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Linking insulin like growth factor-1 (IGF-1) rs6214 gene polymorphism and its serum level with risk of colorectal cancer

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Abstract

Background: Colorectal Cancer is found one of the most profound type of cancer around globe, affecting men and women with different ethnic and racial groups. Insulin-like growth factor 1 is known as peptide growth factor found to increase the proliferation of cell and prevent apoptosis. Insulin pathway might have linked with progression of colorectal cancer.

Methods: This study conducted on total 160 subjects, including 80 patients with colorectal cancer with 80 age and gender match controls. Clinical parameters were compared between the control group and Colorectal cancer group. Blood serum IGF-1 was quantified by using ELISA and IGF-1 rs6214(C/T) variations were investigated using TaqMan allelic discrimination assay.

Results: Blood serum level of Insulin growth factor-I (ng/ml) showed substantial association concerning groups while IGF-1 rs6214(C/T) genotype distribution observed increased in colorectal cancer patients as compared to controls with significant association. The variant TT and CT genotype frequency observed more common in cases as compared to control. However, the wild type CC genotype were common in cases used to compared with controls. The Odds Ratio reveal the risk of variant IGF-1 rs6214 T allele to increase 3 times compared to wild type allele.

Conclusion: The homozygous TT genotypes and T variant allele of IGF-1 rs6214(C/T) showed association with high serum Insulin growth factor level 1, may increase susceptibility to the colorectal cancer. This work will use to investigate the associations between Insulin-like growth factor 1 and rs6214(C/T) gene variant and blood serum level with the vulnerability to treat Colorectal. In summary, we have investigated the relationship between Insulin growth factor level hormone and colorectal cancer. Further studies are required to understand the association between colorectal cancer and polymorphism. However, this study can be serve as an informative study to uncover mechanisms behind main cause of colon cancer. Therefore, the genomic profiling of Insulin-like growth factor-1 can be helpful to treat colorectal cancer patients.

Keywords: Colorectal cancer, Insulin growth factor 1, Gene polymorphism

1 Background

According to GLOBOCAN data, colorectal cancer (CRC) is reported to be third deadliest and the fourth commonly diagnosed cancer in world [1]. CRC found liable for the 10% global cancer incidence leading to 9.4% of cancer deaths [2]. New cases of CRC reported 1.93 million diagnosed patients in 2020, and were estimated to cause 0.94

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million deaths worldwide [3]. The increased incidence of CRC has been observed in developing countries [4], suggested the association with westernization [5]. There are multiple risk factors involve with the predisposition of CRC, including age, life style, dietary habits, obesity, lack of exercise, diabetes, use of alcohol, Cigarette smoking, history of CRC [6].

Genetic predisposition in CRCs have been observed 5–6% associated with germline mutation concluding to utilize biomarker for prognosis and response to treatment [7]. The etiology of CRC results from a number of steps of carcinogenesis, alterations in oncogenes, stimulate cell growth and promote carcinogenesis leading towards further complications and co morbid [8]. These changes can either be acquired, as happens in the random forms, or inherited, as in genetic hereditary syndromes like familial adenomatous polyposis and Lynch syndrome [9]. Insulin-like growth factor 1 (IGF-1), a somatostatin is a hepatokine which regulates cellular mechanism [10]. The IGF family performs cell proliferation and inhibits apoptosis and influence cell transformation through regulatory proteins synthesis [11]. IGF signaling pathway is induced when cell surface receptors like IGF-1R, IGF-2R bind to Insulin-like growth factor 1 and 2 (IGF-1,2) respectively, and activates phosphatidylinositol-3 kinase (PI3k)/Akt signaling pathway once stimulated [12, 13]. Any changes at the genetic level may result in insulin sensitivity [14]. Hence, the study aimed to find association of IGF-1 rs6214(C/T) gene variants, blood serum level with the susceptibility to CRC.

