Indian J. Pharm. Biol. Res. 2026; 14(3):300-307

ISSN: 2320-9267

Indian Journal of Pharmaceutical and Biological Research (IJPBR)

Journal homepage: www.ijpbr.in

RESEARCH ARTICLE

Association Between Vascular Endothelial Growth Factor Gene Polymorphism and Bladder Cancer Risk and its Relationship to Serum Ca19.9, Mmp9 and Timp1 Levels: A Case–Control Study From a Tertiary Care Centre

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ABSTRACT

Background: Bladder cancer represents one of the most frequently diagnosed malignancies of the urinary tract and contributes substantially to cancer-related morbidity and mortality worldwide. The development and progression of bladder cancer involve complex interactions between genetic susceptibility, environmental exposures, angiogenesis, extracellular matrix remodeling, and tumor-associated molecular alterations. Vascular endothelial growth factor (VEGF), a key regulator of tumor angiogenesis, plays an important role in tumor growth, invasion, and metastatic potential. Functional genetic variations within the VEGF gene may influence VEGF expression and thereby modify individual susceptibility to bladder cancer. In addition, circulating biomarkers such as carbohydrate antigen 19.9 (CA19.9), matrix metalloproteinase-9 (MMP9), and tissue inhibitor of metalloproteinase-1 (TIMP1) have been implicated in tumor progression and extracellular matrix degradation.

Objectives: To evaluate the association between VEGF gene polymorphism and risk of bladder cancer and to assess its relationship with serum levels of CA19.9, MMP9, and TIMP1 among bladder cancer patients.

Materials and Methods: This original research study was conducted as a hospital-based case–control study in the Department of Urology and biochemistry, Calcutta National Medical College, Kolkata, from 2020 to 2023. A total of 150 participants were enrolled, including 75 histopathologically confirmed bladder cancer patients (cases) and 75 age- and sex-matched healthy individuals (controls). Peripheral blood samples were collected for genetic analysis of VEGF polymorphism and estimation of serum CA19.9, MMP9, and TIMP1 levels. Genotyping was performed using polymerase chain reaction-based methods. Serum biomarker concentrations were assessed using standardized immunoassay techniques. Statistical analysis was performed using SPSS software. Associations between genetic variants, biomarker levels, and bladder cancer risk were evaluated using appropriate statistical tests.

Results: Bladder cancer patients demonstrated a significantly higher frequency of the VEGF risk genotype compared with controls. The VEGF polymorphism was significantly associated with increased bladder cancer susceptibility (OR=2.74, 95% CI: 1.32–5.69, p=0.006). Serum CA19.9, MMP9, and TIMP1 levels were significantly elevated among cases compared with controls (p<0.001). Patients carrying the VEGF variant genotype showed significantly higher circulating MMP9 and TIMP1 concentrations compared with wild-type carriers. A positive correlation was observed between MMP9 and TIMP1 levels among bladder cancer patients (r=0.62, p<0.001).

Conclusion: The present study suggests that VEGF gene polymorphism may contribute to increased susceptibility to bladder cancer and may influence tumor-associated biomarker expression. Altered VEGF-mediated angiogenic pathways together with increased MMP9 and TIMP1 levels may play an important role in bladder cancer progression. VEGF polymorphism combined with serum biomarkers may serve as a potential molecular tool for risk assessment and disease characterization.

Keywords: Bladder cancer; VEGF polymorphism; angiogenesis; CA19.9; MMP9; TIMP1; genetic susceptibility; molecular biomarkers.

Indian J. Pharm. Biol. Res. (2026): https://doi.org/10.30750/ijpbr.14.3.47

INTRODUCTION

Bladder cancer is a major malignancy of the urinary system and represents a significant global health burden. It is among the most commonly diagnosed cancers worldwide, with considerable differences in incidence patterns according to geographic region, lifestyle factors, occupational exposures, and genetic background. The disease demonstrates marked clinical heterogeneity, ranging from superficial non-muscle-invasive tumors to aggressive muscle-invasive carcinomas associated with poor survival outcomes.[1]

The development of bladder cancer is a multistep biological process involving accumulation of genetic alterations, dysregulation of cellular signaling pathways, impaired apoptosis, uncontrolled proliferation, angiogenesis, and tumor invasion. Although environmental factors such as cigarette smoking, exposure to industrial chemicals, chronic inflammation, and occupational carcinogens are recognized contributors, genetic susceptibility significantly influences individual risk.[2]

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How to cite this article: Biswas NB, Dasgupta A, Roy S, Mondal SN, Dey S. Association Between Vascular Endothelial Growth Factor Gene Polymorphism and Bladder Cancer Risk and its Relationship to Serum Ca19.9, Mmp9 and Timp1 Levels: A Case–Control Study From a Tertiary Care Centre. Indian J. Pharm. Biol. Res. 2026;14(3):300-307.

