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Vascular endothelial growth factor serum level as a prognostic and diagnostic marker for colorectal cancer

Article,

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Abstract

Although early detection is essential, radical surgery remains the main treatment for colorectal cancer, a major cause of cancer-related fatalities. The blood markers used in clinical practice for colorectal cancer (CA19-9) are carbohydrate antigen and carcinoemberyonic antigen (CEA). Both are only used for surveillance and as prognostic markers for disease-free survival because of their limited sensitivity and specificity. They are not used for screening or diagnosis. Therefore, there is an urgent need for a serum marker that facilitates early detection. Since angiogenesis is essential to the development and spread of cancers, targeting it has been shown to be an effective anti-tumor therapy. Vascular endothelial growth factor (VEGF), whose serum quantity has been connected to a variety of human malignancies, is one of the primary inducers of angiogenesis and may be used as a prognostic marker for solid tumors. Examining VEGF expression in patients with colorectal cancer (CRC) and comparing the findings to the patients' clinicopathologic features was the aim of this study. 68 patients and 10 healthy controls had their serum levels of CEA and CA19-9 compared to their VEGF levels. The results showed that higher serum levels of VEGF in CRC patients were significantly correlated with levels of CEA and CA19-9. In conclusion, determining VEGF serum levels can aid in the diagnosis of colorectal cancer (CRC) patients and open the door to VEGF inhibitor-based tailored treatment of CRC patients.

Keywords: Rectal Carcinoma; VEGF; CEA; CA19-9

1. Introduction

One of the leading causes of cancer-related fatalities globally, colorectal cancer (CRC) accounts for over 150,000 new cases, 55,000 deaths in the US, and 125,000 deaths in Europe annually [1], [2]. Approximately one million new cases of colorectal cancer (CRC) are identified globally each year, and the illness is responsible for almost 500,000 deaths. Radical surgery is the primary treatment for those with confined illness, and adjuvant chemotherapy comes next [3], [4]. Nevertheless, a sizable percentage of patients experience recurrence, and patients with identical tumor stages may exhibit disparate outcomes, suggesting that traditional staging methods may not be able to accurately predict cancer prognosis. [5], [6]

Finding new prognostic indicators that can identify high-risk individuals and change treatment options is therefore essential. Carbohydrate antigen (CA19-9) and carcinoembryonic antigen (CEA) are the blood indicators currently used in clinical practice for colorectal cancer (CRC) [7], [8]. Due to their low sensitivity and specificity, these markers are frequently employed for surveillance and as prognostic indicators for disease-free survival but not for diagnostic or screening reasons [9]. Tumor growth and progression are significantly

influenced by angiogenesis, a physiological process that involves the formation of new blood vessels from pre-existing vessels [10], [11]. Tumor angiogenesis targeting has been demonstrated to be a successful strategy for inhibiting tumor growth and metastasis [12]. The creation of new blood vessels can lead to the development of tumors. One of the main factors that promotes angiogenesis is vascular endothelial growth factor (VEGF), and its concentration may serve as a prognostic indicator in solid tumors. Numerous human cancers, including those of the lung, breast, and colon, have been shown to express VEGF [2], [4]. According to certain research, metastasis and a poor prognosis are associated with VEGF expression [6]. Therefore, it has been shown that VEGF plays a significant role in angiogenesis [9]. As a result, people with colorectal cancer had higher serum VEGF levels [10]. The most often reported signs and markers of colorectal cancer (44% of cases) include rectal bleeding, a persistent change in bowel habits, and anemia in the absence of other gastrointestinal symptoms [11]. Stomach ache is the second most common symptom in 40% of cases [12]. This discomfort may be caused by intestinal perforation leading to extensive peritonitis, peritoneal dissemination, or partial blockage [13]. However, it was also mentioned that certain symptoms don't show up until the cancer has progressed significantly [14]. About 55% of patients have advanced colorectal cancer, which is either so locally invasive that surgery to remove the main tumor alone is unlikely to be sufficient for cure, has migrated to the lymph nodes, or has metastasized to other organs [15].

The past several years has seen a significant increase in the survival rates of those with colorectal cancer, presumably due to early detection and better treatment [16]. Despite the fact that there is a wealth of information regarding risk factors, approximately 75% of diagnoses occur in patients who have no evident risk factors other than advanced age [17]. VEGFs, fibroblast growth factors, platelet-derived growth factors, insulin-like growth factor, and transforming growth factors are examples of proangiogenic factors; thrombospondin-1, angiostatin, and endostatin are examples of antiangiogenic factors [18]. Adult reproduction, wound healing, and embryogenesis are the only times physiologic angiogenesis is seen [19]. The closely controlled balance of proangiogenic and antiangiogenic signals distinguishes normal and pathologic angiogenic processes [20].