2 Methods

2.1 Subjects selection

On the basis of medical history and dignosed diseases. All patients found at metastatic stage IV. The patients were following the systemic chemotherapy (FOLFOX4 regimen) and were also evaluated by CTs and tumor markers after 3 cycles of chemotherapy.

2.2 Sample collection

Seven ml of venous blood was collected by venipuncture, divided into two vacutainers tube; 3 ml each was placed into EDTA containing tube.

2.3 Biochemical analysis

Biochemical laboratory investigations comprising of, liver functions test (AST, ALT), estimation of kidney functions (urea, creatinine), serum carbohydrate antigen (CA19-9 levels), and serum carcinoembryonic antigen (CEA) levels. The Serum levels of CEA and CA19-9 were estimated by enzyme-linked immunosorbent assay (Human CEA and CA19-9 ELISA kits, Chemux Bio Science, Inc., USA), serum IGF-1 level was quantified by using (Sun Red Biotechnology company) ELISA kit.

2.4 Genetic analyses

The tube contains EDTA as an anticoagulant that help to prevent blood clots. The genomic DNA was extracted by Zymo Research Quick-g DNA mini prepGenomic DNA purification kit (USA). The rs6214(C/T) gene polymorphism was analyzed by using the TaqMan allelic discrimination Assay technique (real time PCR).

2.5 Statistical analysis

The data collected was analyzed statistically by Statistical Package of Social Science (SPSS) version 20.0. Chi-square test was used to find the possible association for the qualitative variables. For quantitative variables, one way-analysis of variance test (ANOVA), student's t test was used to calculate the statistical significance, while spearman's correlation was applied for skewed distributed quantitative variables. Kruskal–Wallis test was used to compared groups for the non-distributed variables. To observe the effect of risk factors as an independent variable, multiple regression analyses was also performed, while p value < 0.005 was assumed statistically significant.

3 Results

3.1 Clinical parameters

The clinical parameter were compared among studied group. The parameters considered in the study were ALT, AST, Urea, Creatinine, CA19-9, CEA, age and sex. Statistically significant difference between the studied groups, CRC patients and controls were found among C19-9, CEA and serum IGF-1 levels, while there was no significant change with respect to age, sex, AST ALT, urea and creatinine (Table 1).

3.2 IGF-1 rs6214(C/T) genotype distribution

Genotype distribution was observed among CRC and control which showed significant difference between groups and genotypes (χ^2: 38.243, $p < 0.001$). It was found that wild type CC was frequent among controls subjects while variant CT and TT genotype was observed more frequent among CRC subjects as compared to healthy subjects (Fig. 1, Table 2). The strength of genotype association was also observed by calculating odds ratio. It revealed the risk associated with the variant genotype either as homozygous wild type or as heterozygous variant form. The odds ratio for both genotypes were found with the risk of developing CRC by 8.33 to 10.41 folds more with the variant forms as compared to wild genotype (Table 3).

Table 1 Comparison between the two studied groups according to different parameters

Clinical parameters mean (± SD)	Colorectal cancer ($n=80$)	Control ($n=80$)	Test of Sig	*p* value
Sex				
Male	47 (58.8%)	43 (53.8%)	$\chi^2=0.406$	0.524
Female	33 (41.3%)	37 (46.3%)		
Age	12.5 ± 49	51.2 ± 11.2	$t=1.172$	0.243
ALT	4.5 ± 33.2	34.1 ± 5	$t=1.152$	0.251
AST	4.4 ± 31.3	3.8 ± 30.7	$t=1.057$	0.292
UREA	9.6 ± 29	31.4 ± 8.3	$U=2746.0$	0.121
Creatinine	0.2 ± 1	1 ± 0.2	$t=0.590$	0.556
CA19-9 (U/ml)	91.9 ± 41.4	5.4 ± 9.3	$U=1948.0$	< 0.001
CEA (mg/dl)	20.2 ± 44.4	0.46 ± 1.6	$U=0.0$*	< 0.001
Serum IGF-1 (ng/ml)	33 ± 152	16 ± 111.9	$t=9.872$*	< 0.001

