Evaluating The Potential Prognostic Significance of Stem Cell Marker (LGR5) and Its Association with Discoidin Domain Receptor 1 (DDR1) Expression in Colorectal Carcinoma: An Immunohistochemical Study

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ABSTRACT

Background: Colorectal cancer (CRC) is considered as the third most prevalent malignancy globally**.** One of the primary reasons for recurrence of tumor is believed to be the existence of chemotherapy-resistant cancer stem cells.

Objective: This study aimed to study LGR5's roles in colorectal carcinogenesis and its association with DDR1, which could potentially lead to the development of novel integrated modalities in CRC treatments.

Material and methods: This retrospective study was performed on 60 cases: 6 were normal colon, 12 were colorectal adenoma and 42 were CRC. All slides were subjected to staining with LGR5 and DDR1 antibodies utilizing the avidin-biotin complex method.

Results: There was a significant positive statistical association among LGR5, DDR1 expression and grading, staging, distant metastasis, lympho-vascular invasion, perineural invasion and tumor budding ($p<0.001$). There was a significant association among LGR5 and DDR1 expression among colorectal carcinoma cases ($p=0.001$). There was a positive significant correlation among LGR5 & DDR1 and the studied groups ($p<0.001$) and ($p=0.008$) respectively. Using Kaplan-Meier: High LGR5 and DDR1 expression was linked to the lower OS and the lower DFS. ROC curve analysis showed that both markers had high sensitivity in diagnosis of CRC cases.

Conclusion: The overexpression of LGR5 and DDR1 in patients with CRC varies from that in adjacent non-cancerous tissue and adenoma cases, indicating their potential involvement in CRC carcinogenesis. Furthermore, they may be significant in the progression and development of CRC, as well as in adverse prognostic outcomes. Therefore, inhibiting these proteins could serve as an effective multitarget therapeutic approach for CRC cases.

Keywords: LGR5, DDR1, CRC, IHC.

INTRODUCTION

Colorectal cancer (CRC) is regarded as the third most prevalent malignancy worldwide, impacting both genders, and constitutes a significant reason for mortality related cancer. The high rate of mortality, because CRC is primarily driven by delayed detection, with most cases being recognized at an advanced or metastatic stage [1]. In Egypt, colorectal carcinoma ranks the 7th, and constitutes 3.9% of all cancer diagnoses. It stands as the fifth common tumor in women and seventh in men according to GLOBOCAN, 2022. Colorectal carcinoma has a high mortality rate in Egypt as the mortality risk is 3.3% in this cancer [2].

Owing to the rapid advancements in personalized treatment approaches, the function of the pathologist in management of CRC cases has significantly evolved from solely analyzing histomorphologies to be serving as a clinical advisor for gastroenterologists, oncologists, and colorectal surgeons [3]. Age, sex, and genetics are considered as variables that affect the diverse sets of molecular alterations that affect the process of carcinogenesis of CRC [4]. Genetic variants have been associated with the carcinogenic process of CRC. Alterations in particular genes, like oncogenes, tumor suppressor genes, and genes responsible for DNA repair, can lead to colonic and rectal carcinomas [5].

Chemotherapy-resistant cancer stem cells (CSCs) are believed to be among the principal contributors to the recurrence of the tumor. Since these CSCs are resistant to treatment and resume tumor development following a pharmaceutical activity, there is an imperative requirement for a novel, non-toxic cancer therapy capable of achieving sustained clinical remissions [6].

Leucine-rich repeat-containing G-protein coupled receptor 5 (LGR5) is a protein encoded via the LGR5 gene. It has a key function in biology of stem cell, particularly in **adult stem cells maintenance and proliferation**. LGR5 is a receptor for R-spondins, which function as agonists of the WNT signaling pathway. This pathway is essential for cellular differentiation, proliferation of cell, and tissue regeneration [7]. LGR5 is a pivotal factor in the initiation, development, and therapeutic resistance of tumors. Therefore, it may serve as a mark for prospective anti-cancer treatments owing to its function in maintaining tumor proliferation [8]**.**

One of the collagen receptors possessing tyrosine kinase activity, referred to as discoidin domain receptors (DDRs), is discoidin domain receptor 1 (DDR1), which is believed to participate in cellular proliferation, tumor invasion, and metastasis. Different types of cancer, like prostate, breast, ovarian, lung, pancreatic, liver, and gastric malignancies, exhibited increased expression of DDR1 [9]**.**

In certain human malignancies, DDRs may inhibit tumor growth and encourage apoptosis. The latter may result from DDR1's ability to limit cellular migration by stabilizing E-cadherin, which promotes cell-cell adhesion [10]. DDR1 also plays a vital function

Received: 14/11/2025
Accepted: 14/01/2026

in the E-cadherin/β-c atenin complex, which maintains epithelial cell-cell adhesion integrity [11].

