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Diagnostic performance of EGFR2, SYPL1, VTN and some biochemical parameters in women with breast cancer: ROC curve analysis and correlation

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Over two million new cases of breast cancer were reported in 2020, making breast cancer the most common cancer among women worldwide. The epidermal growth factor receptor (EGFR) is a vital cell surface receptor involved in cell proliferation and transformation, and its dysregulation is associated with several types of cancer. Synaptophysin-like protein 1 (SYPL1) is a component of the synaptophysin (SYP) family, sometimes referred to as SYPL or pantophysin. Vitronectin protein (VTN), also known as S protein or serum dispersion factor, is a vesicular membrane protein found in both neural and non-neural tissues. The study included 90 women aged 30–65 years from Anbar Governorate. They were divided into two groups of 45 women each. The groups consisted of patients diagnosed with breast cancer and healthy women of the same age group as a control group. Serum was isolated and stored at –20 °C. Quantitative enzyme immunoassay (ELISA) was used to measure EGFR, SYPL1, and VTN levels. The results showed a significant increase in CA 15-3, CA 19-9, VTN, SYPL1 and calcium levels in the breast cancer group compared to the control group. A significant decrease in EGFR2 and magnesium levels was also observed in breast cancer patients compared to the control group. The data showed a strong association between EGFR2, SYPL1, VTN, and breast cancer. The ROC curve results indicate that SYPL1 is the most effective in detecting breast cancer. Based on these findings, it is suggested that circulating EGFR2, SYPL1, and VTN concentrations can be used to monitor treatment and predict breast cancer.

Keywords: breast cancer; chemotherapy; EGFR2; SYPL1; VTN; cancer diagnostics.

Introduction

Breast cancer is a malignant tumor that originates in breast tissue and has the potential to metastasize to distant organs. The neoplasm proliferates due to uncontrolled cellular reproduction. The cells of breast cancer form a tumor that can be identified via X-ray or palpated as a bump. Although a small number of men develop breast cancer, it predominantly affects women. In 2018, there were 2,080,000 new cases of breast cancer (an 11.6% incidence rate) and 626,679 deaths (6.6% of all cancer-related deaths) from 18.08 million new cases of all cancers and around 9.55 million cancer-related deaths worldwide (Ferlay et al. 2015). Breast cancer is among the most serious malignancies impacting women worldwide, and it is used extensively for screening and monitoring new breast cancers. Cancer Antigen (CA) 15-3 is utilized as a prognostic tool for post-treatment monitoring in patients who have breast cancer (Tarighati et al., 2023; Ibrahim et al., 2023).

Cancer Antigen 125 (CA125), or mucin 16 (MUC16), is a high-molecular-weight transmembrane glycoprotein antigen commonly employed in clinical oncology as a serum tumor marker(Gandhi et al., 2024). CA125 is an epitope found on the cell-surface protein MUC16. It is typically produced by tissues originating from coelomic epithelium, encompassing cells that line organs such as the ovaries, fallopian tubes, peritoneum, pleura, pericardium, endometrium, colon, kidneys, and stomach (Giamougiannis et al., 2021). In healthy, baseline conditions, the CA125 protein is expressed on the cell membrane. Due to stringent structural barriers between cells (junctional complexes), it cannot readily permeate the bloodstream in significant quantities. Pathological conditions that induce tissue inflammation, accelerated cell turnover, or malignant invasion compromise this membrane barrier. This disruption facilitates the release of the antigen into the extracellular fluid and bloodstream, leading to a detectable increase in serological levels (Charkhchi et al., 2020).

Cancer Antigen 19-9 (CA 19-9), known as carbohydrate antigen 19-9 or sialyl Lewis A, is a high-molecular-weight glycoprotein antigen associated with tumors (Ballehaninna & Chamberlain, 2012). It functions as the primary serological biomarker for the management and surveillance of pancreatic cancers. CA 19-9 is a mucinous glycoprotein characterized by a distinct oligosaccharide sequence referred to as the sialyl Lewis A blood group antigen. The antigen is produced and released in negligible quantities by the normal epithelial cells of the gastrointestinal tract, which include the pancreatic and biliary ductal mucosa, gastric and colonic epithelia, as well as the endometrial and salivary glands (Ballehaninna & Chamberlain, 2012).