χ^2: Chi square test, *t*: Student *t*-test, *U*: Mann Whitney test

3.3 IGF-1 rs6214(C/T) allelic distribution

The risk of allelic variation was also observed for both wild allele and variant allele. The wild allele was found more frequent in healthy control as compared to variant allele. The variant allele was more in CRC patients as compared to the healthy control which significantly found associated. The strength of association by means of odds ration showed the risk of developing CRC increases by 5.14 folds compared to wild type allele (Fig. 2, Tables 2, 3). Allelic discrimination plot was also observed, showing presence of all three genotypes CC, CT, TT, where variant genotypes CT and TT was found more in cluster compared to the wild CC genotype (Fig. 3).

3.4 Association of clinical parameters with IGF-1 rs6214(C/T) genotype distribution

The association of clinical parameters including gender, age, ALT, AST, Urea, Creatinine, Ca19-9, CEA and IGF-1 levels were compared to CC, CT and TT genotypes. The significant statistical differences found between genotypes with the serum IGF-1, serum C19-9, CEA levels (Table 4, Fig. 4). The highest levels of serum IGF-1 levels were observed in TT homozygous variant genotype and CT heterozygous variant genotype compared to homozygous wild CC genotype (Fig. 4).

3.5 Correlation analysis

A positive correlation ($r=-0.949$ and $p<0.001$) of serum IGF-1 levels with CEA and with C19-9 was observed ($r=-0.728$ and $p<0.001$) which showed significant association among these parameter as shown in Table 5 and Figs. 5 and 6.

3.6 Multivariate logistic regression

The multivariate logistic regression analysis for the risk of colorectal cancer that TT variant genotype of IGF-1 rs6214 represents to increase the risk of CRC by 10 times compared to CC wild type (odds ratio 10.417, CI 4.42–24.52), followed by CT genotype of IGF-1 rs6214 by 8 folds (odds ratio 8.33, CI 3.39–20.48). Similarly, the biochemical parameters showed significant CRC risk association with IGF-1 levels (odds ratio 1.12, CI 1.07–1.16)

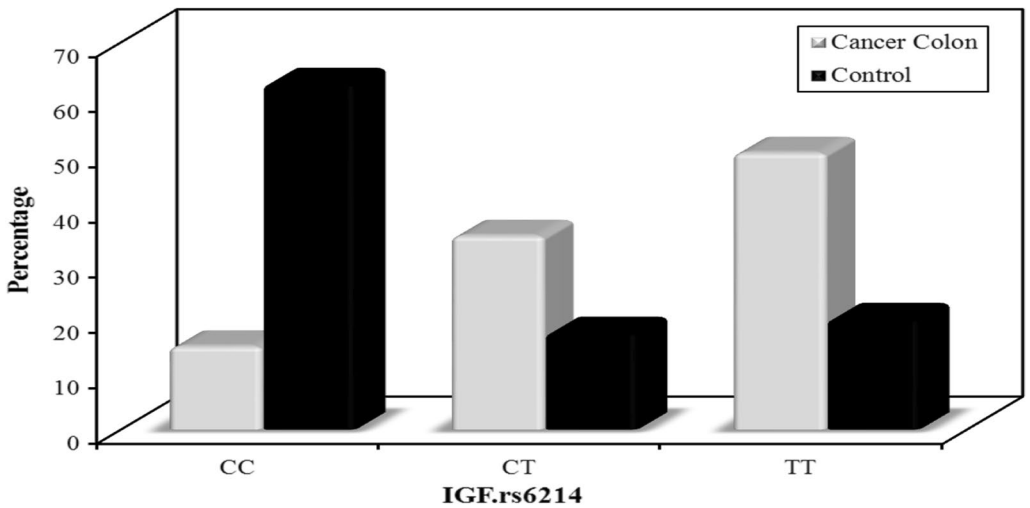

Fig. 1 Comparison between the two studied groups (colorectal cancer group (n.80) and control group (n. 80)) regarding to IGF-1 rs6214(C/T) genotypes

