Journal of Applied Molecular Biology [JAMB]
Molecular biology Research & Studies institute, Assiut University, Egypt
ISSN 2974 – 4008
Volume 3 (2): July 2025

https://jamb.journals.ekb.eg

Leukocyte Expression of V-domain Ig Suppressor of T-cell activation (VISTA) in Patients with Colorectal Cancer

Amira Gamal Eldein Badary[1], Rania Bakry[1,2], Maged AF Amine[3], Khalid Rezk[4], Asmaa M. Zahran[1,2*]

[1]Department of Molecular biology, Molecular Biology Research & Studies Institute, Assiut University, Assiut 71511, Egypt

[2]Department of Clinical Pathology, South Egypt Cancer Institute, Assiut University, Egypt

[3]South Egypt Cancer Institute, Medical Oncology and Hematological Malignancies, Assiut University, Assiut 71511, Egypt

[4]Department of Surgical Oncology, South Egypt Cancer Institute, Assiut University, Egypt

*Corresponding author: zahranam@aun.edu.eg

ARTICLE INFO

Article History:
Received: 26-03-2025
Accepted: 25-06-2025
Online: 27-07-2025

Keywords:
VISTA, immune checkpoint, colorectal cancer.

ABSTRACT

The third most prevalent cancer in the world is colorectal cancer [CRC]. Although the expression of the new immunological checkpoint V-domain Ig suppressor of T-cell activation [VISTA] in CRC has shown promise as a target for cancer treatment, its prognostic value is yet unknown. This work examined VISTA expression on lymphocytes, monocytes, and granulocytes in peripheral blood [PB] from CRC patients by flow cytometric staining. Analysis set up on the relationships between the expression of VISTA and clinicopathologic and laboratory characteristics. The study included 31 patients with CRC and 25 healthy controls. All participants subjected to full history taking, clinical examination, routine laboratory investigations, and flow cytometric detection of VISTA expression on lymphocytes, monocytes, and granulocytes in the PB. The expression of VISTA on neutrophils, monocytes, and lymphocytes was significantly increased in the PB of CRC patients compared to the normal controls. Also, the expression of VISTA on monocytes was considerably higher than its expression on granulocytes and lymphocytes, and its expression on granulocytes was higher than its expression on lymphocytes in the PB of both CRC patients and the normal controls. Our findings prove increased expression of VISTA on circulating leukocytes in CRC patients, particularly in those with complications such as perforation and obstruction. While this supports further investigation into VISTA's role in CRC immunoregulation, additional studies needed to validate its potential as a therapeutic target.

1. INTRODUCTION

Globally, colorectal cancer (CRC) ranks fourth in terms of cancer-related mortality and third in terms of malignancy [1], CRC has an incidence rate of about 6.1% of cases and accounts for 3.8% of cancer-related deaths in Egypt according to Sung et al., [2]. Egypt has one of the highest incidences of early colorectal cancer in the world, with 35% of its 1,600 CRC patients being under 40. A study found that Egyptians under 30 years of age who have colorectal cancer (CRC) are three times more likely to die within five years than those over 50 [3].

According to a number of studies, the immune system contributes to tumor growth, survival, and suppression [4]. Although cytotoxic innate and adaptive immune cells can control tumor growth, cancer cells develop unique defence mechanisms that mimic peripheral immunological tolerance to avoid tumoricidal attack once the tumor has progressed from neoplastic tissue to clinically identifiable tumors [5].

Sets of pathways known as immunological checkpoints govern and manage how long the immune response lasts. Co-stimulatory immune checkpoints, which include CD28, ICOS, and CD137, stimulate immune progress. Co-inhibitory immune checkpoints, which inhibit immune progress, include cytotoxic T lymphocyte-associated molecule-4 (CTLA-4), programmed death-1 (PD-1), T cell immunoglobulin mucindomain-containing-3 (Tim-3), T cell lymphocyte activation gene-3 (LAG-3), B and T lymphocyte attenuator (BTLA), which is essential for lowering T cell activation, promoting T cell exhaustion, and V-domain immunoglobulin suppressor of T cell activation (VISTA). [6,7,8,9,10]. Immune checkpoint blocking was recently authorized by the US Food and Drug Administration to treat patients with CRC whose DNA is mismatch repair-deficient [dMMR] or microsatellite instability-high (MSI-H). However, the rate of reaction to scheduled CRC patients with low levels of (PD-1) or programmed cell death ligand 1 (PD-L1) in comparison to people who have lung cancer and melanoma, among other malignancies [10].