Tumor angiogenesis is the process by which a network of blood vessels enters malignant growths and distributes nutrition, oxygen, and waste products [21]. Tumor angiogenesis basically starts when malignant tumor cells produce molecules that warn the surrounding normal host tissue [22]. This singling encourages the formation of new blood vessels by triggering the production of proteins in the host tissue through the activation of particular genes [23]. This study examined VEGF expression in patients with colorectal cancer (CRC) and contrasted the findings with the patients' clinicopathologic features [24].

1.1. Research Significance

Colorectal cancer remains one of the leading causes of cancer-related morbidity and mortality worldwide, emphasizing the urgent need for reliable biomarkers that can facilitate early diagnosis, improve prognostic assessment, and support personalized treatment strategies. Vascular Endothelial Growth Factor (VEGF) plays a central role in tumor angiogenesis, growth, invasion, and metastatic progression, making it a promising candidate for clinical evaluation in colorectal cancer patients. This study is significant because it investigates the potential utility of serum VEGF levels as both a diagnostic and prognostic biomarker, providing a minimally invasive approach for assessing disease presence and progression. Establishing a strong association between serum VEGF concentrations and clinicopathological characteristics may enhance the accuracy of risk stratification, enable earlier detection of aggressive disease, and assist clinicians in predicting treatment outcomes and overall patient survival. Furthermore, the findings may contribute to a better understanding of the biological

mechanisms underlying colorectal cancer progression and support the development of targeted anti-angiogenic therapies. By evaluating the clinical relevance of serum VEGF, this research has the potential to improve patient management, optimize therapeutic decision-making, and ultimately contribute to better clinical outcomes and reduced disease burden.

2. Materials and Methods

68 patients with histologically proven colorectal cancer undergoing elective surgery at Mansoura University's Gastroenterology Center 39 men and 29 females, ages ranging from 24 to 74 were included in this study. As a control group, ten healthy people of the same age and sex six males and four females were employed [25], [26], [27]. A complete blood count, serum levels for CEA and CA19.9, endoscopic evaluation, radiological evaluation, clinical examination, and liver function tests (serum albumin, serum bilirubin, ALT and AST, and serum creatinine) were among the laboratory tests performed on the patients [28], [29], [30]. Histopathological investigation verified that all patients had colorectal cancer (CRC), and Dukes' staging approach for colorectal cancer was used for grading and staging [31], [32], [33].

2.1 Blood Samples for Controls and Patients

Each individual had an antecubital vein punctured aseptically to extract 1-2 ml of venous blood, which was then allowed to clot in a simple polypropylene tube at 25°C for 30 minutes [34], [35], [36]. After the serum was isolated, it was used for the assay and centrifuged for around fifteen minutes. Samples were kept at -20°C for the following reasons after 1000 × g of serum was extracted: Human VEGF concentrations measured quantitatively using an enzyme-linked immune sorbent assay [18], [22], [24]

2.2 Fundamentals of the Test

In order to make a solid-phase antibody, the kit coats microtiter plate wells with purified human VEGF antibody, measures the amount of human VEGF in the sample, and then adds VEGF to the wells [21], [26], [27]. An antibody-antigen-enzyme-antibody complex is created when the combination antibody and goat anti-human enzyme-labeled antibody are thoroughly washed [24]. It turns blue when the substrate is applied. The HRP enzyme-catalyzed process is stopped by adding a sulfuric acid solution, and the color change is measured spectrophotometrically at 450 nm [15], [25]. The concentration of VEGF in the samples is then determined by comparing their optical density (O.D.) to the reference curve [3], [5].

2.3 Assay Procedure

Set up ten standard wells on the coated microtiter plate, starting with 100 µl in the first and second wells and serially diluting the remaining eight wells every two subsequent wells (density: 900 pg/ml, 600 pg/ml, 300 pg/ml, 150 pg/ml, 75 pg/ml) [8], [9], [11]. Don't add Sample and Enzyme Conjugate to blank comparison wells; instead, set blank sample wells independently. Fill the sample well with 40µL of the sample dilution, followed by 10µL of the sample (the final sample dilution is five times that of the sample) [3], [4]. Mix gently after adding the sample to the wells, being careful not to touch the well walls. Incubate: After using the closure plate membrane to seal the plate, let it sit at 37°C for 30 minutes [13], [16]. Get the wash solution ready: Make a reserve after diluting the wash solution 20 times with 20 times distilled water [19], [21]. Manual Washing: Aspirate the contents of the plate into a sink or appropriate waste container to remove the incubation mixture [30], [31].

