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ORIGINAL PAPER

Association of interleukin-1β gene polymorphisms in the occurrence of gastric ulcer in Southern Odisha, India

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ABSTRACT

Introduction and aim. The occurrence of gastric ulcer (GU) is influenced by many factors including interleukin 1β (*IL-1β*) gene polymorphisms. In this study, the association of GU with *IL-1β* gene polymorphisms was investigated in patients with gastric disorders.

Material and methods. The patients were categorized into two groups, group 1: patients with normal impression in the upper-GI-endoscopy (n=135); group 2: patients with GU (n=135). Three single nucleotide variants (SNVs) of *IL-1β* gene [rs16944 (–511 C/T), rs1143627 (–31 C/T) and rs1143634 (+3954 C/T)] were investigated by PCR-RFLP method.

Results. The association of *IL-1β* gene polymorphisms and occurrence of GU along with other factors (socio-demographic and habits) showed patients with smoking, alcohol intake and NSAID use was high in group 2. For SNVs and occurrence of GU, rs1143627 (–31 'TT') genotype was significantly high in group 2 (21.48%) compared to group 1 (9.63%), while the other two genotypes were comparable. Further, there was no association of any genotypes with smoking, alcohol intake and NSAID use, except NSAID use with rs1143627 (–31 C/T) in group 1.

Conclusion. The findings revealed, the habits like smoking, alcohol intake and recurrent NSAID use may influence the occurrence of GU while, the *IL-1β* gene polymorphisms have minimal impact on the occurrence of GU.

Keywords. gastric ulcer, gene polymorphism, interleukin-1β, non-steroid anti-inflammatory drug

Introduction

Gastric ulcer (GU) is the most common gastrointestinal disease worldwide affecting about four million people annually with an estimated lifetime prevalence of 5–10% in general population.[1] Incidence of GU is associated with many confounding factors including food habits, alcohol consumption, smoking habit, use of non-steroid anti-inflammatory drug (NSAID), *Helicobacter pylori* infection, as well as various genetic polymorphisms etc.[2-5]

Several studies were carried out by taking the single nucleotide variants (SNVs) of interleukin 1β (*IL-1β*) gene against the development of ulcer in upper gastrointestinal (GI) tract especially for duodenal and GU. Three potentially functional SNVs: rs16944 (–511 C/T) and rs1143627 (–31 C/T) in the promoter region, and rs1143634 (+3954 C/T) in exon 5 of *IL-1β* gene have been widely studied and the association with GU are reported to be conflicting.[6-11] These SNVs have also been

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found to be strongly associated with the *H. pylori* infection with increased risk of gastric disorders.[6-12] Further the risk of GU were reported to be contradictory with respect to the genotypes of various SNVs in *IL-1β* gene in different populations worldwide.[6,8,13]

Aim

Keeping the paucity of information on the association of *IL-1β* gene polymorphisms with the occurrence of GU in the Indian population, this prospective study was designed with an aim to analyze the possible association of three SNVs of *IL-1β* gene [rs16944 (–511 C/T), rs1143627 (–31 C/T) and rs1143634 (+3954 C/T)] with the occurrence of GU in patients coming with gastric disorder to a tertiary health care facility of Eastern India.

Material and methods

This case-control (un-matched) study was conducted between March 2019 and February 2021 and included individuals presenting with symptoms of gastric disorders who were referred for upper GI endoscopy. All the consecutive cases were recruited except individuals with other chronic diseases and who refused to be a part of the study. The diagnosis of GU was established on the basis of endoscopic findings. Individuals with normal impression of upper GI endoscopy along with absence of an inflammatory process of any etiology were considered as control (group 1) and individuals diagnosed with GU were considered as case (group 2).