Dysregulation of the epidermal growth factor receptor (EGFR), an important cell surface receptor, has been linked to a variety of carcinomas because it is essential for cell proliferation and differentiation. Most of the EGFRs are expressed in the plasma membranes of epithelial cells. The extracellular portion of each of the four subdomains of EGFR includes the first two subdomains that are responsible for binding to ligands. The extracellular domain of the EGFR is also connected to the cytoplasmic region via a tyrosine kinase (Lax et al., 1989; Wollman et al. 2022).

A multitude of recently examined blood indicators exists. Synaptophysin-like 1 (SYPL1) is a constituent of the synaptophysin (SYP) group, occasionally designated as SYPL or pantophysin. This protein

which forms vesicles is found in both neurons and non-neuronal tissues, and it has been observed to be present on the surface of tumors such ase melanomas, urothelial carcinomas, and some cases of gastric adenocarcinoma. The presence of minimal staining or negative cells in a limited number of cases in malignant gliomas, breast, prostate, colorectal, prostate, and skin cancers was observed in a limited number of cases. SYPL1 has a prognostic importance, and its increased expression is beneficial in renal cancer. Several studies have underscored the importance of biological markers in improving the prognosis and treatment of OSCC. Synaptophysin-like protein 1 (SYPL1) has garnered attention for its involvement in tumor progression (Kosem et al., 2024; Ergun et al., 2025). It is recognized as having a vital role in carcinogenesis, which has an impact on cancer development and prognosis, along with other autophagy-related genes (Chen et al., 2017). SYPL1 was recently discovered to be a crucial downstream effector in an oncogenic pathway that stimulates OSCC proliferation, showing significantly increased levels in tumor tissues, and its expression is associated with a poor prognosis (Ding et al., 2022). The potential to improve patient outcomes and uncover new treatment targets is significant when investigating the function and prognostic significance of SYPL1 in OSCC (Wang et al., 2026).

Vitronectin (VTN) or S Protein, Serum Diffusion Factor (Conlan et al., 1988), is a matrix related protein that serves as a primary regulator of the extracellular milieu (i.e. the environment outside of cells) (Leavesley et al., 2013). It also aids in the adhesion of endothelial cells to each other, and it plays a vital role in the process of tissue remodeling (Ruzha et al., 2022). Integrins play a key role in VTN's multi-protective mechanism by acting as its primary receptors, which facilitate cellular adhesion and responsiveness. Moreover, both integrins αvβ3 and αvβ5 have a significant impact on VTN activity and stimulate angiogenesis in murine models (Preissner & Seiffert, 1998) VTN activity is dramatically bolstered, angiogenesis in murine models is stimulated, and early hematological development of human embryonic stem cells is facilitated with the addition of both integrins αvβ3 and αvβ5 (Shen et al., 2021). Many diseases, including tumors, bleeding disorders and inflammation-related diseases, are associated with VTN and its receptors. VTN has also recently been shown to play a significant role in modulating neuronal activity and function; however, its role in neurodisorders continues to need further evidence (Ruzha et al., 2022). VTN (vitronectin) is a glycoprotein and is one of the most abundant proteins found within the body, being present in blood serum, ECM and blood platelets. It is an important protein that regulates or modulates many different functions including cell adhesion, coagulation, fibrinolysis, compliment activation and apoptosis by interacting with integrin avβ3, PA-1 (plasminogen activator inhibitor) and uPA (urokinase type plasminogen activator). In addition to these functions, VTN has also been associated with inflammatory processes such as acute lung injury, burns, and pneumonia; these processes are characterized by the activation of self-reactive neutrophils, T-lymphocytes, and B-lymphocytes along with tissue damage (Zhang et al., 2022).