This study aimed to study the involvement of LGR5 in CRC and colorectal adenoma, as well as its suggested association with DDR1, which is under-validated and still requires investigation. This may pave the way for novel combination modalities in CRC treatments.

MATERIALS AND METHODS

This retrospective research was performed on 60 colon samples involving 42 patients with CRC, 12 cases with colorectal adenoma, and 6 controls (non-neoplastic tissue). All cases were gathered from the Pathology Department's archive between 2015 and 2019 with a three-year follow-up.

The clinicopathological data were obtained from the patient records. Gender, recurrence status, age, and overall survival (OS) were among the criteria for inclusion. Tumor site, tumor size, and gross description constitute parameters within the gross description.

Furthermore, histopathologic data were assessed and evaluated following. Hematoxylin and eosin (H & E) examination-stained sections, encompassing grade and type of histopathology in accordance with the classification by WHO of colorectal malignancies [12], pathological stage [13], lympho-vascular invasion (LVI) [14], perineural invasion (PNI), and scoring and tumor budding status [12], and lymph nodes metastases [14].

The exclusion criteria: Cases with no clinicopathological data or without available paraffin blocks or cases with a diagnosis other than adenocarcinoma not otherwise specified (NOS) or cases with preoperative chemotherapy.

Survival analysis was conducted with follow-up duration recorded in months (36 months), and the survival time was estimated from surgery date to either the patient's most recent follow-up or the date of death.

Immunohistochemistry technique: Labelled Streptavidin-Biotin 2 System–Horseradish Peroxidase (LSAB2 System-HRP) was used in immunohistochemical staining. The sections were rehydrated through a series of graded alcohols to distilled water following deparaffinization in xylene, then subjected to microwave treatment in citrate buffer 10 ml (sodium citrate, pH 6.0) for 30 minutes to facilitate antigen retrieval. A 0.3% hydrogen peroxide solution in methanol was applied for 15 minutes to inhibit endogenous peroxidase activity. The sections were incubated for 12 hours at room temperature with anti-LGR5 (rabbit polyclonal antibody, Santa Cruz Biotechnology Inc.; CA, USA, diluted at 1/100) and anti-DDR1 (rabbit polyclonal antibody, Santa Cruz Biotechnology, diluted at 1/100). Subsequently, avidin-biotin and secondary antibodies were used for staining according to instructions of manufacturer for each antibody, as well as the standard protocol. Hematoxylin was employed to counterstain the sections, which were subsequently mounted and dehydrated. For LGR5, we utilized a section of normal colonic epithelial cells as a positive control, and for DDR1, we employed normal kidney tissue. PBS served as a negative control for both markers in substitution of the primary antibodies.

Immunohistochemical interpretation: All sections stained with antibody were cautiously studied and evaluated by three independent pathologists. Staining of LGR5-positive was observed as a brown coloration within the cytoplasm of malignant and normal cells. Staining intensity was classified as 0 (no staining), 1 (pale brown), 2 (brown), and 3 (dark brown) for the immunohistochemical assay. Immunoreactive cell counts were classified as 0 (<5% of total cells), 1 (6–25%), 2 (26–50%), 3 (51–75%), and 4 (>75%). The intensity and quantity measurements were subsequently multiplied to derive the IHS score from the original data. Consistent with previous studies, an IHS score of 9–12 was classified as strong immunoreactivity, 5–8 as moderate, 1–4 as mild, and 0 as negative [15].

DDR1 was scored regarding the total proportion of malignant cells that were stained positive (positive expression should be taken into account if the staining of cells was cytoplasmic or membranous brownish): 0 score was 0–5%, 1 score was 6%–35%, 2 score was 36%–70%, and 3 score was more than 70%. In terms of staining intensity, 0 score was no staining, 1 score was faint staining, 2 score was moderately staining, and 3 score was strongly staining.

The last score was categorized into either a low or high expression group regarding the product of the percentage of positively stained cells and intensity of staining. Low expression was characterized by a total score below 4, whereas high expression was defined as a total score of 4 or higher [16].

Ethical approval: The Research Ethics Committee of Benha Faculty of Medicine, Benha University approved the study with Code Number (RC 13-7-2025). Informed signed consents were obtained from all participants. The study adhered to the Helsinki Declaration throughout its execution.