Table 2 Comparison between the two studied groups according to genotypes and alleles of IGFrs6214(C/T) polymorphism

IGF-1 rs6214	Colorectal cancer ($n=80$)	Control ($n=80$)	χ^2	p
CC®	12(15%)	50 (62.5%)	38.243*	< 0.001*
CT	28 (35%)	14 (17.5%)		
TT	40 (50%)	16 (20%)		
Allele				
C®	52 (32.5%)	114 (71.3%)	48.118*	< 0.001*
T	108 (67.5%)	46 (28.8%)		

χ^2: Chi square test

*Statistically significant at $p \leq 0.05$

and C19-9 (odds ratio 1.09, CI 1.05–1.14) as shown in Table 6.

4 Discussion

It has been reported that several molecules are implicated in oncogenesis, metastasis and treatment sensitivity. Increased IGF-1 bioavailability may, over time, surge the risk of developing CRC. IGF axis through its components may have role in colorectal carcinogenesis, also diet and other associated factors like physical activity, sedentary lifestyle and obesity may also increase the risk [15]. However, other studies couldn't establish such finding [16, 17]. Although high levels of IGF-1 in CRC patients compared to controls were observed in this study representing the risk associated with the susceptibility to CRC. The significant association with the increased CEA levels in CRC also found in accordance with the [18], who reported high levels of CA19-9 and CEA in CRC patients in their study.

The association of IGF-1 polymorphism showed significant association with the CRC, where variant CT and TT were frequent in CRC patients compared to controls,

Table 3 Odds ratio of different genotypes and alleles of IGF-1 rs6214(C/T) polymorphism

IGFrs6214	colorectal Cancer ($n=80$)		Control ($n=80$)		OR	p	95% CI
	No	%	No	%			L.L–U.L
CC®	12	15.0	50	62.5	1.000		
CT	28	35.0	14	17.5	8.333	< 0.001*	(3.40–20.48)
TT	40	50.0	16	20.0	10.417	< 0.001*	(4.42–24.52)
C®	52	32.5	114	71.3	1.000		
T	108	67.5	46	28.8	5.147	< 0.001*	(3.20–8.29)

® : Reference or wild type

*Statistically significant at $p \leq 0.05$

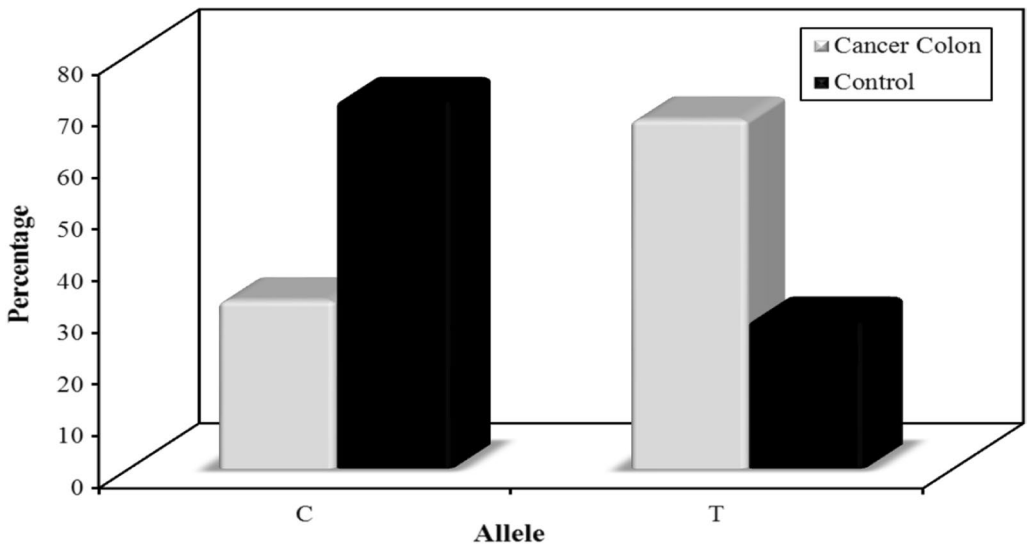

Fig. 2 Comparison between the two studied groups (colorectal cancer group (n.80) and control group (n. 80)) regarding to IGF-1 rs6214(C/T) alleles

