ was significantly higher in both the G1 and G2 groups compared to the control group (C). The G1 group's vitamin E levels were considerably lower than those of the G2 group and the group C. In terms of electrolyte levels, the G1 group had significantly greater potassium levels than the G2 group and the group C, while the G1 group had significantly lower sodium and chloride levels than the G2 group and the group C. as shown in Table 1.

The different letters indicate the presence of statistically significant differences, while the same letters indicate the absence of statistically significant differences.

4.2 ROC Analysis for Parameters Under Investigation

By comparing the area under the Receiver Operating Characteristic (ROC) curve with the Area Under the Curve (AUC) for the parameters being studied, the diagnostic ability was assessed, as indicated in Table 2.

Table 1: Serum concentration of vitamin E, IFN-γ and electrolytes among studied groups.

Groups Parameters	Mean ± SD		
	C	G1	G2
Vitamin E (µg/ml)	16.83±3.83 a	13.38±4.85 b	16.22±5.13 a
IFN-γ (Pg/ml)	44.92±13.67 b	71.13±22.95 a	64.008±18.31 a
Na (mmol/L)	142.56±4.97 a	126.93±3.61 c	136.19±9.33 b
K (mmol/L)	3.84±0.31 b	4.3±0.54 a	3.83±0.48 b
CL (mmol/L)	108.28±5.31 a	96.79±3.54 c	102.28±7.24 b

Table 2: The receiver operating characteristic ROC curve analysis for the tested parameters.

Variables	Cut-off value	Sensitivity %	Specificity %	P Value	AUC
V.E	≤12.2	51.11	92.50	<0.001	0.737
IFN-γ	>42	93.33	62.50	<0.001	0.835
Na	≤131.9	100.00	100.00	<0.001	1.000
K	>4.27	62.22	93.33	<0.001	0.773
CL	≤102.9	100.00	88.89	<0.001	0.961

5 DISCUSSION

From Table 1 and the figure, it is evident that Vitamin E levels were considerably lower in the G1 group as opposed to the control group (C) and the G2 group. Our current study's findings are consistent with those of Abiakaetal., who conducted a study in Kuwait and observed a decrease in Vitamin E levels in women with breast cancer before receiving treatment [14]. Similarly, the current study's results are consistent with those of Torun et al., who reported reduced Vitamin E levels in women with breast cancer compared to healthy wome [15]. Our findings also match a study conducted in Mosul, which measured antioxidant vitamins and showed lower Vitamin E levels in women with breast cancer compared to the control group [16]. However, our findings differ from those of a study conducted in France by Gerber, Richardson, Salkeld, Chappuis, who observed elevated Vitamin E levels in women with breast cancer compared to healthy women [17]. This discrepancy may be due to their control group being selected from a hospital population in neurosurgery departments.

Vitamin E is a natural antioxidant that helps remove Reactive oxygen species and free radicals from the body in addition to its antioxidant role, Vitamin E has other important biological functions, such as maintaining cell membrane integrity, influencing DNA synthesis, and modulating cell signaling. Numerous studies have shown that antioxidants can reduce DNA damage caused by oxidation, which in turn may decrease mutations and carcinogenesis [18]. Vitamin E is crucial for immune system function, as immune activity is associated with the release of free radicals from oxygen that are involved in macrophage function. Therefore, the immune system is more sensitive than other systems to a deficiency of antioxidants in the diet [19].

Regarding IFN-γ, our study's findings are consistent with the ones of Borj et al., who conducted a study in Iran and observed elevated IFN-γ levels in the serum of women with breast cancer [20]. Our results are also in agreement with a study conducted in Baghdad by Hassan & Mohamme in 2021, which included 88 samples (58 breast cancer patients and 30 controls) and discovered that women with breast cancer had greater levels of IFN-γ than the control group. [21]. The elevated levels of IFN-γ in the early stages of breast cancer are likely a natural immune response to fight cancer cells. IFN-γ activates immune cells such as T-cells and natural killer cells, contributing to tumor suppression. However, after chemotherapy, IFN-γ levels may decrease due to the impact of chemotherapy on white blood cells and the immune system, which reduces the body's ability to produce this cytokine naturally [22]. IFN-γ is primarily produced by immune cells such as T-cells and natural killer cells and plays a key role in supporting inflammatory processes and fighting viral infections, which can influence breast cancer progression IFN-γ gene polymorphisms may raise the risk of breast cancer by impairing the immune system's capacity to identify aberrant cells [23].