Statistical analysis

SPSS software version 22.0 was used. Quantitative data were reported as numbers and percentages, with Fisher's exact test and X^2-test applied to assess differences in categorical variables. Kaplan–Meier survival curves were drawn and compared using the Log-rank test for statistical significance. Disease-free survival (DFS) was determined as the time from surgical resection to the first documented recurrence or metastasis, or the last follow-up assessment. OS was measured from the time of primary surgical resection to death from any cause. In cases where death, metastasis, or recurrence had not been confirmed, OS and DFS calculations relied on the patient's most recent known survival date. Statistical significance was demonstrated as $P \leq 0.05$. ROC curve was also used to evaluate AUC,

sensitivity & specificity of both markers, as AUC > 0.7 was regarded well.

RESULTS

1-Clinicopathological results:

The mean age in all cases was 49.19 ± 12.55 ranging from 25 to 85 years old. In all studied cases males were 37 (61.7%) and females were 23 (38.3%). Tumor mass size ranged from 3 to12 cm with a median size of 6 cm. Time of follow-up was 36 months. Other clinicopathological parameters of colorectal carcinoma cases were described in **table (1).**

2- Immunohistochemical expression results:

A-LGR5 immunohistochemical expression between the studied groups & its relations with clinicopathological variables in colorectal carcinoma: All biopsies (100%) showed negative expression according to the control group. Our work revealed that there was a significant increase expression of LGR5 gradually from normal to colorectal adenoma to carcinoma cases (p<0.001) (**Table 2 and figure 1)**. Regarding CRC, LGR5 expression was significantly elevated with grading (p=0.001), staging (p=0.001), invasion depth (T) (p=0.001), distant metastasis (p=0.001), LVI (p=0.001), perineural invasion (p<0.001) and tumor budding (p=0.001). Nevertheless, no significant association with other clinicopathological data**.** These findings were described in table **(1)**.

Table (1): LGR5 and DDR1 expression in colorectal carcinoma and correlation with clinicopathological parameters

Carcinoma	Parameter No (%)	LGR5			P value	DDR1		P value
		Mild N=4(%)	Moderate N=22 (%)	Strong N=16(%)		Low N=16 (%)	High N=26 (%)	
Age (35-80)	59.42±11.95	60±23.09	58.54±10.1	60.5±11.76	0.884	55.25±13.62	62.0±10.23	0.08
Sex								
Females	18 (42.9)	2(11.1)	12(66.7)	4(22.2)	0.183	8(44.4)	10(55.6)	0.463
Males	24 (57.1)	2(8.3)	10(41.7)	12(50)		8(33.3)	16(66.7)	
Site								
Right colon	26 (61.9)	2(7.7)	13(50)	11(42.3)	0.175	8(30.8)	18(69.2)	0.115
Left colon	11 (26.2)	2(18.2)	4(36.4)	5(45.4)		4(36.4)	7(63.6)	
Rectum	5 (11.9)	0	5(100)	0		4(80)	1(20)	
Size (CM)								
6 <	24 (57.1)	2 (8.3)	15 (62.5)	7 (29.2)	0.121	14(58.3)	10(41.7)	**0.005***
≥6	18 (42.9)	2 (11.1)	7 (38.9)	9 (50)		2(11.1)	16(88.9)	
Grade								
I	4 (9.5)	4(100)	0	0	**0.001***	4(100)	0	
II	26 (61.9)	0	22(84.6)	4(15.4)		12(46.2)	14(53.8)	**0.001***
III	12 (28.6)	0	0	12(100)		0	12(100)	
Stage								
I	4 (9.5)	2(50)	2(50)	0	**0.001***	4(100)	0	**0.001***
II	16 (38.1)	2(12.5)	14(87.5)	0		12(75)	4(25)	
III	10 (23.8)	0	6(60)	4(40)		0	10(100)	
IV	12 (28.6)	0	0	12 (100)			12(100)	
T Stage								
T2	8 (19.0)	4(50)	4(50)	0	**0.001***	4(50)	4(50)	0.186
T3	16 (38.1)	0	10(62.5)	6(37.5)		8(50)	8(50)	
T4	18 (42.9)	0	8(44.4)	10(55.6)		4(22.2)	14(77.8)	
N stage								
N 0	30 (71.4)	4(13.3)	14(46.7)	12(40)	0.078	16(53.3)	14(46.7)	**0.006***
N 1	6 (14.3)	0	6(100)	0		0	6(100)	
N 2	6 (14.3)	0	2(33.3)	4(66.7)		0	6(100)	
M stage								
M 0	30 (71.4)	4(13.3)	22(73.4)	4(13.3)	**0.001***	16(53.3)	14(46.7)	**0.001***
M 1	12 (28.6)	0	0	12(100)		0	12(100)	
L.V invasion								
-VE	25 (59.5)	4(16)	19(76)	2(8)	**0.001***	15(60)	10(40)	**0.001***
+VE	17 (40.5)	0	3(17.6)	14(82.4)		1(5.9)	16(94.1)	
Perineural invasion								
-VE	15 (35.7)	4(26.7)	11(73.3)	0	**<0.001***	15(100)	0	**<0.001***
+VE	27 (64.3)	0	11(40.7)	16(59.3)		1(3.7)	26(96.3)	
Tumor budding								
<5	18 (42.9)	4(22.2)	14(77.8)	0	**0.001***	16(88.9)	2(11.1)	
5-9	14 (33.3)	0	8(57.1)	6(42.9)		0	14(100)	**0.001***
≥10	10 (23.8)	0	0	10(100)		0	10(100)	

