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Aldehyde dehydrogenase 2 gene rs671 G>A polymorphism is associated with an increased risk of digestive tract cancer

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Abstract

Objective: Acetaldehyde can accumulate in cells and form acetaldehyde-DNA adducts that result in digestive tract cancer development. Acetaldehyde dehydrogenase 2 (ALDH2) enzymatic activity is involved in this process. Here, we aimed to analyze the relationship between an *ALDH2* gene polymorphism and the digestive tract cancer risk in the Hakka population in China.

Methods: This was a retrospective study, with the *ALDH2* rs671 genotype and medical record information collected from all subjects. The relationships between these factors, including various blood cell parameters, and digestive tract cancer susceptibility were analyzed.

Results: Overall, 307 cancer patients and 317 controls were included. The cancer patients had significantly higher percentages with a history of smoking and drinking alcohol, as well as an increased platelet to lymphocyte ratio and lower lymphocyte to monocyte ratio, compared with the controls. The *ALDH2* rs671 genotype and allele distributions were significantly different between the cancer patients and controls. Logistic regression analysis showed that the *ALDH2* G/A genotype (G/A vs. G/G) and A/A genotype (A/A vs. G/G) in the co-dominant mode were risk factors for digestive tract cancer susceptibility.

Conclusions: *ALDH2* rs671 G/A or A/A genotype carriers may have an increased risk of developing digestive tract cancers among the Hakka people.

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Introduction

Digestive tract malignant tumors mainly include esophageal cancer, gastric cancer, and colorectal cancer, with gradually increasing incidence and mortality rates in recent years. The latest global cancer statistics show that the number of digestive tract malignant tumor cases has exceeded 3.6 million (18.7% of all new cancer cases), with more than 2.2 million deaths (22.6% of all cancer-related deaths).[1] In China, digestive tract malignant tumors accounted for 32.1% of all cancer-related deaths.[2] One study showed that accumulated acetaldehyde in cells can form acetaldehyde-DNA adducts, resulting in genetic abnormalities.[3] Genetic damage of this nature can promote cell decline and result in malignant tumor development.[4,5] In addition, reactive oxygen species (ROS) can lead to an increased amount of DNA mutations, while glutathione functions to scavenge ROS.[6] Acetaldehyde inhibits the antioxidant defense system and can therefore induce tumor formation by binding to glutathione.[7]

Acetaldehyde levels in humans are regulated by acetaldehyde dehydrogenase 2 (ALDH2).[8] The ALDH2 protein is localized in the mitochondria and is a member of the aldehyde dehydrogenase family of enzymes that catalyze acetaldehyde to non-toxic acetic acid during alcohol metabolism.[9] The level of ALDH2 activity in vivo is closely related to *ALDH2* gene polymorphisms.[10] *ALDH2* rs671 is the most studied polymorphism in *ALDH2*. This genetic variant results in glutamate (Glu) being replaced by Lysine (Lys) at position 504 of the protein amino acid sequence.

Because Glu504 is an important amino acid for cross-linked dimer formation, its replacement by Lys greatly affects enzyme activity.[11] Wild-type (WT) ALDH2*1/*1 (G corresponds to the *1 allele, A corresponds to the *2 allele) has normal catalytic activity, but the activity of the ALDH2 enzyme encoded by the *ALDH2* rs671 heterozygote was found to be significantly lower than that of WT ALDH2.[12] The ALDH2 protein encoded by the *ALDH2* rs671 homozygous variant has essentially no enzymatic activity. Interestingly, the frequency of the *ALDH2* rs671 homozygous variant genotype in Asians is up to 40%.[13]

A number of studies have reported that *ALDH2*2 allele carriers have an increased likelihood of developing certain cancers.[14–16] In moderate drinkers, *ALDH2*2 variants also had significant effects on digestive tract cancer development.[14,17] Overall, various studies have shown inconsistent results. In addition, compared with healthy individuals, cancer patient blood cell parameters, such as red blood cell, white blood cell, platelet, and hemoglobin levels, are significantly altered.[18,19] Cancer occurrence rates are related to racial differences, environmental factors, and lifestyle habits.[20,21] Therefore, it is of great significance to explore the clinical characteristics and genetic differences between cancer patients and healthy individuals. In China, the Hakka people have a unique genetic background that was formed by ancestors of the Han people in the central plains, who migrated southward and integrated with the residents of Southern China.[22] Until now, there has been no study focusing on

the relationship between *ALDH2* gene polymorphisms and digestive tract malignant tumors in this population. In the present study, we analyzed the association between *ALDH2* rs671 and digestive tract cancers within the Hakka population.