Calcium is crucial for numerous physiological functions in the human body and plays a role in muscle contraction, hormone and neurotransmitter release, glycogen metabolism, cell proliferation and differentiation, blood coagulation, nerve impulse transmission, skeletal support, and acts as a secondary messenger in several signaling pathways. *Calcium's function in weight regulation*: In significant amounts, calcium binds to dietary fats, creating insoluble compounds that diminish fat absorption and hence lower caloric intake (Ren et al., 2013; Alrayah et al., 2022). Magnesium is the second most prevalent intracellular cation in the human body and functions as an essential cofactor for over 300 enzymatic reactions. Epidemiological studies consistently demonstrate that magnesium-deficient diets are associated with a heightened risk of various solid and hematologic malignancies, especially colorectal and breast cancers (Gile et al., 2020). This study aimed to assess the ability of EGFR2, SYPL1, and VTN to discriminate between women with breast cancer and healthy controls through ROC curve analysis, and to examine the relationship between these biomarkers and serum calcium levels.

Materials and methods

A comparative cross-sectional study was conducted on 90 blood samples from women aged 30 to 65 years. This study was carried out at the laboratories of the Anbar Specialized Oncology Center in Anbar Governorate between September 2024 and February 2025. The study included two groups, each consisting of 45 women. The first group comprised patients diagnosed with breast cancer, and the second group consisted of healthy women of the same age group as a control group. The experiment was designed as follows: Prior to analysis, 5 mL of blood was collected from each patient using sterile methods for puncture site cleaning and a medical syringe. The blood was placed in sterile, clean plastic tubes (gel tubes) and centrifuged at 3500 rpm for 10 minutes to obtain serum. The serum was then placed in Eppendorf tubes and frozen at –20 °C until the required tests were performed. Quantitative enzyme immunoassay (ELISA) was used to quantify EGFR2, SYPL1, and VTN, according to the manufacturer's guidelines from Sunlong Biotech Chain. CA 125, CA 15-3, and CA 19-9 levels were measured using a Roche Cobas analyzer from the German company Roche. Calcium levels were measured using a fully automated Fujifilm analyzer from Japan.

It was conducted using the XLSTAT standard program. Access to this information is provided in the format of mean ± standard deviation (SD) of the de-identified data. The comparisons were conducted using independent t-tests groups) to compare the sick and healthy sample mean values. Pearson's coefficient correlation was used to determine whether there was a relationship between the variables. Any P-value < 0.05 is considered statistically significant.

The study was conducted following ethical approval, and written informed consent was obtained from all participants, including patients and healthy individuals.

Results

The mean ± SD of CA 15-3, CA125 (U/mL) and CA19-9 (U/mL) of patients and control groups levels in the serum were shown in Table 1. The findings showed a marked rise (P < 0.05) of CA 15-3 and CA19-9 (U/mL) levels in the group of breast cancer patients, while the CA125 (U/mL) levels were no significantly decrease (P > 0.05).

Table 1
Serum level of tumor markers

Parameters	Healthy women (n = 30)	Breast cancer (n = 30)	P-value / t-test
CA 15-3, U/mL	15.75 ± 5.85	42.93 ± 11.15	<0.05
CA125, U/mL	18.36 ± 6.54	17.89 ± 8.33	>0.05
CA19-9, U/mL	5.33 ± 0.21	39.61 ± 4.35	<0.05

The mean ± SD of EGFR2, SYPL1 and VTN of patients and control groups levels in the serum were shown in Table 3. The findings showed a marked rise (P < 0.05) of VTN and SYPL1 (pg/mL) levels in the group of breast cancer patients, while the EGFR2 levels were significantly decrease (P < 0.05).