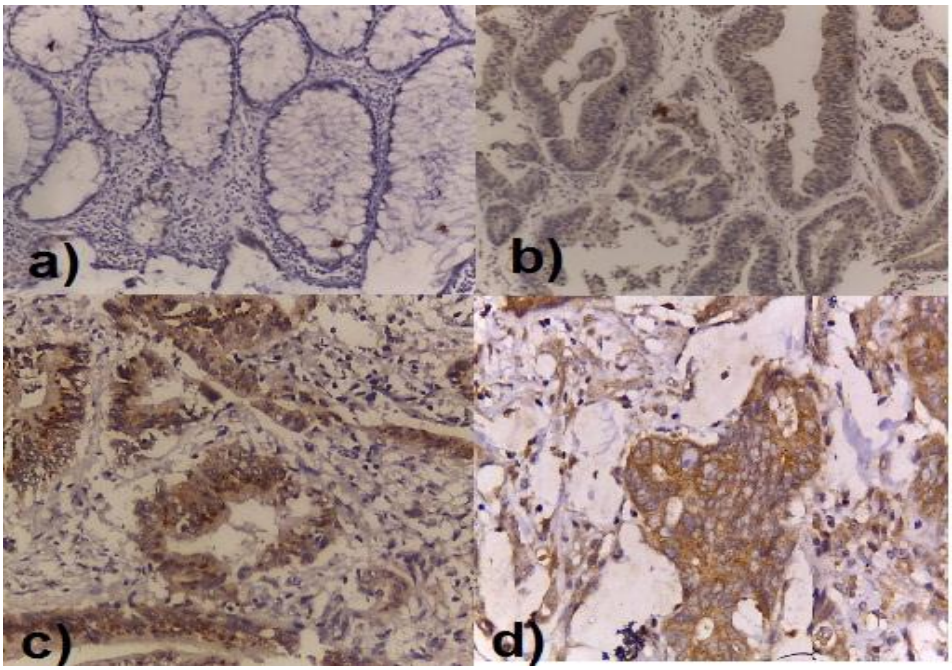


Figure (1): LGR5 expression; **a)** Normal epithelium: LGR5 negative cytoplasmic expression in glandular epithelial cells, **b)** Colorectal adenoma: showed mild positive cytoplasmic expression, **c)** Moderated differentiated carcinoma (GII): showed moderate positive cytoplasmic expression, **d)** Poor differentiated carcinoma (GII): showed strong positive cytoplasmic expression **(ABC, X200)**.

B-DDR1 IHC expression between the studied groups & its correlations with clinicopathological parameters in colorectal carcinoma

All biopsies demonstrated low cytoplasmic expression in control group. There was statistically significant increased expression of DDR1 gradually from normal to colorectal adenoma to carcinoma cases (p=0.008) (**Table 2 and figure 2)**. In association to CRC, DDR1 expression was significantly increased with size (p=0.005), grading (p=0.001), staging (p=0.001), lymph node metastasis (N) (p=0.006), distant metastasis (M) (p=0.001), LVI (p=0.001), perineural invasion (p<0.001) and tumor budding (p=0.001). But no significant association with other clinicopathological data. These findings were described in table (1).