A total of 135 cases each in group 1 and group 2 were recruited considering the prevalence of *IL-1β* gene polymorphisms (variants) in GU patients of 40%, two sided confidence level of 95%, allowable error of 5% and odd ratio of 2. The sample size was calculated by using OpenEpi software, Version 3 (https://www.openepi.com/SampleSize/SSCC.htm). After taking informed consent for the study, 3 milliliters of venous blood was collected in EDTA vial from the individuals and were transported by coolants to the Multi-Disciplinary Research Unit (MRU) of M.K.C.G. Medical College for further *IL-1β* SNVs study. This study was approved by the Institutional Ethical Committee (IEC) of M.K.C.G. Medical College, Berhampur, Odisha (No. 819 /Chairman-IEC, M.K.C.G. Medical College, Berhampur-4).

The genomic DNA was isolated from peripheral blood sample by using phenol-chloroform isolation method. The isolated DNA was quantified and the quality was checked by spectrophotometer (DS-11+Spectrophotometer, DeNovix, Wilmington, DE19810 USA). On analysis, isolated DNA samples with a good purity ratio of 1.7 to 2.0 were allowed for polymerase chain reaction (PCR) and rest samples were re-processed with RNAse treatment where required.

Three SNVs of *IL-1β* gene [rs16944 (–511 C/T), rs1143627 (–31 C/T) and rs1143634 (+3954 C/T)] were investigated by PCR followed by Restriction Fragmented Length Polymorphisms (RFLP) as per the protocol described by Manchanda et al., and Ramis et al.[10,14] The list of primer used, PCR (time, temperatures and cycle) and respective restriction endonuclease (RE) along with resulted product and respective genotypes has been illustrated in Table 1. All the three RE (*Ava I, Alu I* and *Taq I*) used in this study were from New-England Biolabs. Both the PCR products and the RE digested product were run in 3% agarose gel electrophoresis followed by documentation in gel documented system using Image Lab software (GelDoc XR+, Bio-Rad, USA). The agarose gel picture of three SNVs of *IL-1β* gene [rs16944 (–511 C/T), rs1143627 (–31 C/T) and rs1143634 (+3954 C/T)] have been attached as supplementary files (Fig. 1, Fig. 2 and Fig. 3) respectively. For reproducibility in each run, we have used both the positive control and negative control investigated in our own samples. Again, 10 randomly selected samples were re-analyzed for all the three SNVs for further confirmation.

Table 1. Details of primer, PCR cycle, restriction enzymes and length of the products for the analysis of *IL-1β* gene polymorphisms

SNVs	Primers	Sequence	PCR cycle (35 cycles)	PCR product (in bp)	RE	DNA fragments and genotype
rs16944 (–511 C/T)	Forward	TGGCATTGATCTGGTTCATC	95°C for 30 sec 56°C for 30 sec 72°C for 30 sec	304	Ava I	CC 190, 114 CT 304, 190, 114 TT 304
	Reverse	GTTTTAGGAATCTTCCCACTT				
rs1143627 (–31 C/T)	Forward	AGAAGCTTCCACCAATACTC	95°C for 30 sec 56°C for 30 sec 72°C for 30 sec	239	Alu I	CC 239 CT 239,137,102 TT 137,102
	Reverse	AGCACCTAGTTGTAAGGAAG				
rs1143634 (+3954 C/T)	Forward	GTTGTCATCAGACTTTGACC	95°C for 30 sec 55°C for 30 sec 72°C for 30 sec	249	Taq I	CC 135,114 CT 249,135,114 TT 249
	Reverse	TTCAGTTCATATGGACCAGA				

Data collection and statistical analysis

A designed case format containing the set of information along with anthropometric and clinical parameters was filled-up for each study subject. All the data was presented by number followed by percentage. The comparison of variables (socio-demographic, habits, genotypes of respective SNVs) were made between the two groups of study participants. Further, the association of genotypes of three SNVs against various habits (smoking, alcohol intake and NSAID use) were analyzed. All the categorical data was analyzed by Chi square test of significance by using SPSS version 16 (IBM, Armonk, NY, USA). A p value of <0.05 was considered as statistically significant.