V-domain immunoglobulin suppressor of T cell activation (VISTA) also known as PD-1H, B7-H5, VSIR, and c10orf54, is a novel checkpoint regulator [11]. A type I transmembrane protein is known as a unique B7 family member expressed on a variety of immune cells (ICs) including lymphocytes, dendritic cells, and macrophages, and participates in cell activation and functional regulation and tumor-infiltrating lymphocytes has become a current focus of research. VISTA suppresses T cell activation and contributes to the immune evasion of tumors [11,12,13,14,15]. The purpose of this study was to examine the expression of VISTA on granulocytes, monocytes, and lymphocytes in peripheral blood samples from CRC patients and normal control and assess its correlation with laboratory and clinicopathologic features.

2. MATERIALS and METHODS

This was a hospital-based case-control study that was conducted at South Egypt Cancer Institute [SECI], Assiut University from February 2023 to January 2024. The study included 31 patients with CRC who presented and 25 normal controls with age and sex matched with patients and they are selected from people who do not suffer from any immune diseases.

2.1. The Inclusion criteria:

Patients diagnosed with CRC according to the World Health Organization (WHO) classification [16]. Patients who underwent upfront surgical treatment for CRC. Patients aged over 18 years at the time of diagnosis.

2.2. The exclusion criteria included:

Patients with a prior treatment history for CRC. Patients diagnosed with any other type of cancer in addition to CRC. Patients with infectious diseases, chronic liver disease, or chronic renal disease. Patients aged less than 18 years. Patients unwilling or unable to provide consent to participate in the study.

2.3. Aim of the study

To evaluate the expression of VISTA on lymphocytes, monocytes, and granulocytes in the peripheral blood of CRC patients and healthy controls, and to assess the relationships between VISTA expression and relevant laboratory parameters as well as clinicopathological features.

2.4. Method

All patients were subjected to a comprehensive medical history review and clinical examination. Routine laboratory investigations were performed, including Complete Blood Count (CBC) was Conducted using the Sysmex XN-1000 analyzer (Serial No. 45148). Liver and Kidney Function Tests were Performed using Dimension® Xpand® Plus (S.N. 2004082965). Tumor Markers (CEA and CA19-9) were measured using the Beckman Coulter ACCESS2 immunoassay system (S.N. 510552). Expression of VISTA was evaluated on lymphocytes, monocytes, and granulocytes in peripheral blood samples from CRC patients and healthy controls by using flow cytometry.

2.4.1. Flow cytometric detection of VISTA expression on lymphocytes, monocytes, and neutrophils

2.4.1.1. Blood samples for flow cytometry:

A peripheral venous blood sample (3 ml) was collected from each patient and normal control individual in EDTA tubes labeled with the subject's name, sex, age, date of collection, and patient number in the SECI for analyzing of VISTA expression on lymphocytes, monocytes, and granulocytes by flow cytometry.

2.4.1.2. Sample staining, acquisition, and analysis of PB

To detect VISTA expression on lymphocytes, monocytes, and granulocytes in blood samples 100 µl blood samples were mixed with 5 µl from phycoerythrin (PE-Cy7) conjugated anti-VISTA [Invitrogen, USA. The blood was incubated for 15 minutes in the dark at room temperature. After incubation, red blood cells were lysed with BD FACS Lysing solution 10x (Cat. No. 349202) (BD Biosciences, USA) and the cells were then washed with Phosphate Buffer saline Solution (PBS) Magnesium & Calcium free [Cat. No. 17-516F) (Lonza, Bio Whittaker®, USA) and resuspended in PBS. An isotype-negative control was run with each sample. Samples were then analyzed by a flow cytometer FACS Canto II (BD Bioscience-San Jose, CA, USA, serial number (V33896201978); 3 lasers, 8 colors). A minimum of 50.000 events were collected from each sample. Data was analyzed using FACS DIVA software version 8.0.1 on FACS Canto II. Gating was performed based on forward scatter (FSC) and side scatter (SSC) to identify and analyze the different cell populations.