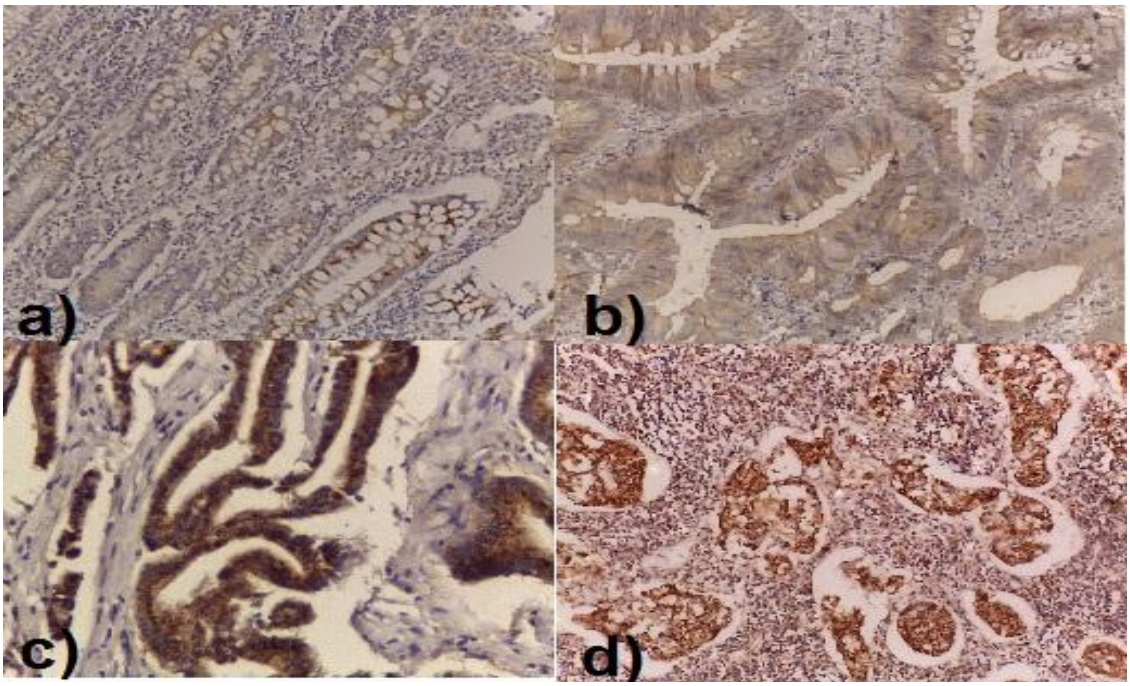


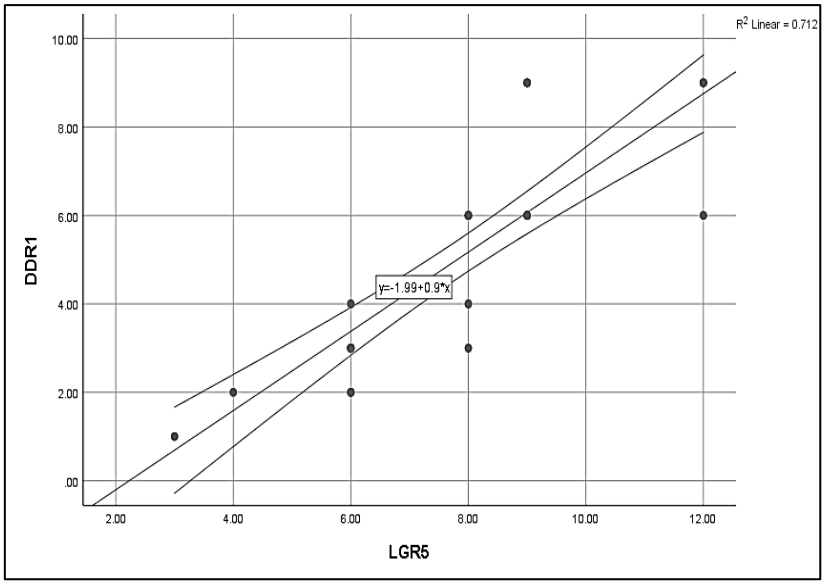
Figure (2): DDR1 expression; **a)** Normal epithelium: showed low positive cytoplasmic expression, **b)** Colorectal adenoma: showed low positive cytoplasmic expression, **c)** Moderate differentiated carcinoma (GII): showed high positive cytoplasmic expression, **d)** Poor differentiated carcinoma (GII): showed high positive cytoplasmic expression **(ABC, X200)**.

C-Correlation of LGR5 and DDR1 expression among the studied colorectal carcinoma cases:

Among LGR5 expression and DDR1 expression, there was a significant correlation within the studied colorectal carcinoma cases (p=0.001) (Graph 1).