Table 2
Serum level EGFR2, SYPL1, VTN

Parameters	Healthy women (n = 30)	Breast cancer (n = 30)	P-value / t-test
EGFR2, ng/mL	0.73 ± 0.11	0.63 ± 0.07	<0.05
SYPL1, pg/mL	121.27 ± 13.80	194.48 ± 32.65	<0.05
VTN, pg/mL	0.81 ± 0.26	1.33 ± 0.25	<0.05

The mean of calcium and magnesium of patients and control groups levels in the serum were shown in Table 3. The findings showed a marked rise (P < 0.05) of calcium levels in the group of breast cancer patients while the magnesium (mg/dL) levels were significantly decrease (P < 0.05).

ROC (receiver operating characteristic) curves were used in this study to either assess the usefulness of different disease biochemical diagnostic tests and find the best cut-off (or value) for each parameter of interest. Common summary statistics for diagnostic accuracy are

sensitivity, specificity, and area under the curve (AUC). Table 4 reports the diagnostic characteristics (criterion, specificity, sensitivity, and AUC) of the levels of EGFR2, SYPL1, and VTN in the patient compared to control groups.

Table 3
Serum level calcium and magnesium

Parameters	Healthy women (n = 30)	Breast cancer (n = 30)	P-value / t-test
Calcium, mg/dL	8.39 ± 0.44	9.69 ± 0.61	<0.05
Magnesium, mg/dL	2.31 ± 0.51	1.76 ± 0.32	<0.05

Table 4
Criterion, specificity, sensitivity, and AUC by ROC analysis in patients and control groups

Parameters	Optimal criterion	Specificity	Sensitivity	AUC
EGFR2	≤0.6252	93.10	53.33	0.772
SYPL1	≤140.3845	100.00	90.00	0.994
VTN	>1.1476	79.31	66.67	0.768

Table 5 displays the Pearson correlation coefficients (r) among three novel biomarkers (EGFR2, SYPL1, and VTN) and additional measured parameters, including tumor markers (CA 15-3, CA125, CA19-9) and electrolytes (calcium and magnesium).

Table 5
Correlation coefficient (r)

Parameters	EGFR2	SYPL1	VTN
CA 15-3, U/mL	–0.42	0.51	0.66
CA125, U/mL	–0.39	0.43	0.38
CA19-9, U/mL	–0.55	0.36	0.46
EGFR2	1.00	–0.22	–0.31
SYPL1	–0.22	1.00	0.44
VTN	–0.31	0.44	1.00
Calcium, mg/dL	–0.34	0.66	0.77
Magnesium, mg/dL	0.36	–0.56	–0.35

Discussion

Breast cancer's tumor marker CA15-3 is an indicator of the illness. It may be able to predict a person's chances for success with treatment when their cancer has spread. Studies to confirm the use of CA15-3 in blood specimens as a valid test for breast cancer prior to obtaining results from the same patient post-treatment remain inconclusive. Patients suffering from recurrent breast cancer (those with higher levels of CA 15-3 at the time of diagnosis) respond poorly to chemotherapy and have low overall survival rates when diagnosed with locally advanced breast cancer, regardless of their degree of lymphocyte invasion and/or whether they have an elevated human epidermal growth factor receptor 2 (HER2) status (Hameed et al., 2022). Earlier research suggested that CA15-3 could assist physicians in diagnosing more cases of metastatic breast cancer than if they were only using clinical evaluations to identify recurrence, thereby resulting in a 37% increase in the number of patients diagnosed with recurrence of metastatic breast cancer when using CA15-3 (Kabir et al., 2024). Duffy confirmed this by showing that CA15-3 was an important marker to help guide therapy for patients with locally advanced breast cancer. Similarly, past research has demonstrated an association between elevated CA15-3 levels and prediction of inadequate response to initial treatment or recurrence in patients with locally advanced breast cancer (Duffy et al., 2004; Kurebayashi et al., 2004; Duffy, 2006). For example, Kurebayashi et al. showed that there was an association between having more than a 20.0% reduction of CA15-3 levels at the end of treatment and positive prognostic outcome in regards to progression free survival during systemic therapy for patients with locally advanced breast cancer (Given et al., 2000).