2.5. Statistical Analysis

Based on determining the main outcome variable, the estimated minimum required sample size is 31 patients and 25 control. The sample was calculated using G*power software 3.1.9.2. Data were verified, coded by the researcher, and analyzed using the Statistical Package for the Social Sciences (SPSS) version 29.0 (SPSS- IBM Inc., Chicago, IL, USA) and GraphPad Prism (version 10.1.1, GraphPad software, LLC). Test of normality was done for deciding the measures of central tendency and statistical methods for data analysis by using Kolmogorov–Smirnov test and Shapiro–Wilk test. Categorical variables were described by number and percentage, whereas continuous variables were described by the mean and standard error (SE). The Mann-Whitney U test was used to analyze data for two independent samples, and the Kruskal-Wallis test was used to compare different groups more than two. The $\chi 2$ test was used to examine the association between the expression of VISTA and categorical variables, Spearman correlation was applied to evaluate the association between variables. P-value ≤ 0.05 was considered statistically significant.

3. RESULTS

3.1. Expression of VISTA on lymphocytes, monocytes, and granulocytes in peripheral blood of patients with CRC and normal controls.

As shown in Table 1 and Figures 1, 2, and 3, the expression of VISTA on granulocytes, monocytes, and lymphocytes in the PB was significantly higher in CRC patients compared to normal controls. Among the cell types, VISTA expression on monocytes was markedly higher than on granulocytes and lymphocytes, while granulocytes exhibited higher VISTA expression than lymphocytes in both CRC patients and normal controls.

Table 1. Different expressions of VISTA on lymphocytes, monocytes, and granulocytes in the PB of CRC patients and the normal controls.

Variables	CRC Patients [n=31]	Normal controls [n=25]	*P*-value
VISTA+ on granulocytes [%]	20.56±0.535	14.59±0.529	<0.001
VISTA+ on monocytes [%]	46.88±1.64	35.516±3.08	<0.001
VISTA+ on lymphocytes [%]	8.5±1.054	2.75±0.286	<0.001

Results are expressed as mean ± standard error of the mean. Mann-Whitney U test, p-value is significant at <0.05 [bold]