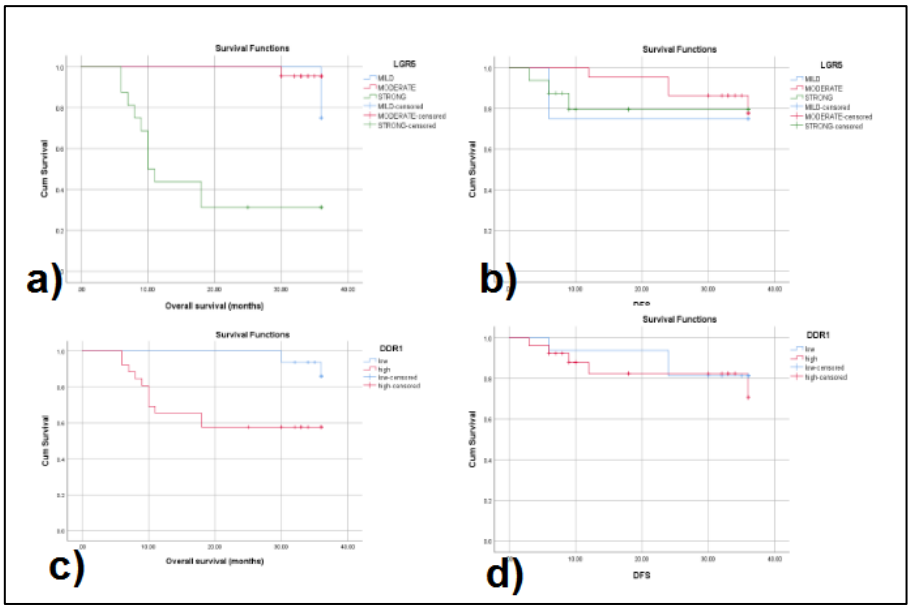
Table (2): Comparison between studied markers in different studied groups

	Normal N=6 (%)	**Adenoma N=12(%)**	**Carcinoma cases N=42(%)**	**P value**
DDR1				
LOW	6(100)	8(66.7)	16(38.1)	**0.008***
HIGH	0	4(33.3)	26(61.9)	
LGR5				
Negative	6(100)	0	0	
Mild	0	5(41.7)	4(9.5)	**<0.001***
Moderate	0	6(50)	22(52.4)	
Strong	0	1(8.3)	16(38.1)	



Graph (1): Scatter diagram showing correlation between LGR5 and DDR1 among studied CRC cases.

D- Survival analysis: The follow-up period was between 6 - 36 months, with a median follow-up time of 24 months. Regarding OS, 30 (71.4%) patients survived, and 12 (28.6%) patients died. Based on DFS, 24 (57.2%) cases were disease-free, and 18 (42.8%) cases experienced recurrence/metastasis/or death. Survival analysis using Kaplan-Meier method identified that high LGR5 and high DDR1 expression were linked to the lower OS (log rank=25.12, P=0.025) & (Log rank=18.31, P=0.001) respectively, and the lower DFS (log rank=28.5, P=0.035) & (Log rank=21.07, P=0.004) respectively as shown in graph (2).

