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EVALUATION OF VASCULAR ENDOTHELIAL GROWTH FACTOR IN LIVER CARCINOMA WITH PROGRESSIVE HEPATITIS B

Original Article

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ABSTRACT

Background: Another significant risk factor of hepatocellular carcinoma (HCC) is chronic hepatitis B (CHB), particularly in places where genetic testing is not widely available. Angiogenesis is central to HCC pathogenesis, and vascular endothelial growth factor (VEGF) has been suggested as a contributor to cancer growth and progression. This research aimed to reveal the significance of serum VEGF levels concerning the presence of HCC in CHB patients and prove the effectiveness of VEGF as a non-invasive diagnostic marker in HCC.

Methods: A comparative study was carried out on a sample size of 70 in a tertiary care hospital. They were subdivided into two groups, including CHB patients with HCC (n = 50) and those without HCC (n = 20). Serum VEGF was measured by enzyme-linked immunosorbent assay (ELISA), along with routine liver tests, including alpha fetoprotein (AFP). A structured proforma was used to record demographic and clinical information. Statistical analyses, including t-tests and Pearson correlation, were conducted with $p < 0.05$ as a significance criterion.

Results: The average levels of VEGF were significantly lower in the control group than in patients with HCC (74.5 ± 18.3 vs 28.6 ± 9.4 pg/mL, p = <0.0001). A positive relationship of VEGF was strongly correlated with a tumor ($r = 0.61$, $p < 0.001$) and AFP ($r = 0.58$, $p = 0.002$), but there was a lack of significant correlations with age or sex. Also, a moderate positive correlation was found with the alanine aminotransferase (ALT) levels ($r = 0.45$, $p = 0.01$).

Conclusion: This study indicates that VEGF can be used as a complementary biomarker to AFP for early screening and surveillance of HCC among CHB patients. Future surveillance strategies may be enhanced by the correction of VEGF measurement in low-resource settings.

Keywords: Vascular Endothelial Growth Factor A, Hepatocellular carcinoma, Chronic hepatitis B, Biomarkers.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most widespread primary liver cancer and the third leading cause of cancer mortality (1). Chronic hepatitis B (CHB) infection is one of the most significant risk factors of HCC, especially in low- and middle-income countries where the prevalence of chronic hepatitis B and hepatitis C is high and the vaccine coverage is inconsistent (2). Even with improved surveillance and antiviral therapy, several patients with CHB develop cirrhosis. However, recent studies highlighted the importance of vascular endothelial growth factor (VEGF), gaining more popularity due to its versatile contribution to angiogenesis, tumor vascularization, and progression in the liver (3). Moreover, the clinical significance of VEGF in pathological angiogenesis is not restricted to oncologic cases; it is also implicated in remodeling processes involving cardiovascular disease, including those with heart failure patients undergoing resynchronization therapy, illustrating the extended clinical impact of VEGF on a broader medical scope (4). VEGF systemic upregulation has been documented in chronic inflammation, including diabetic retinopathy, where leptin and VEGF are reported to be considerably higher in serum and vitreous in patients (5). The role of HUWE1 in regulating EGFR turnover to diminish fibrosis, a leading cause of HCC, was also identified by influencing growth factor signaling pathways (6). Similarly, the S100A16 calcium-binding proteins are triggers of cytoskeletal remodeling in fibrosis, which correlates with HCC cell invasiveness (7). Simultaneously, chronic liver stress and angiogenesis-based mechanisms have been linked to metabolic disorders, such as diabetes and prediabetes, which may facilitate malignant transformation in the context of hepatitis viruses (8).