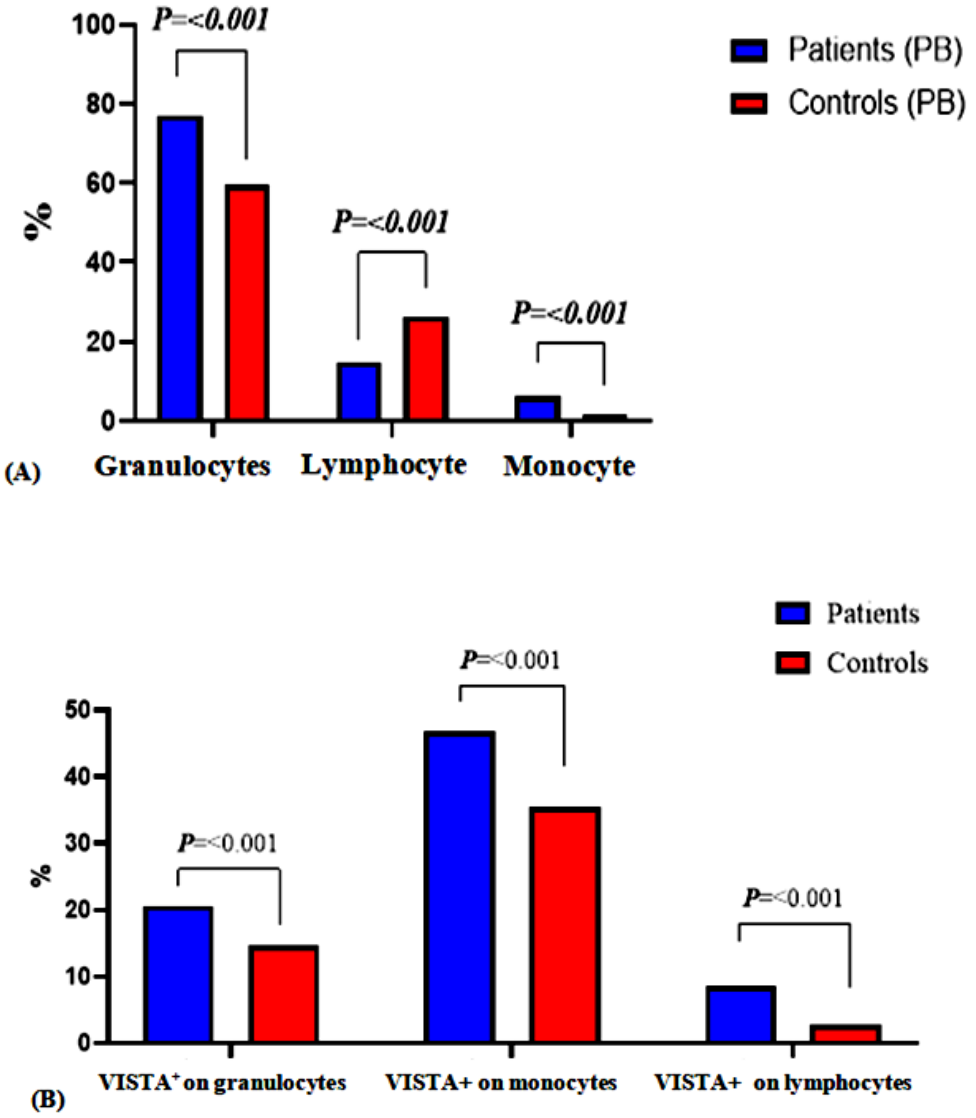

Figure 1. [A] Represent the frequency of granulocytes, monocytes and lymphocytes in PB of CRC patients and normal controls. [B] Represent the expression of VISTA on granulocytes, monocytes and lymphocytes in PB of CRC patients and normal controls.