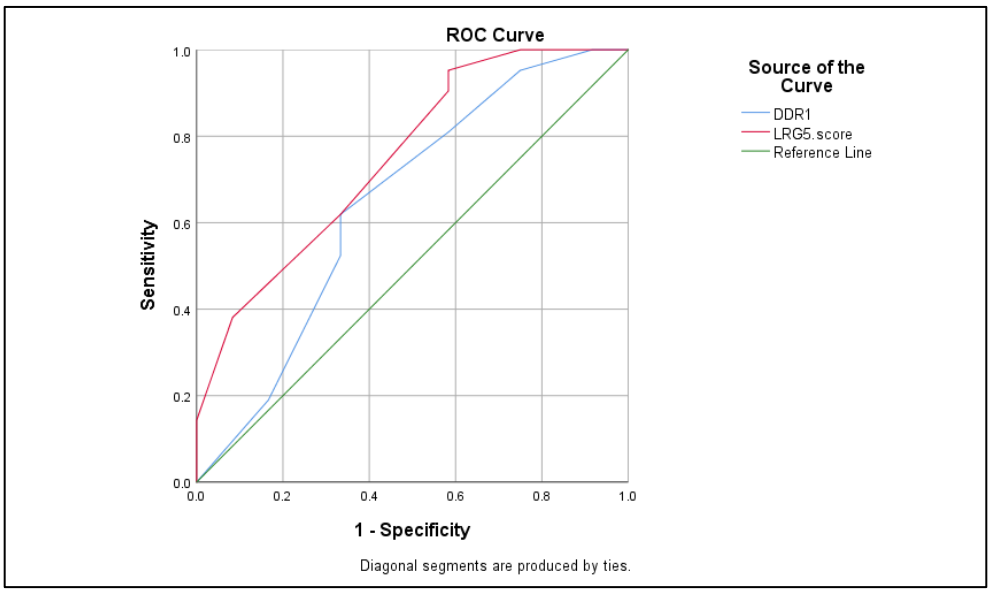


Graph (2): Kaplan-Meier survival analysis for 3-year OS & DFS of the colorectal carcinoma cases studied in association with LGR5 expression (A & B) and DDR1 expression (C & D).

Through ROC analysis, LGR5 demonstrated a sensitivity of 41.7% and a specificity of 67.44%, while DDR1 exhibits a sensitivity of 81.1% and a specificity of 41.7% in the diagnosis of CRC cases. These findings were demonstrated in table (3) and graph (3).

Table (3): ROC curve of DDR and LGR 5 in differentiation carcinoma from adenoma

Test Result Variable(s)	Area	Std. Error[a]	P value	Asymptotic 95% Confidence Interval		Cut off point	Sensitivity	Specificity
				Lower Bound	Upper Bound			
DDR1	0.647	0.101	0.024	0.449	0.844	≥2.5	81.0	41.7
LRG5 score	0.750	0.081	0.009	0.591	0.909	≥3.5	95.2	41.7



Graph (3): ROC analysis for assessing sensitivity and specificity of the two markers in diagnosis of the studied CRC cases**.**

DISCUSSION

CRC is among the predominant malignancies globally, and the main reason for mortality associated with the disease is a diagnosis at a late metastatic stage [17]. Initiation, growth, metastasis, progression, recurrence [18], and chemotherapy resistance of tumor is mainly caused by CSC [19].

The persistence of cancer stem cells makes the treatments of conventional cancer that randomly destroy proliferating cells ineffective. Therefore, treatments could be developed to target CSCs by either preventing them from maintaining their stem-cell status or by stimulating their differentiation [20].

In this study, LGR5 was examined immunohistochemically in 6 cases of normal colon, 12 patients with colorectal adenoma and 42 patients with colorectal carcinoma to assess its co-expression with DDR1 and to assess the relationship among their expression and clinicopathological features. The current study showed negative expression in LGR5 in all six normal cases while in adenoma cases 42% showed mild expression, 50% exhibited moderate expression and 8% of cases demonstrated strong expression. In addition to 10% of CRC cases showed mild expression, 50% revealed moderate expression and 40% of cases revealed strong expression. Also, **Zeng *et al.*** [21] revealed that correlations among LGR5 expression and the histopathological data was statistically significant ($p < 0.05$). Due to elevated levels of LGR5 immunoreactivity in CRC and adenoma contrasted to non-neoplastic tissue.

According to the current study, aggressive characteristics such as high tumor grade (p=0.001), lymph node metastasis (p=0.001), vascular invasion (p=0.001), advanced stages (p=0.001), and tumor budding (p=0.001) were substantially correlated with positive LGR5 expression. Also, **Sadek *et al.*** [22] and **Gao *et al.*** [23] established that increased LGR5 expression was significantly associated with aggressive behavior as high grade, positive nodal metastasis, vascular invasion, and advanced stages. These results suggested that LGR5 could be crucial for both the progress and growth of tumors.

Conversely, **Ahmed *et al.*** [8] demonstrated non-significant association among LGR5 expression and grade of tumor or stage. Also, **Amer *et al.*** [24] demonstrated in his study that there was insignificant statistical association among LGR5 score and the grade of CRC. One potential explanation for these discrepancies was that an immunohistochemical variability might be influenced by discrepancies in antibody selection, dilution concentrations, and antigen retrieval methodologies, which could be based on enzymatic treatment or immunofluorescence techniques [25].

Our finding concerning LGR5 could be explained by the fact that LGR5 enhanced WNT signaling by inhibiting negative regulators like RNF43/ZNRF3, increasing β-catenin levels, promoting cell proliferation**,** stemness and tumor growth [26]. Also, LGR5 promotes epithelial–mesenchymal transition **(EMT)**, elevating metastatic and invasiveness of CRC cells [23]. The pro-oncogenic function of LGR5 in colorectal tumorigenesis is indicated by its overexpression in primary tissue, its correlation with unfavorable prognosis, and its demonstrated pro-tumorigenic activity in in vitro functional assays.