Results

During the study period, a total of 135 cases each in both the groups were considered for further analysis. There was no significance difference between the groups with respect to age, gender, occupation and place of liv-

ing. However, the number of cases with smoking, alcohol intake and NSAID use was significantly high in group 2 with GU compared to group 1 (Table 2).

Table 2. Comparison of variables (socio-demographic and habits) between the patients with and without gastric ulcer

Variables	Group 1 (without GU) (n=135)	Group 2 (with GU) (n=135)	χ^2 value, p
<40	38 (28.15)	28 (20.74)	3.367, 0.1857
40-60	43 (31.85)	48 (35.56)	
>60	54 (40.0)	59 (43.70)	
Gender			
Male	96 (71.11)	101(74.81)	0.469, 0.493
Female	39 (28.89)	34 (25.19)	
Occupation			
Service	30 (22.22)	57 (42.22)	8.398, 0.78
Business	14 (10.37)	9 (6.67)	
Farmer	40 (29.63)	32 (23.70)	
Others	35 (25.93)	26 (19.26)	
Housewife	16 (11.85)	11 (8.15)	
Place of living			
Urban	42 (31.11)	43 (31.85)	0.017, 0.896
Rural	93 (68.89)	92 (68.15)	
Smoking			
Yes	18 (13.33)	33 (24.44)	5.439, 0.02
No	117 (86.67)	102 (75.56)	
Alcohol intake			
Yes	32 (23.70)	47 (34.81)	4.026, 0.045
No	103 (76.30)	88 (65.19)	
NSAID use			
Yes	11 (8.15)	32 (23.70)	12.119, 0.001
No	124 (91.85)	103 (76.30)	

The genotypes and allelic frequency of three SNVs [rs16944 (–511 C/T), rs1143627 (–31 C/T) and rs1143634 (+3954 C/T)] of *IL-1β* gene were compared between group1 and group 2. Among the three, two SNVs, that is, rs1143634 (+3954 C/T) and rs16944 (–511 C/T), both the genotypes and alleles distribution were found to be comparable in group 1 and group 2 respectively. However, the 'TT genotype of rs1143627 (–31 C/T) was significantly high (χ^2 7.437; P value 0.024) in group 2 (21.48%) compared to group 1 (9.63%). Similarly, the 'T' allele was high in group 2 compared to group 1, however, it did not reach to a statistical significant level (χ^2 2.909; P value 0.088). The comparison of genotypes and alleles distribution of three SNVs of *IL-1β* gene between the two groups of patients has been depicted in Table 3.

Further, the habit like smoking, alcohol intake and NSAID use were compared among the genotypes of the three SNVs separately. On comparison, there is no specific significant association is observed among the variables and genotypes of all the three SNVs in both group 1 and group 2, except use of NSAID in group 1 for rs16944 (–511 C/T). Here 'CT' genotypes were reported to be low (zero) in those who had used NSAID (Table 4).

Table 3. Comparison of genotype and allele distribution of *IL-1β* gene polymorphisms between the patients with and without gastric ulcer

rs16944 (–511 C/T)	Group 1 (without GU) (n=135)	Group 2 (with GU) (n=135)	χ^2 value, p
CC	33 (24.44)	43 (31.85)	2.114, 0.347
CT	46 (34.07)	38 (28.15)	
TT	56 (41.48)	54 (40.00)	
C	0.41	0.46	0.508, 0.476
T	0.59	0.54	
rs1143627 (–31 C/T)	**Group 1 (without GU) (n=135)**	**Group 2 (with GU) (n=135)**	**χ^2 value,p**
CC	83 (61.48)	69 (51.11)	**7.437, 0.024**
CT	39 (28.89)	37 (27.41)	
TT	13 (9.63)	29 (21.48)	
C	0.76	0.65	2.909, 0.088
T	0.24	0.35	
rs1143634 (+3954 C/T)	**Group 1 (without GU) (n=135)**	**Group 2 (with GU) (n=135)**	**χ^2 value,p**
CC	91 (67.41)	84 (62.22)	1.073, 0.585
CT	34 (25.19)	37 (25.19)	
TT	10 (7.41)	14 (10.37)	
C	0.80	0.76	0.466, 0.495
T	0.20	0.24	