Chronic inflammation and persistent metabolic stress can contribute to angiogenic signaling through VEGF, which triggers abnormal neo-vascularization, hepatocyte proliferation pathways, and increases the possibility of malignant transformation (9). Systematic reviews have highlighted the importance of histopathological and molecular biomarkers that reflect tumor biology. VEGF, as a major angiogenic factor, complements alpha-fetoprotein (AFP) by showing tumor vascular activity, where the tumor burden is not the only determinant (10). With hepatokines in non-alcoholic fatty liver disease, the similarities in pathways mediated have been demonstrated, including those involved in viral hepatitis, again echoing the idea of VEGF as a common factor (11). Similarly, metabolic and genetic disorders, including GBA and HEXA mutations, further describe the relations between chronic metabolic stress, cytokine dysregulation, vascularization, and disease progression (12).

The reported effects of Berberine in beta-cell physiology suggest the therapeutic potential of targeting inflammatory and metabolic pathways in chronic conditions, such as liver disorders (13). Similarly, the incorporation of newer imaging modalities such as CT and MRI highlights the fact that there is still a need to improve the accuracy of the diagnosis of small or early liver HCC lesions (14). Nevertheless, imaging can be insufficient, especially in resource-limited contexts, and the potential search for reliable serum biomarkers is necessary to achieve more objective measurements (15). The use of PROM2 and other molecular markers helps explain the possibility of risk-stratifying patients and intervening at the right time using biomarkers (16). Remarkably, the implication of HLA haplotype in immune-mediated conditions, such as in celiac cohorts, shows the importance of genetic host susceptibility in terms of vascularization modulation (17).

Although there is increasing evidence regarding the clinical applications of VEGF as a prognostic biomarker used in early detection of HCC in CHB subjects, it is underutilized in regional contexts in clinical settings. This knowledge gap constrains clinicians from adhering to individualized surveillance approaches (18). Measuring the iron-regulators, such as hepcidin, can additionally change the biomarker profile, shedding light on the disruption of iron homeostasis in cases of vascular remodeling, paving the way to direct liver disease development (19). Population-based research in Pakistan has confirmed the relevance of biomarker research related to the local context, particularly at a time when chronic viral hepatitis burdens are high (20).

Nonetheless, the lack of local evidence to support the use of VEGF as a non-invasive biomarker that is simple and effective in detecting early HCC in chronic hepatitis B patients remains evident. The justification of this study is to address this gap and provide regional data that may be used by policymakers in establishing better screening strategies. The potential utility of VEGF monitoring may contribute to the early detection of HCC, which increases patient survival.

The goal of the study was to compare serum VEGF concentrations in patients with CHB with or without HCC. It also evaluated the correlation between VEGF and tumor size, AFP, and liver functional tests. The aim was to determine VEGF as a potential marker to detect and monitor the disease at its early stages.

METHODOLOGY

The study was conducted using a cross-sectional comparative design at a tertiary care facility, collaboratively at SAHS Lahore and Punjab University Lahore, where serum VEGF concentrations with and without HCC in patients with CHB were assessed from July 2023 to December 2023 (ref#112/SZH/Admin).

Non-probability purposive sampling was employed to recruit. The sample size was calculated using OpenEpi version 3.0.0 (released 2013, Atlanta, GA, USA) based on previous literature, which presented a mean difference in IL-6 levels between groups, and the calculated sample size was 70 patients (fifty with confirmed HCC and twenty with CHB without HCC).

Inclusion criteria included adults aged between 18 and 70 years who had confirmed chronic HBV infection, with the case group also having radiologically or histologically documented HCC. Patients who were co-infected with hepatitis C or HIV, had other autoimmune liver diseases, locoregional therapy within the last 4-6 weeks, active extra-hepatic malignancies, prior or current angiogenic therapy, uncontrolled ischemic events, and other inflammatory conditions known to raise VEGF.

The sample was stratified into two comparative groups: CHB with HCC (cases) and CHB without HCC (controls). All the participants were subjected to routine clinical examination and laboratory tests. A structured proforma was used to record relevant clinical and demographic data such as age, gender, liver functional test, and AFP level. 5ml of venous blood was taken after standard clinical phlebotomy into EDTA tubes. The samples were processed within 60 minutes, aliquoted, and stored at -80 °C. The concentration of VEGF-A was analyzed using sandwich ELISA in duplicates. Liver routine function tests, AFP, and imaging reports were also reviewed to ensure the status of the disease and match the tumor features. The protocol was followed by the participants who provided fasting blood samples and required follow-ups.