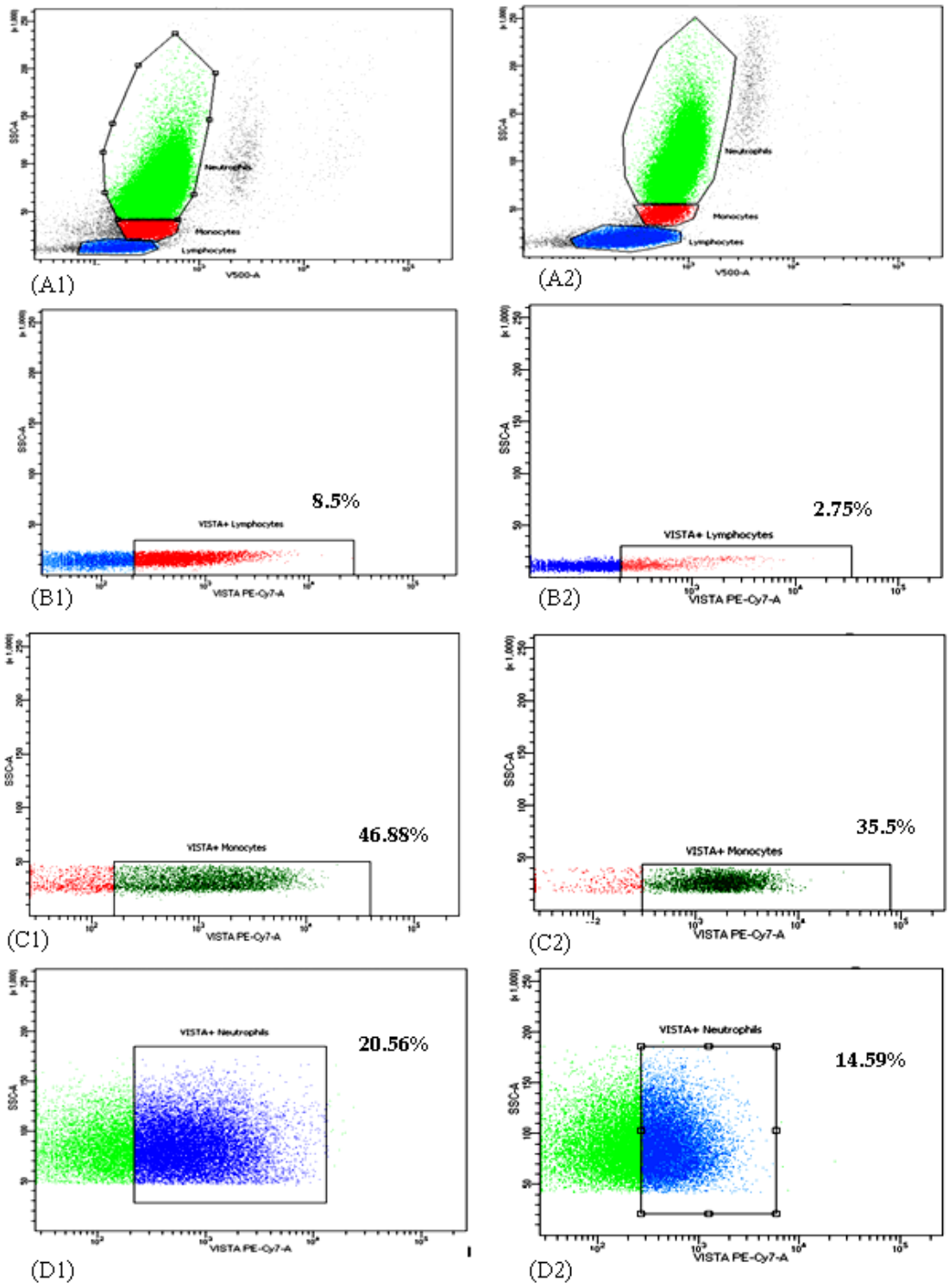

Figure 2. (A1 and A2) represents the distribution of lymphocytes, monocytes, and granulocytes in PB of CRC patients and the normal controls, respectively. (B1 and B2) represent the expression of VISTA on lymphocytes in PB of CRC patients and the normal controls, respectively. (C1 and C2) represent the expression of VISTA on monocytes in PB of CRC patients and the normal controls, respectively. (D1 and D2) represent expression of VISTA on granulocytes in PB of CRC patients and the normal controls, respectively.

3.2. Relation between expressions of VISTA on lymphocytes, monocytes, and granulocytes with demographic data of CRC patients:

No significant association was found between the sex, smoking status, age, or BMI of CRC patients and the expression of VISTA on lymphocytes, monocytes, or granulocytes in the PB samples.

There was no significant difference in the expression of VISTA on granulocytes, monocytes, or lymphocytes in the PB of CRC patients in relation to clinical outcomes.

3.3. Association between expression of VISTA on lymphocytes, monocytes, and granulocytes with obstruction and perforation of CRC patients

As shown in Table 2, the expression of VISTA on granulocytes, monocytes, and lymphocytes in the peripheral blood of CRC patients was significantly higher in those presenting with perforation and obstruction compared to patients without these complications.

Table 2. Association between expression of VISTA on lymphocytes, monocytes, and granulocytes with obstruction and perforation of CRC patients

Variables	Perforation				
	No		YES		
	N	%	N	%	
	28	90.33%	3	9.67%	
	Mean± SE		Mean± SE		*P* value
VISTA+ on Granulocytes [%]	22.66±1.63		38.00±1.00		<0.001
VISTA+ on Monocytes [%]	41.48±3.16		58.00±9.50		0.023
VISTA+ on Lymphocytes [%]	2.58±0.19		16.8±1.2		0.038
Variables	Obstruction				
	No		YES		
	N	%	N	%	
	28	90.33%	3	9.67%	
	Mean± SE		Mean± SE		*P* value
VISTA+ on Granulocytes [%]	23.14±1.58		28.33±10.17		0.02
VISTA+ on Monocytes [%]	41.14±2.16		55.67±4.33		<0.001
VISTA+ on Lymphocytes [%]	8.04±1.09		13.37±3.18		0.018

N: Number of cases, %: Percentage. Results are expressed as mean ± standard error of the mean. $\chi 2$ test was used, p-value is significant at <0.05.

3.4. Association between expression of VISTA on lymphocytes, monocytes, and granulocytes with pathological findings of CRC patients

No significant association was observed between pathological data and the expression of VISTA on lymphocytes, monocytes, or granulocytes in the PB of CRC patients. Also, there was no significant association between TNM staging and the expression of VISTA on lymphocytes, monocytes, or granulocytes in the PB of CRC patients.

No significant association was found between tumor laterality or pathological findings and the expression of VISTA on lymphocytes, monocytes, or granulocytes in the PB of CRC patients.

3.5. Relation between CRC prognostic markers and expression of VISTA on granulocytes, monocytes, and lymphocytes in PB:

A negative correlation was observed between the expression of VISTA on granulocytes in the peripheral blood of CRC patients and both the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR).