Regarding sodium levels, our research aligns with the findings of Chanihoon etal [24], who conducted a study on women with breast cancer aged 25–73 years and found lower sodium levels in patients compared to healthy women. However, our results do not agree with those of Yousif et al., who reported higher sodium levels in women with breast cancer [25]. The reduction in sodium levels may be due to increased secretion of antidiuretic hormone (ADH), which causes fluid retention and dilutes sodium concentration in the blood. This phenomenon can occur due to abnormal secretion of vasopressin by cancer cells. Additionally, low sodium concentration can stimulate cancer cell proliferation. Cancer cells cause metabolic changes

and fluid imbalance, which can lead to low sodium, particularly in advanced stages or in patients with severe symptoms such as anorexia or vomiting, Certain chemotherapy treatments for breast cancer can also trigger vasopressin secretion or affect fluid and electrolyte balance, leading to reduced sodium levels [26].

From Table 1, it is evident that potassium levels were significantly higher in the G1 group compared to both the G2 group and the control group (C). Our findings are consistent with Al Dleemy study conducted in Nineveh, which found elevated potassium levels in women with breast cancer compared to healthy women [16].

However, our results differ from those of Chanihoon et al., who reported reduced potassium levels in women with breast cancer, with further declines in potassium as the disease progressed [24]. The increased potassium levels in the G1 group may be due to the movement of potassium between cells and extracellular fluid, which is regulated by the Na+/K+-ATPase pump. This pump helps maintain cell membrane functions by creating a concentration gradient across the cell membrane. Various factors, including the blood pH, can influence potassium movement. When the serum is alkaline (high pH), potassium moves into the cells, while in acidic conditions (low pH), potassium moves out of the cells [27]. Rapidly growing tumors lead to the destruction or breakdown of surrounding tissues, causing the release of potassium from damaged cells into the bloodstream. Additionally, tumor side effects may decrease kidney function in excreting potassium. Potassium channels play a role in promoting cancer cell growth and metastasis, and these channels increase in cancer cells. Elevated lactate levels in the blood are indicative of increased metabolic activity, which is linked to tumors and decreased blood pH, contributing to potassium efflux from cells and raising potassium levels in the serum [28], [29]. The chloride levels in the G1 group were significantly lower compared to both the G2 group and the control group (C), and chloride levels were also significantly lower in the G2 group compared to the control group, as shown in Table 1. Hypochloremia is a common electrolyte disturbance in breast cancer patients due to chemotherapy treatments that lead to changes in pH balance and cause electrolyte imbalances such as reduced sodium and chloride levels, often resulting from kidney damage or fluid loss due to vomiting and diarrhea [29]. This decrease may also be due to metabolic changes caused by cancer, as some cancers, including breast cancer, lead to the syndrome of inappropriate antidiuretic hormone secretion, which causes fluid retention and lowers chloride concentration in the blood. In this syndrome, excess ADH is secreted, increasing water reabsorption in the kidneys and diluting electrolyte levels such as chloride [30], [24]. The ROC results are presented in Table 2. According to the ROC analysis, varying performance levels of biological markers are revealed in distinguishing positive and negative breast cancer cases. Vitamin E showed lower sensitivity (51.11%) but high specificity (92.50%), making it effective in detecting negative cases. Vitamin E had a modest ability to correctly identify positive cases, but its high specificity suggests that it can effectively reduce the occurrence of false positives. Interferon-gamma (IFN-γ), on the other hand, demonstrated high sensitivity (93.33%) and moderate specificity (62.50%), indicating a strong ability to correctly identify positive cases, but it had a higher rate of false positives. Sodium (Na) exhibited perfect sensitivity and specificity (100%), with an AUC of 1.000, highlighting its excellent ability to distinguish between positive and negative cases. Potassium (K) showed moderate sensitivity (62.22%) and high specificity (93.33%), with an AUC of 0.773, suggesting good diagnostic potential but slightly reduced performance compared to other markers. Chloride (Cl) displayed 100% sensitivity and 88.89% specificity, with an AUC of 0.961, reflecting its strong diagnostic capability, although not as perfect as sodium. All markers showed statistically significant results ($P<0.001$), reinforcing the reliability of these findings.

6 CONCLUSIONS

The results of the current study demonstrated a significant decrease in the levels of Vitamin E (V.E) and Sodium (Na) in the G1 group (newly diagnosed breast cancer patients) compared to the C group (healthy controls). A significant increase in the levels of Interferon-gamma (IFN-γ) was observed in G1 compared to C. As for the Potassium (K) levels, G1 exhibited the highest value compared to C, while Chloride (CL) levels were higher in C compared to G1 and G2 (chemotherapy-treated women). These results indicate distinct biological and physiological effects on biochemical parameters between newly diagnosed breast cancer patients, chemotherapy-treated women, and healthy controls.

Furthermore, Na (Sodium) and CL (Chloride) showed the highest accuracy in distinguishing between positive and negative cases, achieving

100% sensitivity and specificity with high AUC values (1.000 and 0.961, respectively). On the other hand, IFN-γ demonstrated elevated sensitivity with a good AUC value (0.835). Meanwhile, V.E and K exhibited lower accuracy, with AUC values of 0.737 and 0.773, respectively.

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