CA 19-9 is a carbohydrate antigen, chemically designated as sialyl-Lewis A (sLea), which arises from alterations in glycosylation pathways. Traditionally associated with gastrointestinal cancers (pancreatic and colorectal), several mechanisms explain its elevation in breast cancer (Cazet et al., 2010). In an initial tissue analysis of breast specimens, researchers discovered that the CA 19-9 antigen was present in roughly 62% of breast carcinomas, revealing a significant correlation between its expression and poor tumor differentiation, indicating that its elevation signifies the extent of malignancy (Tissues, 1986). Recent studies have shown that CA 19-9 expression is upregulated in the most malignant and hypoxia resistant cell clones that tend to predominate in advanced stage cancers and often develop hematogenous metastasis. Sialyl-lewis a has been shown to be expressed on breast epithelial tumors and gastrointestinal tumors. Overexpression of sialyl-Lewis an is considered to be a key event in invasion and metastasis in many tumor types (Sawada et al., 2011).

The present findings indicate a decrease in EGFR, which contradicts the observations of Agenor de Araújo Rogério et al. (2022), who observed an elevation in EGFR in breast cancer. Additionally, there was a marked decrease in sEGFR levels in all patients compared to those in healthy women, which agree with existing literature and lacks a logical explanation (Tas et al., 2015; Banys-paluchowski et al., 2017; Kjær et al., 2020). The existence of positive regulation mechanisms pertaining to the development of both growth and physiological division in healthy women is important because there are multiple potential negative regulatory mechanisms (internally limiting the proliferation of cancerous cells virus through receptor internalization and other EGFR Inhibitors) present. sEGFR is not a good marker for community screening as the levels of sEGFR vary widely between different patients with the use of varying analytical techniques during study (de Araújo et al., 2022).

The current results contradict those of Uzun, Kosem et al. (2024), Ergun et al. (2025) and Wang et al. (2026), who saw an increase in SYPL1. The noted reduction in serum SYPL1 levels in breast cancer patients may indicate tumor-related changes in vesicular trafficking, altered extracellular vesicle cargo composition, increased intracellular protein degradation, or the absence of differentiation-associated vesicle proteins. Since SYPL1 is not a conventional secreted protein, its circulating levels likely reflect alterations in vesicle dynamics and tumor-related cellular reprogramming rather than direct secretion (Kerr et al., 1972; Spataro et al., 1998; Hanahan & Weinberg, 2011).

Further investigations reveal that pre-operative patients demonstrate hypercalcemia (Almas, 2017). Hypercalcemia is present in virtually all cases of advanced breast cancer, particularly in stage III and stage IV cases (Booth et al., 2002). Hypercalcemia in cancer patients may result from malignancy (Zagzag et al., 2018). A separate study indicated that of 3602 individuals diagnosed with breast cancer, all displayed symptoms related to hypercalcemia (Hashizume et al., 2022). Hypercalcemia may occasionally occur in advanced breast cancer instances. Numerous research studies demonstrate that metastatic breast cancer causes hypocalcemia (Darawshi et al., 2022). The role of calcium in regulating cell proliferation, differentiation, migration, invasion, metabolism, and apoptosis makes it important to examine changes in calcium levels in patients with breast cancer to help develop treatment regimens (Kirom et al., 2025).

Hypomagnesemia is a common problem in patients with solid tumors and is frequently related to the stage of malignancy. The most common mechanism of hypomagnesemia in cancer patients is magnesium renal wasting. Also common is a decreased intake of magnesium, mostly due to a modified absorption, secondary to diarrhea, vomit and malabsorption syndromes (Grupińska et al., 2025). Clinical controlled study showed that plasma magnesium level of female breast cancer patients was significantly lower than that of normal population. It is reasonable to believe that magnesium ions play an important role in the occurrence and development of breast cancer and that proper dietary supplementation of magnesium could effectively inhibit the progression of breast cancer (Huang et al., 2024). Dietary magnesium intake was inversely associated with the risk of breast cancer and a higher CRP level was recognized as a risk factor for the development of breast cancer. A case-control study in Italy showed that breast cancer patients had a significantly lower serum magnesium level compared to control subjects. Several experimental studies have suggested that the effect of magnesium on tumorigenesis is through two mechanisms: inflammation and free radical-induced

oxidative stress, both of which can cause DNA damage and subsequently lead to tumor onset (Huang et al., 2019).