Source of support: Nil

Conflict of interest: None.

Received: 07/06/2026 **Revised:** 19/07/2026 **Accepted:** 26/08/2026 **Published:** 08/08/2026

Tumor angiogenesis is an essential process that supports malignant growth by providing oxygen and nutrients required for expanding tumor tissue. Among angiogenic mediators, vascular endothelial growth factor (VEGF) is considered one of the most important regulators of endothelial cell proliferation, migration, and vascular permeability. Increased VEGF expression has been associated with enhanced tumor vascularity, aggressive behavior, invasion, and poor prognosis in several malignancies, including bladder cancer.[3]

The VEGF gene, located on chromosome 6p21.3, encodes a family of vascular growth factors involved in normal physiological angiogenesis and pathological neovascularization. Functional single nucleotide polymorphisms (SNPs) within regulatory regions of the VEGF gene may influence transcriptional activity and alter VEGF production. Such genetic variations may modify angiogenic responses and contribute to differences in cancer susceptibility among individuals.[4]

Among various VEGF polymorphisms, promoter and untranslated region variants have gained attention because of their potential effect on VEGF expression. Individuals carrying specific VEGF alleles may exhibit increased angiogenic activity, which can facilitate tumor initiation, progression, and metastatic spread. Previous studies have reported associations between VEGF polymorphisms and risk of several cancers; however, findings have varied across populations, indicating the influence of ethnic and environmental factors.[5]

Apart from angiogenic regulation, tumor progression depends on degradation and remodeling of the extracellular matrix (ECM). Matrix metalloproteinases (MMPs) are a family of proteolytic enzymes that contribute to tumor invasion by breaking down basement membranes and connective tissue barriers. Among these, matrix metalloproteinase-9 (MMP9) has been strongly implicated in cancer invasion, metastasis, and angiogenesis.[6]

The activity of MMP9 is regulated by endogenous inhibitors known as tissue inhibitors of metalloproteinases (TIMPs). TIMP1, while initially described as an inhibitor of metalloproteinase activity, also participates in cellular proliferation, survival signaling, and tumor progression. Altered balance between MMP9 and TIMP1 has been associated with malignant transformation and aggressive tumor behavior.[7]

Serological biomarkers have gained importance as minimally invasive tools for cancer detection and monitoring. Carbohydrate antigen 19.9 (CA19.9), although traditionally associated with gastrointestinal malignancies, has also been investigated in urothelial carcinoma due to its association with tumor burden and altered glycoprotein expression. Elevated CA19.9 levels have been reported in subsets of bladder cancer patients and may reflect tumor-associated biological changes.[8]

The interaction between genetic susceptibility markers and circulating biomarkers may provide deeper insight into tumor biology. VEGF polymorphisms may influence angiogenic signaling, which in turn may affect extracellular matrix degradation pathways involving MMP9 and TIMP1. Understanding these relationships may help identify individuals at increased risk and improve molecular characterization of bladder cancer.[9]

Bladder cancer remains an important clinical challenge in India, where variations in genetic background, environmental exposure, and healthcare accessibility may influence disease patterns. Molecular epidemiological studies evaluating genetic polymorphisms and serum biomarkers are valuable for developing population-specific risk prediction strategies.[10]

Although several investigations have evaluated VEGF expression and individual biomarkers in bladder cancer, limited data are available regarding the combined relationship between VEGF gene polymorphism and serum CA19.9, MMP9, and TIMP1 levels, particularly among the Indian population.[11]

Identification of genetic markers associated with altered angiogenic pathways may improve understanding of bladder carcinogenesis and may provide potential targets for early detection and personalized therapeutic approaches.[12]

Therefore, the present study was designed to investigate the association between VEGF gene polymorphism and bladder cancer risk and to evaluate its relationship with serum CA19.9, MMP9, and TIMP1 levels among patients attending a tertiary care centre in Kolkata.[13]

The study aims to contribute additional evidence regarding molecular factors involved in bladder cancer development and progression and may support future research focusing on biomarker-based risk assessment and targeted interventions.[14]

MATERIALS AND METHODS

Study Design

The present study was designed as a hospital-based original case–control study to evaluate the association between vascular endothelial growth factor (VEGF) gene polymorphism and susceptibility to bladder cancer and to determine its relationship with circulating serum levels of CA19.9, MMP9, and TIMP1.