However, no significant associations were found between VISTA expression on lymphocytes, monocytes, or granulocytes and other prognostic markers. Additionally, as presented in Tables 3 and 4, there was no significant correlation between the serum levels of carcinoembryonic antigen (CEA) or carbohydrate antigen 19-9 (CA19.9) and VISTA expression on peripheral blood lymphocytes, monocytes, or granulocytes in CRC patients.

Table 3. Correlation between expression of VISTA on lymphocytes, monocytes, granulocytes and other prognostic markers

Variables		urea	Glucose	LDH	AST	ALT	ALP	Albumin
VISTA+ on Granulocytes	r	0.197	-0.187	-0.276	-.033	0.124	-.265	0.129
	P value	0.287	0.315	0.133	0.860	0.505	0.150	0.489
VISTA+ on Monocytes	r	-0.09	-0.156	-0.225	0.130	0.193	-0.268	-0.270
	P value	0.630	0.403	0.223	0.485	0.299	0.145	0.141
VISTA+ on Lymphocytes	r	-0.039	-0.030	-0.143	-0.448	-0.216	-0.134	-0.002
	P value	0.836	0.871	0.443	0.012*	0.243	0.473	0.990
Variables		RBCs	HB	PLT	WBCs	LMR	NLR	PLR
VISTA+ on Granulocytes	r	-0.131	-0.086	-0.085	-0.104	0.031	-0.373	-0.413
	P value	0.483	0.646	0.651	0.576	0.870	0.039*	0.021*
VISTA+ on Monocytes	r	-0.132	-0.264	-0.128	0.094	-0.184	0.040	-0.078
	P value	0.479	0.152	0.492	0.613	0.321	0.830	0.677
VISTA+ on Lymphocytes	r	0.063	0.073	-0.053	0.042	0.040	-0.016	-0.057
	P value	0.738	0.695	0.777	0.821	0.832	0.934	0.761

r: correlation coefficient. *$P<0.05$ is considered a statistically significant, analysis done by Spearman correlation. Hb: hemoglobin, WBC: white blood cells, LDH lactate dehydrogenase, AST Aspartate transaminase, ALT Alanine transaminase, ALP Alkaline phosphatase, NLR neutrophils/lymphocytes ratio, LMR lymphocytes/monocytes ratio and PLR platelets/lymphocytes ratio.

Table 4. Correlation between expression of VISTA on lymphocytes, monocytes, and granulocytes and CA19.9 and CEA

Variables		CA 19.9	CEA
VISTA+ on Granulocytes	r	-0.121	0.004
	P value	0.518	0.985
VISTA+ on Monocytes	r	0.141	0.261
	P value	0.450	0.156
VISTA+ on Lymphocytes	r	-0.066	0.240
	P value	0.725	0.193

r: correlation coefficient. *P<0.05 is considered a statistically significant, analysis done by Spearman correlation. CEA Carcinoembryonic Antigen, CA19.9 Cancer Antigen 19.9.

4. DISCUSSION

Colorectal cancer (CRC) is the third most common cancer globally, with over 1.2 million new cases diagnosed annually. It ranks as the second and third most frequently diagnosed cancer in men and women, respectively [1,2]. CRC typically arises due to mutations in epithelial cells of the colon and rectum, affecting oncogenes, tumor suppressor genes, and DNA repair mechanisms.

VISTA (V-domain Ig suppressor of T cell activation) is an immune checkpoint regulator predominantly expressed on cells of the myeloid lineage, including monocytes and neutrophils, under steady-state conditions [17]. In healthy individuals, monocytes express low levels of VISTA, allowing effective antigen presentation and T cell activation. In this study, VISTA expression was significantly higher on peripheral blood (PB) monocytes, neutrophils, and lymphocytes compared to controls. Among these, monocytes showed the highest expression, followed by neutrophils, then lymphocytes. This suggests an immune modulation profile consistent with tumor-induced immune suppression.

High VISTA expression on monocytes may suppress T cell responses, hindering antigen presentation and allowing tumor cells to evade immune detection. Monocytes with elevated VISTA levels may differentiate into tumor-associated macrophages (TAMs), which secrete immunosuppressive cytokines like IL-10 and TGF-β, further impairing T cell activity [18]. Myeloid lineage cells, such as monocytes, neutrophils, macrophages, and DCs, express VISTA at higher levels than the T lymphocyte compartment [17]. Consequently, these myeloid immune cell types are also the ones that express VISTA the greatest in human cancer [19–21].