SPSS version 26.0 (released 2019, IBM Corp., Armonk, NY) was used in the analysis of the data. The mean level of VEGF between groups was compared using an independent t-test. Pearson correlation coefficient was used to determine the association between VEGF, tumor size, AFP, and liver enzymes. Statistically significant changes were determined at $p < 0.05$.

RESULTS

The study population consisted of 70 patients, of whom 50 had HCC and CHB (patients), and 20 were without it (controls). The HCC group had significantly elevated serum VEGF levels compared with the controls. There was a strong positive correlation between VEGF and tumor size and AFP. There was also a moderate positive relationship between VEGF and ALT. There was no notable correlation with either age or gender. Table 1 summarizes the clinical and demographic characteristics of study participants.

Table 1: Clinical and Demographic Characteristics of the Study Population

Characteristic	HCC Patients (n = 50)	Controls (n = 20)	Test Used	Test Value	Significance (p-value)
Age (years) Mean ± SD	55.8 ± 8.4	54.3 ± 7.9	Independent t-test	t = 0.72	p = 0.47 (NS)
Gender (Male :Female)	38 (76%):12 (24%)	16 (80%): 4 (20%)	Chi-square test	$\chi^2 = 0.01$	p = 0.92
ALT (U/L)	78.5 ± 15.6	45.2 ± 10.3	Independent t-test	t = 9.5	p < 0.001
AFP (ng/mL)	320 ± 105	12 ± 4	Independent t-test	t = 18.2	p < 0.001
HBV DNA Positive (%)	80% (40/50)	75% (15/20)	Chi-square test	$\chi^2 = 0.17$	p = 0.68
Serum VEGF (pg/mL)	74.5 ± 18.3	28.6 ± 9.4	Independent t-test	t = 13.2	p < 0.001
Tumor Size (cm)	4.5 ± 1.2	N/A	N/A	N/A	N/A

*HCC = Hepatocellular Carcinoma, HBV = Hepatitis B virus, ALT = Alanine amino transferase, AFP = Alpha fetoprotein, IL-6 = Interleukin-6, n = Number of participants, SD = Standard Deviation, * = Significance at p<0.05*

There was no statistically significant difference between the mean ages of CHB patients with HCC (55.86 ± 8.4 years) and controls (54.3 ± 7.9 years, p = 0.47). The distribution of gender was also similar, p=0.92. HCC patients had significantly elevated ALT levels (78.5 ± 15.6 U/L) compared to controls (45.2 ± 10.3 U/L; p = 0.001), and average AFP levels were significantly higher in the HCC group (320 ± 105 ng/mL) than in controls (124 ng/mL; p = 0.001). As observed, mean serum VEGF was 74.5 ±18.3 pg/mL in the HCC group compared with 28.6 ± 9.4 pg/mL in controls (p < 0.001). These results suggest that VEGF, similarly to AFP, can be used to differentiate between CHB patients with and without HCC. Correlation of VEGF with clinical parameters of the study participants is presented in Table 2.

Table 2: Correlation of VEGF with Clinical Parameters

Parameter	Test Used	Test Value	Significance (p-value)
Correlation with Tumor Size	Pearson correlation	r = 0.61	p < 0.001
Correlation with AFP	Pearson correlation	r = 0.58	p = 0.002
Correlation with ALT	Pearson correlation	r = 0.45	p = 0.01
Association with Age	Pearson correlation	r = 0.05	p = 0.65
Association with Gender	Pearson correlation	r = 0.06	p = 0.39

*ALT = Alanine amino transferase, ALT = Alpha fetoprotein, * = Significance at p<0.05*

Tumor size and AFP were both positively correlated with VEGF (r=0.61, p<0.001 and r=0.58, p=0.002, respectively). These results showed that higher levels of VEGF correlate with a larger size of the tumor and increased tumor markers. A weak positive correlation was found with ALT (r = 0.45, p = 0.01), suggesting that VEGF could represent continued liver inflammation. It showed no significant correlation with age (r = 0.05, p = 0.65) or with gender (p = 0.39). These findings indicate that VEGF may become a disease-specific biomarker, regardless of demographic factors, and be used to track tumor progression in patients with CHB.