Table4. Association analysis of social parameters and the genotypes of *IL-1β* gene polymorphisms

	Group 1 (without GU) (n=135)				Group 2 (with GU) (n=135)			
rs16944 (–511 C/T)								
Variables	CC	CT	TT	χ^2 value, p	CC	CT	TT	χ^2 value, p
Smoking (Yes)	6 (33.33)	3 (16.67)	9 (50.00)	2.882,	6 (18.18)	11 (33.33)	16 (48.48)	3.766,
Smoking (No)	27 (23.08)	43 (36.75)	47 (40.17)	0.237	37 (36.27)	27 (26.47)	38 (37.25)	0.152
Alcohol intake (Yes)	8 (25.00)	14 (43.75)	10 (31.25)	2.216,	21 (44.68)	10 (21.28)	16 (34.04)	5.575,
Alcohol intake (No)	25 (24.27)	32 (31.07)	46 (44.66)	0.33	22 (25.00)	28 (31.82)	38 (43.18)	0.062
NSAID (Yes)	6 (54.55)	0	5 (45.45)	8.565,	9 (28.13)	8 (25.00)	15 (46.88)	0.826,
NSAID (No)	27 (21.77)	46 (37.10)	51 (41.13)	0.014	34 (33.01)	30 (29.13)	39 (37.86)	0.662
rs1143627 (–31 C/T)								
Variables	CC	CT	TT	χ^2 value, p	CC	CT	TT	χ^2 value, p
Smoking (Yes)	12 (66.67)	4 (22.22)	2 (11.11)	0.458,	17 (51.52)	12 (36.36)	4 (12.12)	3.061,
Smoking (No)	71 (60.68)	35 (29.91)	11 (9.40)	0.795	52 (50.98)	25 (24.51)	25 (24.51)	0.216
Alcohol intake (Yes)	23 (71.88)	8 (25.00)	1 (3.13)	2.799,	25 (53.19)	12 (25.53)	10 (21.28)	0.155,
Alcohol intake (No)	60 (58.25)	31 (30.10)	12 (11.65)	0.247	44 (50.00)	25 (28.41)	19 (21.59)	0.925
NSAID (Yes)	8 (72.73)	3 (27.27)	0	1.41,	12 (37.50)	13 (40.63)	7 (21.88)	4.197,
NSAID (No)	75 (60.48)	36 (29.03)	13 (10.48)	0.494	57 (55.34)	24 (23.30)	22 (21.36)	0.123
rs1143634 (+3954 C/T)								
Variables	CC	CT	TT	χ^2 value, p	CC	CT	TT	χ^2 value, p
Smoking (Yes)	14 (77.78)	4 (22.22)	0	1.942,	22 (66.67)	9 (27.27)	2 (6.06)	0.921,
Smoking (No)	77 (65.81)	30 (25.64)	10 (8.55)	0.379	62 (60.78)	28 (27.45)	12 (11.76)	0.631
Alcohol intake (Yes)	20 (62.50)	10 (31.25)	2 (6.25)	0.838,	28 (59.57)	14 (29.79)	5 (10.64)	0.235,
Alcohol intake (No)	71 (68.93)	24 (23.30)	8 (7.77)	0.658	56 (63.64)	23 (26.14)	9 (10.23)	0.889
NSAID (Yes)	6 (54.55)	4 (36.36)	1 (9.09)	0.934,	17 (53.13)	10 (31.25)	5 (15.63)	1.901,
NSAID (No)	85 (68.55)	30 (24.19)	9 (7.26)	0.627	67 (65.05)	27 (26.21)	9 (8.74)	0.387

Discussion

In this case-control study a total of 270 patients with symptoms of upper GI tract disorders advised for upper GI tract endoscopy were included. The anthropometric, socio-demographic, behavioral and three SNVs of *IL-1β* gene [rs16944 (–511 C/T), rs1143627 (–31 C/T) and rs1143634 (+3954 C/T)] were compared between the two groups (patients with and without GU) of patients.