Myeloid cells are important contributors to antitumor immunity and comprise a significant fraction of the immune cell population. However, by causing anti-inflammatory phenotypes in myeloid cells, cancer cells can use these cells to elude immune surveillance and ultimately promote immunological tolerance in the TME. VISTA suppresses myeloid immunological responses by acting as a negative checkpoint regulator of innate immunity [22].

Through direct tumoricidal actions or by stimulating the adaptive immune response, innate immune cells can support antitumor immunity. Leukocyte infiltration into the

TME and effector cell activity can both be facilitated by the production of chemokines and cytokines. Therefore, VISTA's control on innate immunity may be crucial for the development and upkeep of anticancer immunity [22].

Similarly, neutrophils expressing VISTA may contribute to chronic inflammation and promote a pro-tumor phenotype. On lymphocytes, particularly CD8+ T cells, VISTA is associated with T cell exhaustion, reducing their cytotoxic effectiveness [22–24]. VISTA has been demonstrated to be a negative regulator of innate inflammation in a variety of myeloid cell subsets. By inhibiting downstream signaling cascades, VISTA has been demonstrated to limit the immunological response to Toll-like receptor (TLR) stimulation in macrophages, which ultimately leads to a decrease in TLR-mediated cytokine production [24,25]. Additionally, by controlling transcriptional programming and inhibiting the expression of effector genes that produce proinflammatory (M1-like) phenotypes, VISTA may influence the fate of macrophages by shifting the balance in favor of anti-inflammatory (M2-like) phenotypes during macrophage activation and polarization [26].

Previous studies align with this finding. For example, Xie S et al reported predominant VISTA expression in monocytes in CRC patients [27], and others in [17,18,22,28] noted that neutrophils exhibit higher VISTA levels than lymphocytes.

Our study found that VISTA expression was significantly elevated in patients with CRC who presented with perforation and obstruction. These conditions, often markers of advanced disease, may trigger inflammatory responses that in turn upregulate immune checkpoint molecules like VISTA.

No significant correlation was observed between VISTA expression and patient age, gender, tumor laterality, tumor stage, lymph node involvement, or metastasis. The small sample size could have limited the detection of such associations. Furthermore, peripheral blood expression may not fully reflect VISTA dynamics within the tumor microenvironment. According to [29,30], found that, in patients with CRC, VISTA expression was not linked to tumor size, gender, age, tumor stage, lymph node metastases, or distant metastases, and with [18]. Mulati k et al. found that age, gender, or WBC did not significantly affect VISTA expression in AML patients [31] and there were no discernible variations in VISTA expression between the ovarian cancers' original and metastatic locations.

However, our result incompatible with [30], found that the stage of the disease and the pathogenic grade and lymph node status had a substantial impact on VISTA expression in patients with breast cancer. A negative correlation was noted between VISTA expression on granulocytes and the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR). Since NLR and PLR are systemic inflammation markers, this inverse relationship may reflect enhanced immune suppression rather than active inflammation in advanced disease states. No significant associations were found between VISTA expression and biochemical markers such as CEA, CA19.9, urea, LDH, AST, ALT, ALP, total protein, or albumin. This suggests that VISTA expression in PB may operate independently of commonly used tumors or liver function markers.

5. CONCLUSION

Our findings prove increased expression of VISTA on circulating leukocytes in CRC patients, particularly in those with complications such as perforation and obstruction. While this supports further investigation into VISTA´s role in CRC immunoregulation, additional studies needed to validate its potential as a therapeutic target.

Ethics statement

The study was approved by Research Ethics Committee of the Molecular Biology Research & Studies Institute (MBRSI), Assiut University, Egypt (Approval No. MB - 23 - 10 - A). Informed written consent to participate in the study was provided by all participants.

Authors' contributions

A.G., R.B, M.A., K.R. and A.M.Z contributed to the conceptualization, methodology, practical work, and writing of the original draft. All authors have read and approved the final manuscript and agree to its submission.

Acknowledgements

Not Applicable

Funding

This research received no external funding.

Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request. The authors declare no competing interests.

Conflicts of Interest

The authors declare no competing interests.

Consent to Participate

Written informed consent for publication of their details was obtained from all participants included in the study.

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