This study has shown a significant correlation between EGFR2, SYPL1 & VTN with breast cancer. The ROC curve analysis suggested that SYPL1 is the most useful marker for detecting breast cancer in women. The data support the use of circulating levels of EGFR2, SYPL1 and VTN as a means of monitoring response to therapy and predicting breast cancer: EGFR2 showed negative correlations with conventional tumor markers, including CA 15-3 ($r = -0.42$), CA125 ($r = -0.39$), and CA19-9 ($r = -0.55$), suggesting that these biomarkers are associated with distinct molecular pathways and breast cancer subtypes. HER2/EGFR2-positive tumors often exhibit lower expression of classical mucin-based tumor markers due to differences in receptor signaling and tumor biology. EGFR2 was also negatively correlated with calcium ($r = -0.34$) and positively correlated with magnesium ($r = 0.36$), reflecting its role in magnesium homeostasis and the regulation of calcium metabolism. Additionally, negative correlations with SYPL1 ($r = -0.22$) and VTN ($r = -0.31$) indicate that EGFR2 overexpression characterizes a molecularly distinct tumor phenotype. Overall, these findings highlight the biological heterogeneity of breast cancer and the involvement of different signaling pathways in tumor progression.

SYPL1 demonstrated positive correlations with tumor markers, including CA 15-3 ($r = 0.51$), CA125 ($r = 0.43$), and CA19-9 ($r = 0.36$), suggesting an association with tumor burden and disease progression. The strongest correlation with CA 15-3 supports the role of SYPL1 as a potential biomarker in breast cancer, reflecting shared mechanisms of tumor growth and vesicular secretion. SYPL1 also showed a strong positive correlation with calcium ($r = 0.66$) and a negative correlation with magnesium ($r = -0.56$). These findings may indicate that elevated SYPL1 levels are linked to advanced disease characterized by increased bone turnover and calcium release, while magnesium levels decline. Additionally, a moderate positive correlation with VTN ($r = 0.44$) suggests coordinated upregulation of these proteins in more aggressive breast cancer phenotypes, supporting their complementary diagnostic value.

VTN showed positive correlations with tumor markers, including CA 15-3 ($r = 0.66$), CA125 ($r = 0.38$), and CA19-9 ($r = 0.46$), with the strongest association observed for CA 15-3. This finding supports the role of vitronectin as a marker of tumor progression and suggests that its levels increase alongside established breast cancer biomarkers. VTN also demonstrated the strongest correlation in the analysis with calcium ($r = 0.77$), indicating a close relationship between vitronectin expression and processes involved in tumor invasion, extracellular matrix remodeling, angiogenesis, and bone-related metastasis. These mechanisms may contribute to altered calcium homeostasis in advanced disease. In contrast, VTN showed a negative correlation with magnesium ($r = -0.35$), reflecting the inverse relationship between calcium and magnesium frequently observed during breast cancer progression. Overall, these findings support the potential utility of VTN as a complementary biomarker in breast cancer assessment.

Conclusion

High levels of CA 15-3 and VTN before treatment could serve as prognostic factors for cancer growth in people. Lower levels of SYPL1 have been noted in many breast cancer patients, especially those receiving chemotherapy, and this may indicate that SYPL1 has an effect on the aggressiveness of breast cancer. Therefore, VTN and SYPL1 could potentially be used as a non-invasive diagnostic tool for evaluating and monitoring patients with breast cancer who have received chemotherapy.

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