Study Setting

The study was conducted at Calcutta National Medical College and Hospital, Kolkata, West Bengal, India, a tertiary care teaching hospital providing diagnostic and therapeutic services to a large urban and surrounding population.

Study Duration

The study was carried out over a period of three years, from 2020 to 2023.

Study Population

The study population consisted of patients diagnosed with bladder cancer attending the Department of Urology/ Oncology and healthy individuals serving as controls.

A total of 150 participants *were enrolled*

- *Cases*

75 histopathologically confirmed bladder cancer patients

- *Controls*

75 apparently healthy individuals without any history of malignancy or chronic inflammatory disease

Controls were frequency matched with cases according to age and sex distribution.

Sample Size

The study included a total sample size of 150 participants based on feasibility and availability of eligible cases during the study period.

Study Groups

Case Group

Patients were included as cases if they fulfilled the following criteria

Inclusion Criteria

- Patients with newly diagnosed or histologically confirmed bladder carcinoma.
- Patients willing to participate in the study.
- Availability of clinical records and laboratory investigations.
- Patients of either sex.
- Age ≥18 years.

Exclusion Criteria

- Patients with previous history of other malignancies.
- Patients receiving chemotherapy or radiotherapy before sample collection.
- Patients with chronic inflammatory or autoimmune disorders.
- Patients with severe hepatic or renal dysfunction.
- Patients with incomplete clinical or laboratory data.

Control Group

- Healthy volunteers without evidence of malignancy were recruited from individuals attending routine health check-ups or accompanying patients.

Inclusion Criteria

- Age- and sex-matched healthy individuals.
- No history of cancer.
- No active infection or inflammatory disease.
- No previous chemotherapy or radiotherapy exposure.

Exclusion Criteria

- History of malignancy.
- Chronic inflammatory disease.
- Metabolic or systemic illness affecting biomarker levels.
- Refusal to participate.

Ethical Approval

The study protocol was reviewed and approved by the Institutional Ethics Committee of Calcutta National Medical College, Kolkata, West Bengal, India

Written informed consent was obtained from all participants before enrollment. Confidentiality of participant information was maintained throughout the study.

Clinical and Demographic Data Collection

Detailed clinical information was obtained from medical records and direct patient interviews.

The following parameters were recorded

- Age
- Sex
- Smoking history
- Presenting complaints
- Duration of symptoms
- Tumor characteristics
- Histopathological diagnosis
- Clinical stage (where available)
- Treatment history

Sample Collection

Approximately 5 ml of peripheral venous blood was collected from each participant under aseptic precautions.

The collected blood sample was divided into

- *EDTA-containing tube*

Used for DNA extraction and VEGF gene polymorphism analysis.

Plain serum tube

Used for estimation of serum CA19.9, MMP9, and TIMP1 levels.

Serum samples were separated by centrifugation and stored at appropriate temperature until analysis.

DNA Extraction and VEGF Genotyping

Genomic DNA was extracted from peripheral blood leukocytes using a standard DNA extraction method.

The extracted DNA was assessed for

- Purity
- Concentration
- Integrity

VEGF gene polymorphism analysis was performed using polymerase chain reaction (PCR)-based genotyping methods.

PCR amplification was carried out using specific primers targeting the selected VEGF polymorphic region.

The amplified products were analyzed using gel electrophoresis and appropriate genotyping methodology.

The VEGF polymorphism was categorized into:

- Wild-type genotype
- Heterozygous variant genotype
- Homozygous variant genotype

Serum Biomarker Estimation

Serum concentrations of

- CA19.9
- MMP9
- TIMP1

were estimated using commercially available enzyme-linked immunosorbent assay (ELISA) kits according to manufacturer instructions.

All samples were analyzed in duplicate to minimize analytical variation.

The obtained absorbance values were converted into concentration units using standard calibration curves.

Outcome Measures

Primary Outcome

To determine the association between VEGF gene polymorphism and risk of bladder cancer.

Secondary Outcomes

- *To compare serum levels of*
- CA19.9
- MMP9
- TIMP1

between cases and controls.

To evaluate the relationship between VEGF polymorphism and serum biomarker levels among bladder cancer patients.