DISCUSSION

This study aimed to determine whether the serum level of VEGF was significantly related to HCC in patients with CHB and evaluate whether it has a possible use in early detection as a simple biomarker. These results demonstrated that serum VEGF levels were significantly elevated in patients with CHB and HCC compared to those without HCC and emphasized that chronic inflammation is a central mechanism in liver carcinogenesis.

The findings also revealed that VEGF was strongly correlated with tumor size and AFP levels, and showed no significant correlation with age or gender, implying specificity to the disease. This aligns with global literature, which has demonstrated that VEGF-driven angiogenesis stimulates HCC growth and progression in chronic viral hepatitis (21, 22). Similar dysregulation in processes can be observed in other diseases with long-term molecular dysregulations present, which progress the disease. For example, laboratory studies of bioactive compounds demonstrated their ability to interfere with cellular signaling and stress pathways, showing the effects of external factors to undermine tissue homeostasis (23). Similarly, areas of clinical management prototype susceptibility, including prescription and diagnostic mismanagement, point to system-level openings that can exacerbate patient outcomes (24). These analogies highlight that sustained angiogenic imbalance, as manifested by high VEGF, can perpetuate tissue-specific pathology, leading to HCC emergence. Furthermore, a study highlighted the growing clinical interest in angiogenic pathways, particularly VEGF-driven mechanisms, and the opportunities they introduce to early cancer diagnosis and treatment (25).

The absence of VEGF correlation with gender and age also aligns with other studies. Similar strategies have been implemented in hematological diseases, with platelet indices proving to distinguish between thrombocytopenia subtypes, further supporting the importance of laboratory indicators that are not dependent on demographics (26). Consistent with cardiology findings, in diabetics, BNP levels and the Killip grading are used to determine the severity of myocardial infarction, and where risk stratification has been applied to ventricular tachycardia cases (27, 28). Another notable finding was the correlation between VEGF and ALT level, showing continued liver inflammation. The concept is relevant to chronic kidney disease studies, where urinary electrolytes have been associated with

markers of disease severity, and in the context of metabolic diseases, where disturbance in plasma cholesterol is correlated with systemic imbalance, as exemplified in phenylketonuria (29, 30). Furthermore, studies on endometriosis have shown that neurotrophin-related pathways play a role in multi-organ inflammation, and nutritional research showed that the short-chain fatty acid metabolism of infants is affected by low zinc levels in the body (31, 32). Investigations of stress biology in care providers during the COVID-19 pandemic demonstrated predisposition associated with systemic inflammatory reactions (33).

Similarly, a study demonstrated that choosing targeted treatments based on a precise diagnosis enhances patient outcomes, highlighting prompt clinical decisions (34). The same phenomenon has been reported in trauma-induced coagulopathy with an excess inflammatory reaction, further increasing its complications (35). As part of health-care administration, implementation of WHO-recommended regimens has been proven to enhance patient outcomes, a factor that resonates with the necessity of resilient biomarker-based screening approaches (36). The incorporation of technology, e.g., the Internet of Things (IoT), can also improve biomarker monitoring and patient care (37). Uterine tract infection studies demonstrated how unresolved inflammation in another system can result in chronic conditions, a similar effect of unresolved inflammation in hepatitis B (38).