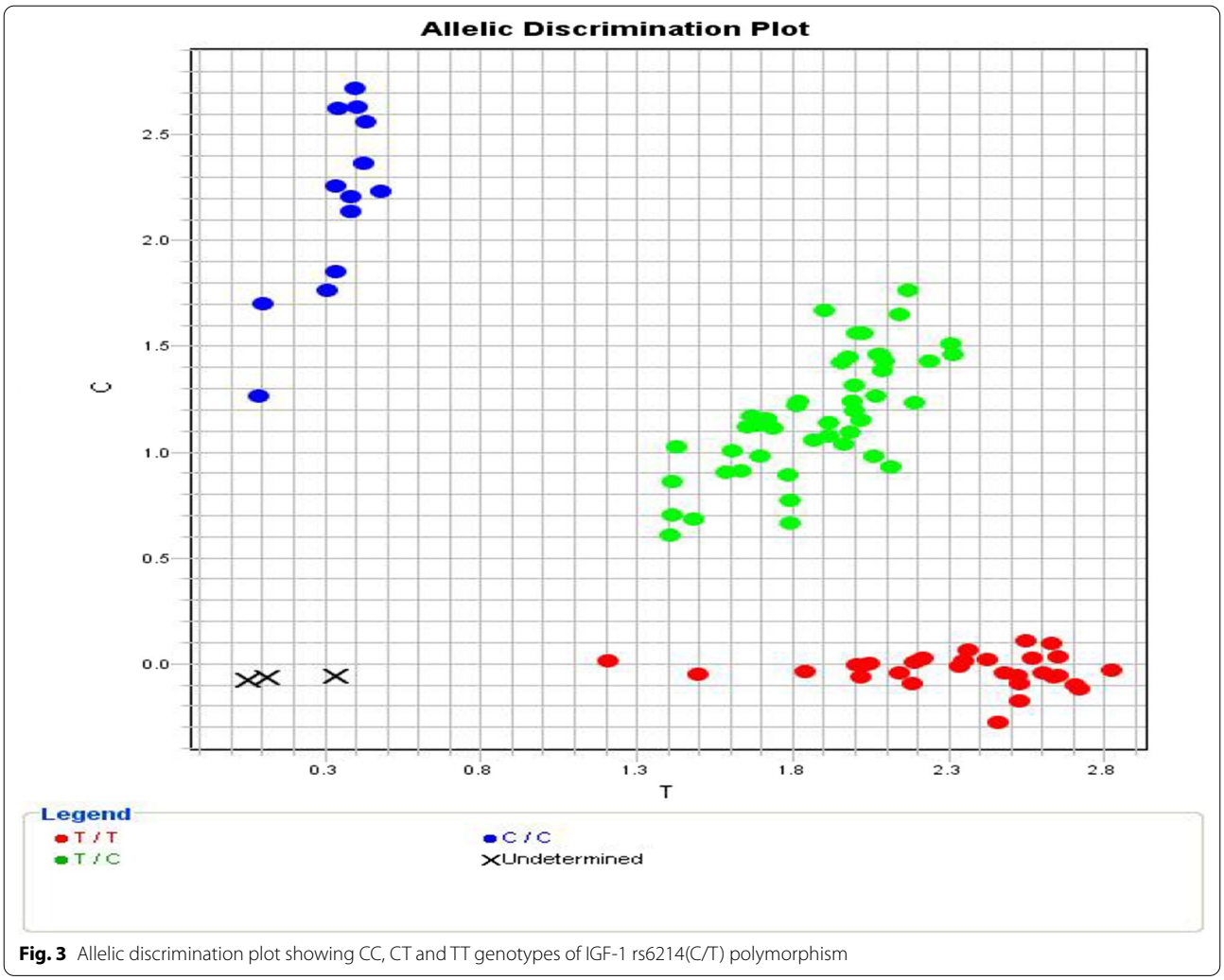

Fig. 3 Allelic discrimination plot showing CC, CT and TT genotypes of IGF-1 rs6214(C/T) polymorphism