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± SD or median with IQR, while categorical variables were presented as frequency and percentage. Normality was assessed using the Shapiro–Wilk test. Differences in serum CA19.9, MMP9, and TIMP1 levels between cases and controls were analyzed using the Student's *t*-test or Mann–Whitney U test as appropriate. The association between VEGF polymorphism and bladder cancer risk was evaluated using the Chi-square test, and odds ratio (OR) with 95% confidence interval (CI) was calculated. Multivariate logistic regression was performed to identify independent risk factors. Correlation between biomarkers was assessed using Pearson or Spearman correlation analysis. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 150 participants were included in the present case–control study, comprising 75 histopathologically

Table 1: Demographic Characteristics of Study Participants

Variable	*Cases (n=75)*	*Controls (n=75)*	*p-value*
Mean age (years)	59.6 ± 10.8	57.9 ± 11.2	0.34
Male	62 (82.7%)	60 (80.0%)	0.66
Female	13 (17.3%)	15 (20.0%)	—
Male:Female ratio	4.7:1	4:1	—

Table 2: Distribution of VEGF Gene Polymorphism Among Cases and Controls

VEGF Genotype	*Cases n (%)*	*Controls n (%)*
Wild type	24 (32.0)	41 (54.7)
Heterozygous variant	38 (50.7)	28 (37.3)
Homozygous variant	13 (17.3)	6 (8.0)
Total	75 (100)	75 (100)

confirmed bladder cancer patients (cases) and 75 healthy controls. The demographic characteristics, VEGF gene polymorphism distribution, serum biomarker levels, and correlation analyses were evaluated.

Demographic Characteristics of Study Participants

The mean age of bladder cancer patients was 59.6 ± 10.8 years, whereas the mean age of healthy controls was 57.9 ± 11.2 years. No statistically significant difference was observed between the two groups regarding age distribution (p=0.34). A male predominance was observed among both cases and controls, with males constituting 82.7% (n=62) of cases and 80.0% (n=60) of controls. The demographic profile of study participants is presented in Table 1.

Distribution of VEGF Gene Polymorphism

The genotype distribution of VEGF polymorphism differed between bladder cancer patients and healthy controls. The wild-type genotype was more frequent among controls, whereas heterozygous and homozygous variant genotypes were more commonly observed among bladder cancer cases. The distribution of VEGF genotypes among the study groups is shown in Table 2.

Table 3: Association Between VEGF Polymorphism and Risk of Bladder Cancer

Genotype	*Odds Ratio*	*95% CI*	*p-value*
Wild type	Reference	—	—
Heterozygous variant	2.32	1.14–4.72	0.020
Homozygous variant	3.69	1.25–10.86	0.018
Combined variant genotype	2.74	1.32–5.69	0.006

Table 4: Comparison of Serum Biomarker Levels Between Cases and Controls

Biomarker	*Cases (Mean ± SD)*	*Controls (Mean ± SD)*	*p-value*
CA19.9 (U/ml)	48.6 ± 18.9	18.7 ± 7.4	<0.001
MMP9 (ng/ml)	312.4 ± 86.5	146.8 ± 51.2	<0.001
TIMP1 (ng/ml)	284.7 ± 74.6	132.5 ± 42.7	<0.001

Table 5: Biomarker Levels According to VEGF Genotype Among Bladder Cancer Patients

Biomarker	*Wild Type*	*Variant Genotype*	*p-value*
CA19.9 (U/ml)	42.8 ±15.7	51.9 ±19.4	0.041
MMP9 (ng/ml)	268.5 ±72.1	333.6 ±84.8	<0.001
TIMP1 (ng/ml)	245.3 ±62.8	303.9 ±77.2	<0.001

A statistically significant difference was observed in VEGF genotype distribution between cases and controls (χ^2=8.42, p=0.015).

Association Between VEGF Polymorphism and Bladder Cancer Risk

To determine whether VEGF genetic variation influenced bladder cancer susceptibility, odds ratio analysis was performed. Individuals carrying the VEGF variant genotype demonstrated significantly increased risk of bladder cancer compared with individuals carrying the wild-type genotype. The risk estimation is presented in Table 3.