Variables like age, gender, occupation, place of living and habit like smoking, alcohol intake, NSAID use were evaluated for the association of GU. There was no association between age, gender, occupation and place of living with GU. The occurrence of GU is significantly higher in patients with alcohol intake, smoking and NSAID use in many earlier studies. Smoking may lead to the development of ulcer in the upper GI tract and found to be reversible after stopping of smoking.[15-18] There was also inconsistent report on the association of smoking habit and occurrence of GU.[7,19] The frequent use of NSAID has been reported to be associated with ulcer disease due to its action on inhibiting the cyclooxygenase enzyme in the GI tract leads to a reduction of prostaglandin secretion and cytoprotective effects in gastric mucosa, increasing the susceptibility to mucosal injury.[20,21] The ulcer can be effectively treated by stopping the use of NSAID. However, Treatment may be recommended to speed up the healing process, else surgery may be needed.[22,23]

The association of three SNVsof *IL-1β* gene [rs16944 (–511 C/T), rs1143627 (–31 C/T) and rs1143634 (+3954 C/T)] with the occurrence of GU showed absent of any possible association with GU with two SNVs that is, rs16944 (–511 C/T) and rs1143634 (+3954 C/T). Similar interpretation was also reported in a study undertaken in Brazilian and Spanish Caucasian population, where the SNVrs1143634 (+3954 C/T) had no association with GU.[10,24] There is also contradictory result on the involvement of SNVrs1143634 (+3954 C/T), in which the 'TT' genotype found to be a genetic risk factor for *H. pylori* induced GU in Iranian population.[8] Further, rs1143634 (+3954 C/T) 'TT' genotype was also associated with peptic ulcer and 'T' allele (CT/TT) is correlated with gastritis.[8] The association of rs1143634 (+3954 'T') allele with gastric disorders have also been reported from the populations of African Americans and Caucasian, and Poland.[25,26]

For SNV rs16944 (–511 C/T) there was also inconsistent results. Briefly, In Chinese population the rs16944 (–511 'T') allele is more frequent and has association between peptic disease and *H. pylori*.[27] In Japanese population the rs16944 (–511 'C') allele is more dominant with advance atrophic gastritis.[28] There was no difference in the frequency of rs16944 (–511 'C' and 'T'allele) in Thai and Vietnamese populations in occurrence of chronic gastritis respectively.[28,29] In Korean population the rs16944 (–511 'C') allele leads to enhancement of production of *IL-1β* by gastric mucosa.[30] The presence of 'C' allele ('CC' and 'CT' genotypes) of rs16944 (–511 C/T) was associated with chronic gastritis and gastric cancer development especially individuals with *H. pylori*-infection in the Brazilian population.[12]

Unlike rs16944 (–511 C/T) and rs1143634 (+3954 C/T), the SNV rs1143627 (–31 C/T) was found to be associated with the GU in the present study, that is, the 'TT' genotype was significantly higher in group 2 with GU. The 'T' allele could act as a pro-inflammatory allele in rs1143627 (–31 C/T) and its presence may be an independent risk factor for gastric carcinoma. This was resulted by the study carried out in Korean population indicating the importance of rs1143627 (–31 'T') allele as well as *H. pylori* infection for the development of ulcer.[30] Few studies have reported with contradictory finding where presence of 'TT' genotype acts as a protector for *H. pylori* infection and gastritis.[31] Further the 'CC' genotype was more frequent in gastric carcinoma patients in Chinese population in Northern region.[27] The SNVs of *IL1 β* gene especially rs1143627 (–31 C/T) and rs16944 (–511 C/T) have been linked to the expression of IL-1β mRNA leads to the development of gastric inflammation as well as gastric carcinoma.[32,33] A detail comparative analysis on the association of *IL1 β* gene polymorphisms and gastric disorders has been illustrated as Table 5.