Materials and methods

Population samples

This was a retrospective study that used individual data collected from Meizhou People's Hospital, Guangdong, China, from January 2016 to November 2020. The reporting of this study conforms to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[23] The inclusion criteria for the study subjects were: (1) patients clinically diagnosed with at least one type of digestive tract cancer; (2) patients with relatively complete medical records; (3) age ≥18 years. Control subjects were persons aged ≥18 years who visited the physical examination center of Meizhou People's Hospital during the same period and did not develop a digestive system tumor. The subjects included in this study were continuous cases during this period. Information on age, sex, history of smoking, history of alcohol consumption, hypertension, and diabetes was collected from the Hospital Information System (HIS) of Meizhou People's Hospital.

All participants were informed of the study procedures and goals. Written informed consent was obtained from all participants. The study was performed under the guidance of the Declaration of Helsinki and approved by the Ethics Committee of Meizhou People's Hospital, Meizhou Academy of Medical Sciences (Clearance No. 2022-A-60). The details of all subjects were de-identified to protect their privacy. According to some cancer statistics, there are significant differences in cancer incidence and mortality rates between people >65 years and those ≤65 years

of age.[1,24,25] In this study, the subjects were therefore divided into two groups: ≤65 years old, and >65 years old.

Blood cell parameter detection

Blood samples were collected at admission and 2 to 3 days before treatment. Specifically, a 2-mL blood sample was taken via venipuncture of an antecubital vein from each subject and collected in a tube with ethylenediaminetetraacetic acid (EDTA) as an anticoagulant. Erythrocyte correlative indices were detected using a Sysmex XE-2100 blood analyzer (Sysmex Corporation, Kobe, Japan) according to the standard operating procedures (SOPs).

Blood cell parameters were determined before treatment, including neutrophil count, monocyte count, lymphocyte count, platelet count, platelet distribution width, red blood cell count, red blood cell distribution width, and mean hemoglobin concentration. The neutrophil count to lymphocyte count ratio (NLR), platelet count to lymphocyte count ratio (PLR), and lymphocyte count to monocyte count ratio (LMR) were then calculated.

DNA extraction and genotyping assay

An adsorption column method was used to extract genomic DNA from leukocytes using the TIANamp Blood DNA Kit (Tiangen, Beijing, China). A Nanodrop 2000™ Spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA) was used to determine DNA concentration and purity. Only high-quality DNA was used in further work. The *ALDH2* rs671 polymorphism was amplified by polymerase chain reaction (PCR) using the following cycling conditions: 94°C for 5 minutes, followed by 35 cycles of 94°C for 25 s, 56°C for 25 s, and 72°C for 25 s. PCR products were analyzed by microarray, and sample genotypes were determined by microarray

detection (BaiO Technology Co., Ltd., Shanghai, China).

Statistical analysis

Statistical analysis was performed using SPSS 21.0 software (IBM Corp., Armonk, NY, USA). The Student's t-test or Mann–Whitney U test was used to compare continuous variables, such as blood cell parameters. The Hardy–Weinberg equilibrium (HWE) values of *ALDH2* rs671 genotypes were assessed using the χ^2 test. The distribution of *ALDH2* rs671 genotypes and alleles between the disease group and control group was compared using the χ^2 test. The optimal cut-off value of each blood cell parameter for digestive tract cancer risk prediction was determined by receiver operating characteristic (ROC) curve analysis. The associations between *ALDH2* rs671 genotypes and other factors with digestive tract cancer susceptibility were evaluated using logistic regression analysis. A *P*-value <0.05 was considered statistically significant.

Results

Population characteristics

The study included 624 participants, with 317 controls and 307 patients with digestive tract cancer. Of the cancer patients, there were 180 with colorectal cancer (58.6%), 75 with gastric cancer (24.4%), 51 with esophageal cancer (16.6%), and 1 with gastric cancer combined with esophageal cancer (0.3%). The average age was 66.26 ± 12.61 years for the digestive tract cancer patients and 65.53 ± 13.03 years for the controls. Compared with the control group, the cancer patient group had significantly higher percentages of individuals with a history of smoking (28.3% vs. 17.0%, $P < 0.001$) and history of alcohol drinking (20.2% vs. 8.5%, $P < 0.001$), as well as a significantly higher monocyte count