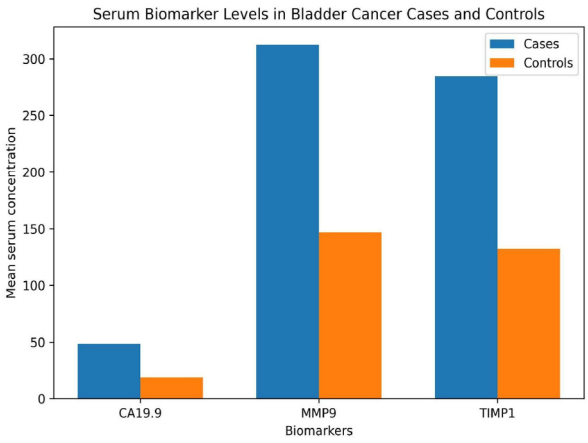

Figure 1: Comparison of Serum Biomarker Levels Between Cases and Controls

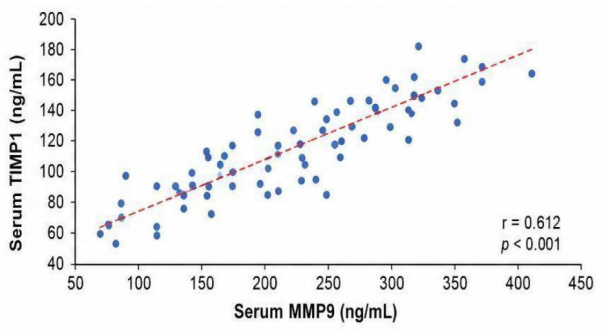

Figure 2: Correlation Between MMP9 and TIMP1 Levels

The combined variant genotype was significantly associated with increased bladder cancer risk (OR=2.74, 95% CI: 1.32–5.69, p=0.006) (Table 3).

Serum CA19.9, MMP9 and TIMP1 Levels in Cases and Controls

Serum concentrations of CA19.9, MMP9, and TIMP1 were compared between bladder cancer patients and controls. All three biomarkers showed significantly higher levels among cases compared with healthy controls (p<0.001). The comparative analysis of serum biomarkers is shown in Table 4.

The increased biomarker concentrations among bladder cancer patients are illustrated in Figure 1.

Figure 1 demonstrates markedly increased serum CA19.9, MMP9, and TIMP1 levels among bladder cancer patients compared with controls.

Relationship Between VEGF Genotype and Serum Biomarkers

The association between VEGF polymorphism and biomarker expression was evaluated among bladder cancer patients. Patients carrying VEGF variant genotypes demonstrated higher serum MMP9 and TIMP1 levels compared with wild-type genotype carriers. The genotype-wise biomarker distribution is summarized in Table 5.

The findings indicate a significant relationship between VEGF genetic variation and altered expression of tumor-associated biomarkers (Table 5).

Table 6: Correlation Analysis of Serum Biomarkers

Correlation	*r value*	*p-value*
MMP9 vs TIMP1	0.62	<0.001
CA19.9 vs MMP9	0.41	<0.001
CA19.9 vs TIMP1	0.38	0.001

Table 7: Multivariate Logistic Regression Analysis for Predictors of Bladder Cancer Risk

Variable	*Adjusted OR*	*95% CI*	*p-value*
Age >60 years	1.84	0.91–3.71	0.088
Male sex	1.52	0.62–3.72	0.35
VEGF variant genotype	2.61	1.21–5.62	0.014

Correlation Between Serum Biomarkers

Correlation analysis showed a significant positive association between MMP9 and TIMP1 levels among bladder cancer patients. The correlation coefficients between evaluated biomarkers are presented in Table 6.

The positive correlation between MMP9 and TIMP1 is represented graphically in Figure 2.

A significant positive correlation was observed between MMP9 and TIMP1 levels (r=0.62, p<0.001).

Multivariate Logistic Regression Analysis

After adjusting for potential confounding factors including age and sex, VEGF variant genotype remained independently associated with increased bladder cancer risk. The regression analysis is presented in Table 7.

The VEGF variant genotype was identified as an independent predictor of bladder cancer susceptibility (Table 7).

DISCUSSION

Bladder cancer is a multifactorial malignancy influenced by environmental exposures, genetic susceptibility, and alterations in molecular pathways involved in tumor development and progression. Angiogenesis and extracellular matrix remodeling are considered important mechanisms contributing to tumor growth, invasion, and metastasis. The present study evaluated the association between VEGF gene polymorphism and bladder cancer risk and assessed its relationship with serum CA19.9, MMP9, and TIMP1 levels among patients attending a tertiary care centre in Kolkata.