Aspirate the contents of the plate into a sink or suitable waste container after using a squirt bottle to fully fill each well with wash solution. For a total of five washes, repeat this process four more times. After the last wash, flip the plate over and use paper towels or absorbent paper to blot it dry until there is no more moisture. (Note: To guarantee that every

strip stays firmly in the frame, hold the plate frame's sides firmly when cleaning the plate. Wash and incubate [9], [35]. Color: Fill each well with 50µl of substrate; stop the reaction by filling each well with 50µl of stop solution. Mix thoroughly. Using a microplate reader set to 450 nm, find each well's optical density in 15 minutes.

2.4 Calculations

For the horizontal axis, the standard density is employed, and for the vertical axis, the O.D. value. On graph paper, a standard curve was created. The sample curve was used to determine the corresponding density based on the sample O.D. value, which was then multiplied by the dilution factor to determine the sample density. The actual density of the sample is the outcome. A standard curve was constructed by plotting the mean optical density for each standard on the y-axis against the concentration on the x-axis and drawing a best-fit curve through the points on the graph. Regression analysis was used to determine the best-fit line.

2.5 Analysis of Statistics

SPSS statistical software version 10 (SPSS, Inc., Chicago, IL, USA) was used for data entry and analysis. The mean and standard deviation were used to display quantitative data, while percentages and numbers were used to display qualitative data. To determine the relationship between row and column variables of qualitative data, the chi-square (X^2) was utilized. The P-value, or significance level, is set at 5%. Results are considered non-significant if the P-value is greater than 0.05, and significant if the P-value is less than 0.05.

3. Results

The male-to-female ratio of the 68 colorectal cancer patients in this study was 1.34:1 (57% and 43%, respectively), with 39 men and 29 females. The median age was 53 $\pm$ 12.26 years, while the age range was 24–74 years. The rectum (n = 33), distal colon (n = 24), and proximal colon (n = 11) were the most frequently impacted sites, according to clinical analysis of the cases. The majority of patients experienced irregular bowel habits (70%) and per-rectal hemorrhage (82%). There were no discernible variations between age and gender when VEGF, CA 19-9, and CEA levels were analyzed. 49 (72.1%) classic adenocarcinomas, 18 mucoid adenocarcinomas (26.5%), and 1 squamous cell carcinoma were found in the pathological analysis of the tumors removed from the patients.

The tumors were classified as grade I (12%, 17.6%), grade II (47%, 69%), and grade III (8%, 11.8%) according to the pathological grade of differentiation. Nineteen (28%) of the resected tissues had secondary nodal metastases, according to the lymph node status. In the cases under study, there was a strong positive connection between the serum levels of CEA, CA19.9, and VEGF. Figure 1 illustrates that there was no significant link found between the lymph node status and the levels of CEA, CA19-9, and VEGF. Figure 2 illustrates that the levels of CEA, CA19-9, and VEGF did not significantly correlate with the type of cancer. Figure 3 illustrates that there was no significant link found between the pathologic grade of cancer and the levels of CEA, CA19-9, and VEGF.

4. Conclusion

In the Western World, colorectal cancer (CRC) is the second most common cause of cancer-related mortality and the third most common cancer overall. Alcohol, food, and family history have all been linked to colorectal cancer (CRC), which is probably a multifactorial disease. Since primary prevention programs are hampered by the inability to identify the fundamental cause of colorectal cancer, screening programs have received more attention. Tumor growth and metastasis depend on angiogenesis. The multistep process of cancer has the potential to grow aggressively. Although an increased tumor marker level is a non-specific

sign of malignancy, it can be helpful in monitoring individuals who have received treatment. This study looked at Vascular Endothelial Growth Factor (VEGF) expression in patients with colorectal cancer (CRC) and correlated the results with the clinicopathologic characteristics of the patients. We discovered that the patients under study ranged in age from 24 to 74 years, with a mean age of 50 ± 12.26 years. This outcome was consistent with that of Khafagy et al., who discovered that Egyptian patients with colorectal cancer ranged in age from 17 to 78 years, with a median age of 45. Conversely, the average age of CRC patients was found to be 59.5 ± 12.6 years. The mean age of patients with colorectal cancer was 43.1 ± 9.3 years, according to another big study with 607 individuals. Males had a slightly higher incidence of CRC than females, according to the current study. This was consistent with research showing that CRC is more prevalent in men. 31, 32 However, a study found that CRC is more prevalent in women. 32. The huge number of cases in the Jover (754 patients) and Aljebreen (113 patients) trials may account for the disparity in the outcomes.