Table 4 Relation between IGF rs6214 genotypes and different parameters in colorectal Cancer group ($n=80$)

	IGF rs6214			Test of Sig	*p*
	CC ($n=12$)	CT ($n=28$)	TT ($n=40$)		
Sex					
Male	7 (58.3%)	17 (60.7%)	23 (57.5%)	$\chi^2=0.071$	0.965
Female	5 (41.7%)	11 (39.3%)	17 (42.5%)		
Age (years)	11.6 ± 44.9	11.8 ± 46	12.6 ± 52.4	$F=3.115$	0.050
ALT	4.6 ± 33.3	4.8 ± 32.6	4.3 ± 33.7	$F=0.443$	0.643
AST	4.6 ± 32.1	4.2 ± 31.7	4.6 ± 30.9	$F=0.450$	0.639
UREA	10.1 ± 30.2	10.2 ± 28.9	9.3 ± 28.7	$H=0.314$	0.855
Creatinine	0.2 ± 1	0.2 ± 1	0.3 ± 1	$F=0.285$	0.753
CA19-9 (U/ml)	6.9 ± 8.5	6.4 ± 10.5	72.9 ± 122.7	$H=34.668$*	< 0.001*
CEA (mg/dl)	1.6 ± 31.1	2.9 ± 33.5	23.4 ± 55.9	$H=50.170$*	< 0.001*
Serum IGF-1 (ng/ml)	1.9 ± 122.2	4.9 ± 131.6	32.6 ± 175.3	$F=40.227$*	< 0.001*

χ^2: Chi square test, *F*: *F* for ANOVA test, *H*: for Kruskal Wallis test

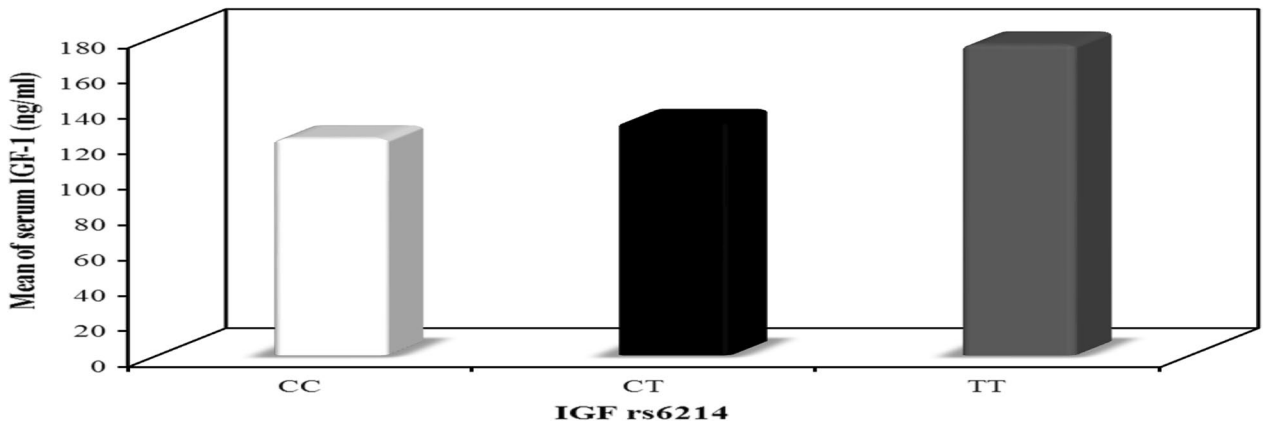

Fig. 4 The levels of Serum IGF-1 in different genotypes of IGF-1 rs6214 in colorectal Cancer group ($n=80$)