In the present study, bladder cancer showed a clear male predominance, with males constituting 82.7% of cases and a male-to-female ratio of 4.7:1. This observation is consistent with previous epidemiological reports indicating higher bladder cancer incidence among males. Differences in occupational exposure, smoking prevalence, hormonal factors, and genetic susceptibility have been proposed as possible contributors to this sex-related variation.[15]

The mean age of bladder cancer patients in the present study was 59.6 ± 10.8 years, suggesting that bladder cancer predominantly affects older adults. Similar age distributions have been reported in population-based cancer registries, where incidence increases substantially with advancing

age due to cumulative genetic alterations and prolonged exposure to carcinogenic factors.[16]

Genetic susceptibility plays an important role in cancer development. In this study, VEGF polymorphism was significantly associated with increased bladder cancer risk. Individuals carrying the combined VEGF variant genotype demonstrated a significantly higher risk compared with wild-type carriers (OR=2.74, 95% CI: 1.32–5.69, p=0.006). These findings suggest that functional VEGF genetic variations may influence angiogenic activity and contribute to bladder carcinogenesis.

VEGF is a central mediator of tumor angiogenesis and promotes endothelial cell proliferation, vascular permeability, and formation of new blood vessels. Enhanced VEGF activity provides a favorable microenvironment for tumor growth by improving oxygen and nutrient supply. Genetic variants affecting VEGF expression may therefore modify individual susceptibility to malignant transformation.[17]

The present findings are in agreement with previous studies demonstrating that VEGF polymorphisms are associated with altered cancer risk and clinical behavior. Genetic variation in regulatory regions of VEGF may influence transcriptional activity, resulting in increased protein expression and enhanced angiogenic potential.[18]

Serum biomarker analysis showed significantly elevated levels of CA19.9, MMP9, and TIMP1 among bladder cancer patients compared with controls. Increased CA19.9 levels may reflect altered glycoprotein expression associated with malignant urothelial transformation. Although CA19.9 is primarily recognized as a marker of gastrointestinal malignancies, previous investigations have suggested its potential relevance in selected urological cancers.[19]

MMP9 plays an important role in tumor invasion by degrading extracellular matrix components and facilitating cancer cell migration. In the current study, MMP9 levels were markedly elevated among cases and showed significant association with VEGF variant genotype. This finding suggests a possible interaction between angiogenic signaling and matrix remodeling pathways in bladder cancer progression.[20]

TIMP1 levels were also significantly increased in bladder cancer patients. Although TIMP1 inhibits metalloproteinase activity, it has been reported to have additional biological functions including regulation of cell survival, proliferation, and tumor progression. The simultaneous elevation of MMP9 and TIMP1 observed in this study may indicate an imbalance in extracellular matrix regulatory mechanisms during malignant progression.[21] The positive correlation observed between MMP9 and TIMP1 ($r=0.62$, $p<0.001$) supports the coordinated involvement of these molecules in tumor biology. Previous studies have demonstrated that altered MMP/TIMP balance contributes to invasion, angiogenesis, and metastatic behavior in various cancers.[22]

The association between VEGF polymorphism and increased MMP9 and TIMP1 concentrations suggests that genetic variation may influence downstream molecular pathways involved in tumor aggressiveness. Such interactions between inherited genetic factors and circulating biomarkers may provide additional information regarding disease susceptibility and biological behavior.[23.

The findings of this study highlight the potential value of combining genetic markers with serum biomarkers for improved molecular characterization of bladder cancer. Conventional clinicopathological parameters remain essential; however, incorporation of molecular indicators may improve risk stratification and support personalized management strategies.[24]

The present investigation provides region-specific data from an Indian population regarding the relationship between VEGF genetic variation and tumor-associated biomarkers. Further multicentric studies with larger sample sizes, detailed staging information, survival analysis, and evaluation of additional molecular markers are required to validate these findings.[25]

CONCLUSION

The present study demonstrates that VEGF gene polymorphism is significantly associated with increased susceptibility to bladder cancer. Individuals carrying VEGF variant genotypes showed higher risk of developing bladder malignancy compared with wild-type genotype carriers.Serum levels of CA19.9, MMP9, and TIMP1 were significantly elevated among bladder cancer patients, and VEGF variant genotypes were associated with increased expression of MMP9 and TIMP1, suggesting a possible role of VEGF-mediated angiogenic pathways in tumor progression.

The combination of genetic susceptibility markers and circulating biomarkers may provide useful information for understanding bladder cancer biology and may have potential applications in future risk prediction and molecular profiling.

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