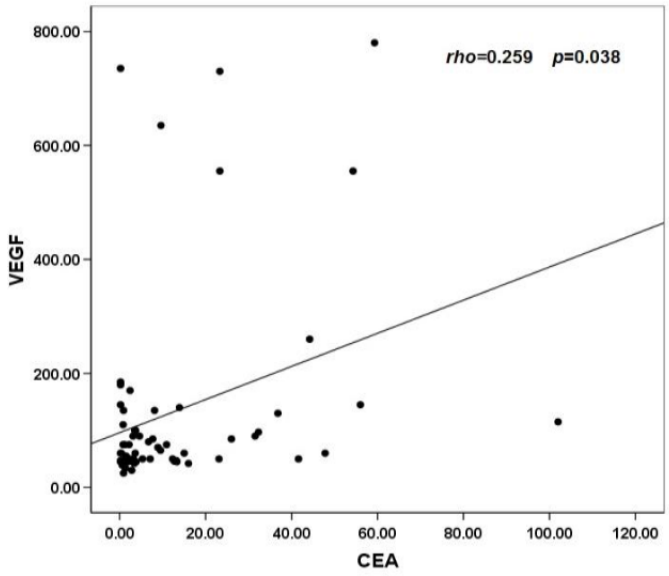

Figure 1. Positive correlation between VEGF serum level and serum level of CEA ($p<0.05$).

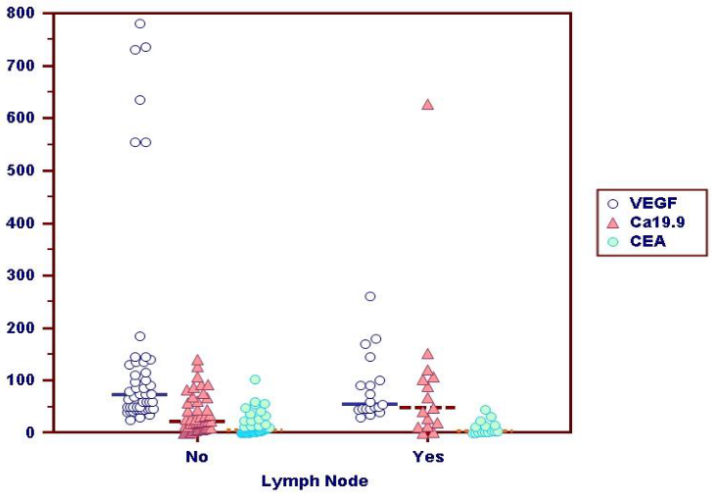

Figure 2. Relationship between the lymph node status and serum levels of VEGF, CA 19-9, and CEA

The most prevalent histopathologic type (69.1%) in this investigation is a moderately differentiated tumor (grade II). This was consistent with the findings of Gryfe et al. 30, who

discovered a moderately differentiated tumor in roughly 69% of cases. Additionally, the histology of colorectal cancer revealed that 56% of tumors were moderately differentiated, according to a study. 32. The most prevalent histopathologic type in the current study was adenocarcinoma (72.1%). This outcome was consistent with the findings of Weitz et al. 34, who discovered that 85% of the patients under study had adenocarcinoma, and Fenoglio 35, who discovered that 90% of the patients under study had adenocarcinoma. The majority of the cases in this study were at stage C. These results are consistent with the findings of Abou-zeid et al. 36, who discovered that 58% of CRC patients had Dukes' C.