A study on intrauterine insemination emphasized the value of biological markers in predicting reproductive survival, which has suggested that molecular signals could be used to inform clinical outcomes (39). Similarly, research on ABO blood groups and obesity demonstrated how hereditary influences may affect the inflammatory phenotype and predisposition towards disease (40). The immune response in autoimmune diseases was also associated with hematological indices like red blood cell parameters and further stressed the general applicability of laboratory parameters (41). The study of the antimicrobial and antioxidant activity of spice extracts reveals the way that inflammation regulation is a cross-disciplinary area of interest (42). Animal experiments on antiviral agents such as Sofosbuvir confirm that treatment may affect the biochemical parameters of the liver (43).

The high incidence of hepatotoxicity in the context of HIV-tuberculosis co-infection reinforces the importance of the idea that liver health can be readily affected by various factors (44). Stress-induced hypertension predictors indicate that physiological indicators can be used to detect patients likely to develop a chronic illness (45). Self-assessment and feedback have already proven useful in medical education (46), where patient empowerment may similarly be helpful in HCC surveillance. The correlation between the level of vitamin D3 and left ventricular hypertrophy demonstrates the importance of nutritional factors and inflammation, and their relationship with the pathologies (47). Associations among insomnia, melatonin, and stress demonstrate how the factors of physiological burden multiply the impact on inflammation (48).

The correlation of vitamin D deficiency and obesity in premenstrual syndrome provides another piece of evidence that chronic metabolic imbalance can drive persistent inflammation and disease progression (49). Biomarkers such as IL-6 and VEGF are essential in cases like liver disease because the inflammation is chronic, and environmental pollutants have been proven to elevate them (50).

The use of mean platelet volume has been effective in measuring the severity of chronic kidney disease, which provides a parallel to the application of VEGF in liver disease (51). The functional importance of olive oil in dermatitis highlights the overall importance of inflammatory modulation (52). Studies on vitamin D3 and parathyroid hormone in the treatment of hypertension also confirm the interconnection of metabolic control and inflammation (53).

The introduction of multiple indicators to improve the management of hypertensive patients in comparative risk assessment has found synergy in combining VEGF and AFP in the detection of HCC (54). The impact of nerve growth factor on airway inflammation demonstrates how, similarly, local mediators can contribute to the systemic response, as VEGF does with tumor microenvironments (55). Another example of inflammatory and molecular pathways intersecting in the carcinogenesis process is the notch signaling pathways in oral cancer (56). Studies of adipokines in polycystic ovary syndrome indicate that metabolism regulators have a connection with inflammatory pathways, similar to that of VEGF (57). Recently, salivary diagnostics highlight the potential of non-invasive parameters to check inflammatory diseases (58). The case of dual-mechanism thrombocytopenia is a rare example of how immune-related pathways can complicate the disease and make its progression problematic without early identification (59). Taken together, the findings have significant meaning for enhancing the early diagnosis of HCC among CHB patients in low-resource facilities where easily accessible and less invasive biomarkers are valuable tools (60).

This study has limitations in terms of a cross-sectional nature, a single-center environment, and a rather limited sample size, thus decreasing the possibility of results generalizability. Potential confounders, including nutritional status, co-comorbid metabolic problems, viral co-infections, and use of drugs, were not properly addressed. Longitudinal, multi-centric research design with larger

cohorts needs to be conducted to establish valid VEGF cut-offs, predictive accuracy, and biomarker screening incorporated with standard imaging would improve early HCC diagnosis.

CONCLUSION

The results of this investigation indicated that there were significant relationships with elevated serum VEGF, which was associated with CHB patients with HCC compared to serum VEGF in CHB patients without HCC, and that it was closely correlated with tumor size and the AFP level. The results indicated that VEGF can be an effective non-invasive biomarker for the early detection and monitoring of HCC in high-risk CHB patients. There is no strong correlation with age or sex, implying that VEGF measures disease-specific processes and not demographic characteristics.

These results suggest that the inclusion of VEGF measurement in regular surveillance might help in improving early-stage diagnosis in cases where imaging or conventional markers are not enough.

AUTHOR CONTRIBUTION

Author	Contribution
Saba Safdar	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Muhammad Akram*	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published

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