Table 5 Correlation between IGF rs6214 with CA19.9 and CEA in colorectal cancer group ($n=80$)

	Serum IGF.1	
	r_s	p
CA19.9	0.728	< 0.001*
CEA	0.949	< 0.001*

r_s: Spearman coefficient

*Statistically significant at $p \leq 0.05$

while the presence of wild type CC genotype found more common in controls compared to CRC. The risk of developing susceptibility was observed to increase by 10.41 folds with TT genotype and with CT genotype the risk increase by 8.33 folds. The results were found in agreement with [19, 20]. The clinical parameters showed the positive correlation between serum IGF-1 and CEA levels ($r=0.94$, $p<0.001$), IGF-1 and C19-9 level in CRC patients ($r=0.72$, $p<0.001$) which significant association. However, Yilmaz et al. [21] reported the higher levels of CEA and CA19-9 in CRC patients but no significant association was found between IGF-1 levels with CEA or CA19-9. There are multiple biochemical and genetic alterations involved in the risk association of different types of cancers, for instance the current study showed IGF-1 polymorphism was found associated with the increased risk developing CRC. The obtained data highlighted the significance of targeted molecular detection to utilize them for clinical settings including prognostic,

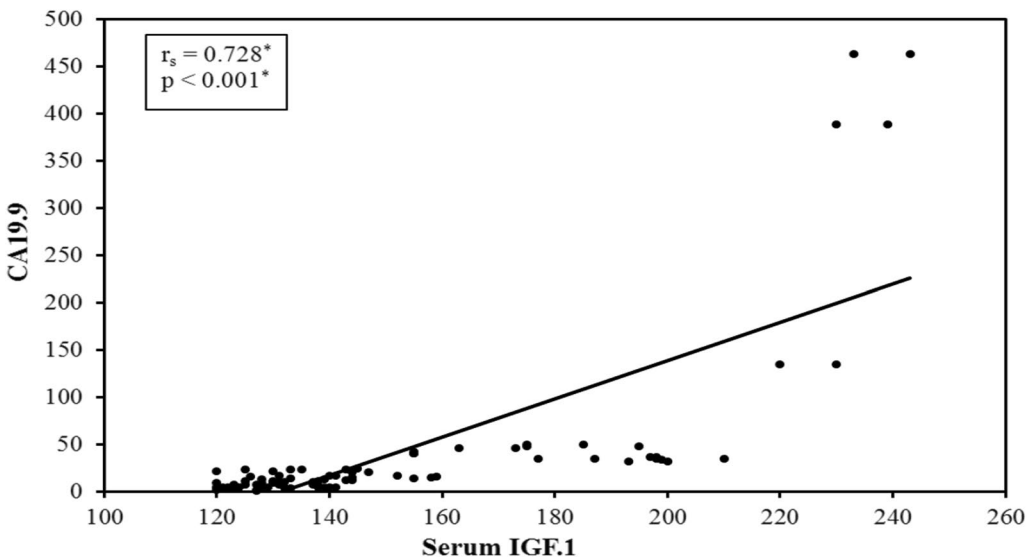

Fig. 5 Correlation between IGF rs6214 with CA19.9 in colorectal cancer group ($n=80$)