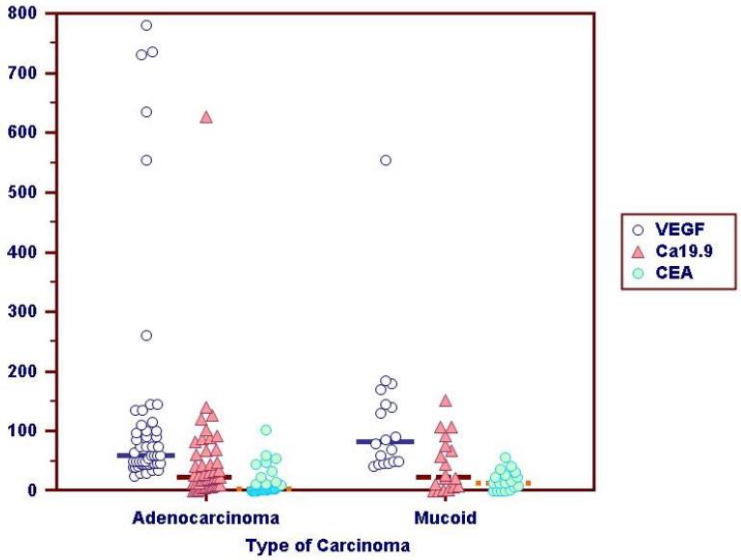

Figure 3. Link between the pathologic type of cancer and serum levels of VEGF, CA 19-9, and CEA

Because serum CEA levels can be measured precisely and consistently, this marker was thought to offer potential as a serological screening tool for early detection. According to the current study, serum CEA rises with Dukes' grades and stages. These findings were in line with research showing that CEA levels rose with tumor differentiation stages and grades. Additionally, studies reporting high preoperative serum CEA levels were consistent with significantly elevated CEA levels in CRC patients with lymph node metastases. The degree of lymph node metastasis and the depth of tumor invasion were substantially correlated with these levels. However, CA19.9 cannot be suggested for CRC early diagnosis. In terms of sensitivity, the majority of research indicated that CEA is a more sensitive marker for CRC, despite the fact that increased levels of CA19.9 have been found in up to 75% of patients with advanced CRC. Patients with colorectal cancer had significantly higher serum CA19.9 levels. This outcome was consistent with research showing that as Dukes' disease stage advanced, so did the CA19.9 level and sensitivity. Additionally, it was in line with research showing an increase in serum CA19.9 levels with tumor stage. This study demonstrated significantly substantial VEGF expression in CRC patients' peripheral blood when compared to controls. This result is in line with studies that found that patients with colorectal cancer had higher serum VEGF levels than control subjects.

In CRC patient groups, serum VEGF levels were significantly higher. This outcome suggests that VEGF expression rises as Dukes' stages progress in CRC patients, which is consistent with research showing a strong positive connection between VEGF expression and Dukes' stages. According to Dukes' stages, VEGF expression rose as colorectal carcinogenesis progressed. Patients with the greatest VEGF expression had a far worse prognosis than those with intermediate or low expression levels, with recurrence and mortality occurring earlier.

This outcome was in line with another study that found a strong correlation between angiogenesis and VEGF expression at the deepest site of tumor invasion, which may be a valuable predictor of a bad prognosis in advanced colorectal cancer. The high molecular changes that take place in advanced colon cancer may account for the high VEGF expression, which was connected with Dukes' stages and the existence of distant metastases. Furthermore, this outcome was in line with research showing that VEGF influences the proliferation and migration of endothelial cells, which plays a significant role in the invasion, progression, and spread of colorectal cancer. Anti-VEGF therapy has been used to try to prevent VEGF synthesis in patients with advanced colorectal cancer.

CEA levels showed a strong positive correlation with VEGF. This outcome was in line with research that quantitatively assessed the amount of VEGF and CEA in protein extracts taken from 69 CRC patients' tissue biopsies. These investigations discovered a strong correlation between VEGF and the amount of CEA in either the matched normal mucosa or the tumor tissue. VEGF had a better diagnostic sensitivity for colorectal carcinoma than CEA, and when combined, the sensitivity for predicting colorectal carcinoma was higher than when either marker was used alone. In CRC patients, there was a highly significant connection between serum VEGF and CA19.9. This outcome was in line with research that measured plasma VEGF in CRC patients prior to surgery and discovered a rise in VEGF with a strong positive connection with serum CA19.9 and metastatic dissemination.

Additionally, there was a strong link between CEA and CA19.9 levels in the patients under study, which was consistent with research showing a significant positive correlation between plasma CEA, CA19.9 levels, and the CRC stage (Duke's classification). It was hypothesized that 50.6% of patients had elevated serum levels of CEA and 29.6% of CA19.9 at the time of CRC diagnosis. 54.3% of CRC patients had this increase when both antigens were present. Patients at high risk were successfully identified by the widespread use of CEA and CA19.9. The sensitivity of CRC diagnosis was not significantly increased by the combined assay of CEA and CA19.9.

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