Table 5. Comparative analysis on the association of *IL-1 β* gene polymorphisms and gastric disorders

Studies	rs1143627 (–31 C/T)	rs16944 (–511 C/T)	rs1143634 (+3954 C/T)
Thai and Vietnamese populations[29]		No association with chronic gastritis	
Chinese population[27]	'CC' genotype with gastric carcinoma	'T' allele with peptic disease and H. pylori infection	No association
Korean population[30]	'T' allele in the development of gastric carcinoma	'C' allele enhanced the production of IL-1β by gastric mucosa	
African Americans and Caucasian[25]	No association	No association	'T' allele with multifocal atrophic gastritis
Turkish population[31]	'CC' and 'CT' genotype as an marker of Gastric Cancer		
Brazilian population[12]		'C' allele with chronic gastritis and gastric cancer	
Poles population (Poland)[26]			'T' allele with gastric disorders
Japanese population[28]		'C' allele with advanced atrophic gastritis	
Iranian population[8]			'TT' genotype with high risk of gastritis and peptic ulcer
Indian population (present study)	'TT' genotype with gastric ulcer	No association	No association

On comparison, rs16944 (–511 C/T) was found to be significantly associated with NSAID use in group 1 patients especially the 'CT' genotype. This may be due to the low sample size as there were only 11 cases who used NSAID in group 1 patients. It has been reported that, the use of aspirin may induce peptic ulcer as per a study carried out in Japanese Korean Ethnic group.[34] In a study carried out in Japanese population, rs1143627 (–31 C/T) and rs16944 (–511 C/T) were significantly associated with the development of peptic ulcer in cardiovascular diseases patients taking 100 mg of aspirin as well as those with *H. pylori* infection. However, the authors did not report any association in *H. pylori* negative patients suggesting *H. pylori* negative patients without past infection had no effect on development of aspirin related ulcer.[35] The information on which *IL-1β* gene polymorphisms are significant risk factors for the development of GU in individuals using NSAID are still lacking and need large-scale clinical studies. The current study has certain limitations like, lack of investigation of *H. pylori* in the study participants as *H. pylori* infection have a major impact on the GU, gastric cancer, peptic ulcer and gastritis.

Conclusion

The current study revealed the significant positive association of smoking, alcohol intake and NSAID use on the occurrences of GU. Secondly, the *IL-1β* gene polymorphisms found to have a minimal impact on the occurrence of GU in Indian patients that is, SNV rs1143627 (–31 'TT') genotype of *IL-1β* gene only was found to be associated with development of GU. Further, the possible effect of *IL-1β* gene polymorphisms on the occurrence GU was independent of other risk factors like smoking, alcohol intake, NSAID use etc. However, a large cohort study with *H. pylori* investigation, associated genetic polymorphisms and mRNA expression may be helpful for the better understanding of this genotype-phenotype relation in the study population.

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Declarations

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Author contributions

Conceptualization, S.A., P.P. and S.S.M.; Methodology, S.A., P.P. and S.S.M.; Validation, P.P. and S.S.M.; Formal Analysis, P.P.; Investigation, S.A. and P.P.; Resources, S.A., A.N. and P.P.; Data Curation, P.P.; Writing – Original Draft Preparation, S.A., A.N. and P.P.; Writing – Review & Editing, S.K.B., P.P. and S.S.M.; Supervision, P.P. and S.S.M.; Project Administration, S.S.M.; Funding Acquisition, S.A., P.P. and S.S.M.

Conflicts of interest

The authors declare no conflict of interest.

Data availability

Data will be available on request.

Ethics approval

This study was approved by the Institutional Ethical Committee (IEC) of M.K.C.G. Medical College, Berhampur, Odisha (No. 819 /Chairman-IEC, M.K.C.G. Medical College, Berhampur-4).

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