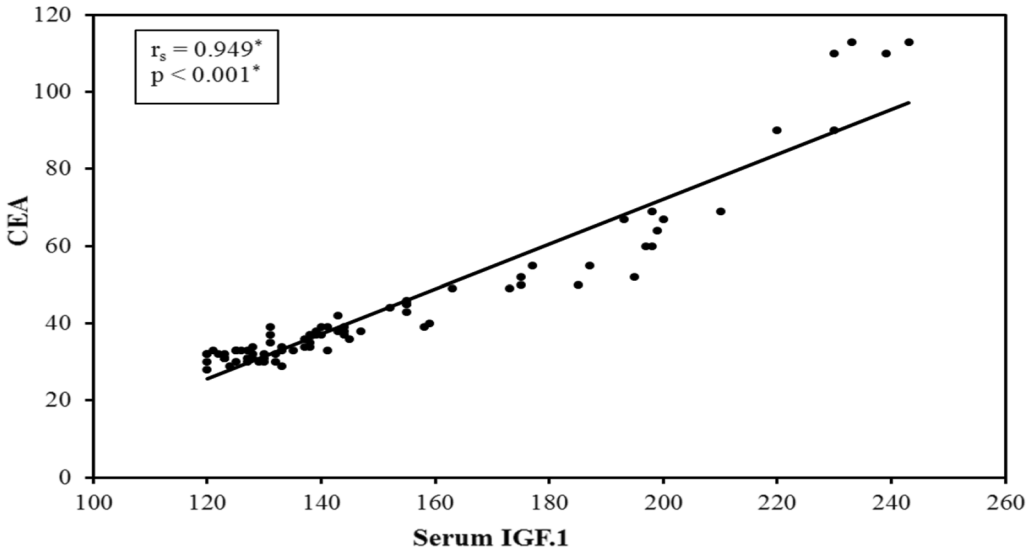

Fig. 6 Correlation between IGF rs6214 with CEA in colorectal Cancer group ($n = 80$)

Table 6 Univariate and multivariate analysis for the risk factor of colorectal cancer

	Univariate		#Multivariate	
	p	OR (95% CI)	*p*	OR (95% CI)
Sex (female)	0.524	1.226 (0.656–2.291)		
Age	0.242	0.984 (0.959–1.011)		
ALT	0.250	0.962 (0.900–1.028)		
AST	0.290	1.042 (0.966–1.124)		
UREA	0.092	0.970 (0.937–1.005)		
Creatinine	0.554	1.513 (0.385–5.949)		
CA19-9 (U/ml)	< 0.001*	1.097 (1.051–1.145)	< 0.001*	0.936 (0.904–0.969)
CEA (mg/dl)	0.992	4.031 (0.0–6.511037753104e)		
Serum IGF-1 (ng/ml)	< 0.001*	1.121 (1.079–1.164)	< 0.001*	1.413 (1.222–1.634)
IGF.rs6214				
CC®				
CT	< 0.001*	8.333 (3.391–20.480)	0.103	0.264 (0.053–1.308)
TT	< 0.001*	10.417 (4.425–24.523)	< 0.001*	0.002 (0.0–0.037)

*Statistically significant at $p \leq 0.05$

diagnostic purposes and further, for the personalized medicines. Therefore, the molecular signatures or the genomic profiling insights can be beneficial for treatment plan for CRC.

5 Conclusion

As the number of CRC cases increasing, it is posing a growing health concern globally. The molecular signatures or the genomic profiling insights can be beneficial for treatment plan for CRC. For promoting better lifestyle, a strategic management is required for providing awareness, proper screening methods including credential prognostic and diagnostic biomarkers in order to reduce the CRC morbidity and mortality worldwide.

Abbreviations

CRC: Colorectal cancer; IGF-1: Insulin like growth factor-1; ELISA: Enzyme-linked immunoassay; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CEA: Carcinoembryonic antigen.

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Authors' contributions
SK: Writing manuscript and laboratory work. AMKA: Writing manuscript and laboratory work. KM: Statistics and revising manuscript. AMA: Statistics and revising manuscript. AH: Picking cases and writing manuscript. EE: Idea of the study and writing manuscript. All authors read and approved the final manuscript.

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Declarations

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An informed written consent was achieved from every subject participated in this study and this work was approved by the Ethical Committee of Medical Research, Faculty of Medicine, Menoufia University No. (2/2020B104).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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