DDRs are collagen receptors possessing tyrosine kinase action and have been correlated with metastasis, tumor invasion, and cellular proliferation [27]**.** Activation of transforming growth factor-beta (TGF-β) signaling, matrix remodeling pathways, upregulation of epithelial-mesenchymal transition genes, stromal infiltration, angiogenesis, and complement-mediated inflammation increase all have been associated with DDR1 expression [16]**.** In this work, there was a significant association (p=0.008) between DDR1 among the studied groups as there was increased expression of DDR1 from normal colonic tissue to colorectal adenoma to carcinoma. These findings are consistent with previous research demonstrating a progressive increase in DDR1 expression across the three groups, from the adjacent non-neoplastic group to the carcinoma group and throughout the adenoma group [28].

Also, **Duan *et al.*** [1] and **Ben Arfi *et al.*** [16], revealed that in CRC tissues DDR1 was more abundantly expressed compared to nearby normal tissues. Furthermore, the association between DDR1 and ECM collagens activates various intracellular kinases, subsequently triggering multiple tumorigenic pathways, including the mTOR and JAK-STAT signaling cascades [29].

Among DDR1 expression and grading of CRC (p=0.001), lymph node metastasis (p=0.006), distant metastasis (p=0.001), staging of CRC (p=0.001), LVI (p=0.001), perineural invasion ($p<0.001$) and tumor budding (p=0.001) there was a significant correlation. No significant difference among DDR1 and other clinicopathological variables ($p> 0.05$).

Similarly, **Dawoud *et al.*** [28] demonstrated that elevated levels of expression were observed in higher-grade, more advanced tumors' stage and were substantially correlated with lymph node metastasis presence. Also increased expression with distant metastasis but no significant correlation with tumor budding. Furthermore, study of **Ben Arfi *et al.*** [16] showed no significant correlation with tumor budding. This discrepancy may be because of different cases number or different immune interpretation methods. The detrimental impact of elevated DDR1 expression in CRC may be attributed to its tissue and ligand-dependent promotion of EMT [30]. So, this facilitates the evolution of malignant tumors and an increase in incidental metastases.

Lafitte and associates [31] hypothesized that DDR1 facilitates the migration of CRC cells via a Wnt/β-catenin-dependent mechanism.

Additionally, it was discovered that DDR1 contributes to extracellular matrix disintegration by upregulating MMP2, which promotes cancer cell invasion [32].

On survival analysis, Kaplan-Meier analysis showed that cases with higher LGR5 expression showed worse OS (log rank=25.12, P=0.025), and worse DFS (log rank=28.5, P=0.035).

Similarly, **Wu *et al.*** [21] and **He *et al.*** [33] linked increased expression of LGR5 with lower OS using immunohistochemical assessment of expression of LGR5 in main cases samples. However, **Nagata et al**[34], discovered that in cases with pT4 colon cancer, a negative expression of LGR5 was a significant predictor of peritoneal recurrence.

According to the **Sato *et al.*** [35] the OS of the LGR5-negative and LGR5-positive groups differed significantly, with a Cox proportional hazards model showing that the LGR5-positive group had improved OS.

The elevated expression of DDR1 in the CRC group within our investigation was associated with the shortest OS (p=0.049), as these patients exhibited the highest disease stage, positive lymph node involvement, and poor histological grade, which is consistent with findings from a previous study by **Dawoud *et al.*** [28].

The results agree with a study done by **Duan *et al.*** [1], which revealed that increased DDR1expression was associated with poor survival.

According to ROC analysis, LGR5 and DDR1 may be considered, a good marker, in prediction of CRC cases with high sensitivity and lower specificity.

Also, **Ben Arfi *et al.*** [16] that revealed DDR1 was substantially expressed in colon cancer as opposed to colonic adenoma and normal colonic mucosa, indicating a function for DDR1 in colorectal carcinogenesis. Moreover, a study done by **He *et al.*** [33] demonstrated that expression of mRNA levels of LGR5 was obviously shown in CRC tissue, in comparison with the paired non-neoplastic tissues and adenoma cases.

CONCLUSION

Our recent research indicated that the overexpression of LGR5 and DDR1 in CRC cases differed from that observed in normal tissue and adenoma cases, suggesting their involvement in the carcinogenesis of CRC. Furthermore, our findings suggest that these markers may play significant roles in the progression and advancement of CRC, as well as in predicting bad prognosis. The significant role of LGR5 in the regulation of DDR1 in CRC suggests that targeting these proteins may serve as a potentially effective multi-target therapeutic approach for CRC patients.

No conflict of interest.

No funding.

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