$(0.59 \pm 0.30$ vs. $0.53 \pm 0.28 \times 10^9$ cells/L, $P = 0.009$), platelet count (257.19 ± 104.75 vs. $223.25 \pm 93.66 \times 10^9$ cells/L, $P < 0.001$), PLR (205.66 ± 145.34 vs. $156.14 \pm 103.22 \times 10^9$/L, $P < 0.001$), red blood cell distribution width (46.25 ± 7.40 vs. 44.34 ± 6.00 fL, $P < 0.001$), and mean hemoglobin concentration (323.98 ± 18.78 vs. 329.82 ± 14.43 g/L, $P < 0.001$). Additionally, the cancer patient group had a significantly lower lymphocyte count (1.55 ± 0.76 vs. $1.77 \pm 0.96 \times 10^9$ cells/L, $P = 0.002$), LMR (3.12 ± 2.09 vs. 4.04 ± 4.09, $P < 0.001$), and red blood cell count (4.24 ± 0.88 vs. $4.46 \pm 0.85 \times 10^{12}$ cells/L, $P = 0.002$) than the control group. There were no statistically significant differences observed for age, sex distribution, neutrophil count, or platelet distribution width (Table 1).

The optimal cut-off value of each blood cell parameter for digestive tract cancer risk prediction was determined by ROC analysis. With digestive tract cancer as the endpoint, the cut-off values were 3.690 for NLR, 2.155 for LMR, and 161.255 for PLR.

Genotype and allele frequencies of the ALDH2 gene

The *ALDH2* rs671 genotype distributions in the digestive tract cancer patients were consistent with HWE ($\chi^2 = 3.092$, $P = 0.079$). Similar results were found in the control group ($\chi^2 = 0.743$, $P = 0.389$). The proportions of WT, mutant heterozygous, and mutant homozygous *ALDH2* rs671 genotypes were 47.9%, 45.6%, and 6.5%, respectively, in the cancer patients and 60.9%, 35.3%, and 3.8%, respectively, in the controls. The genotype distribution differences between the two groups were statistically significant ($P = 0.003$). The G and A allele frequency distributions were significantly different between the patients and controls (70.7% and 29.3%, respectively, in the cancer patient group; 78.5% and 21.5%, respectively, in the control group)

Table1. Clinical characteristics of digestive tract cancer patients and controls.

Clinical characteristics	Total (n = 624)	Cases with digestive tract cancer (n = 307)	Controls (n = 317)	*P*-value
Age (years)				
≤65, n (%)	296 (47.4)	138 (45.0)	158 (49.8)	0.230
>65, n (%)	328 (52.6)	169 (55.0)	159 (50.2)	
Sex				
Male, n (%)	459 (73.6)	234 (76.2)	225 (71.0)	0.147
Female, n (%)	165 (26.4)	73 (23.8)	92 (29.0)	
History of smoking				
Never, n (%)	483 (77.4)	220 (71.7)	263 (83.0)	0.001*
Ever or Current, n (%)	141 (22.6)	87 (28.3)	54 (17.0)	
History of alcohol drinking				
Never, n (%)	535 (85.7)	245 (79.8)	290 (91.5)	<0.001*
Ever or Current, n (%)	89 (14.3)	62 (20.2)	27 (8.5)	
Type of digestive tract cancer				
Colorectal cancer, n (%)		180 (58.6)	–	
Gastric cancer, n (%)		75 (24.4)	–	
Esophageal cancer, n (%)		51 (16.6)	–	
Gastric cancer + Esophageal cancer, n (%)		1 (0.3)	–	
Neutrophil count, $\times 10^9$ cells/L	7.21 ± 4.28	6.90 ± 4.47	7.51 ± 4.07	0.076
Monocyte count, $\times 10^9$ cells/L	0.56 ± 0.29	0.59 ± 0.30	0.53 ± 0.28	0.009*
Lymphocyte count, $\times 10^9$ cells/L	1.66 ± 0.88	1.55 ± 0.76	1.77 ± 0.96	0.002*
Neutrophil to lymphocyte ratio (NLR)	5.79 ± 6.57	6.24 ± 8.47	5.36 ± 3.90	0.095
Lymphocyte to monocyte ratio (LMR)	3.59 ± 3.29	3.12 ± 2.09	4.04 ± 4.09	<0.001*
Platelet count, $\times 10^9$ cells/L	239.95 ± 100.63	257.19 ± 104.75	223.25 ± 93.66	<0.001*
Platelet to lymphocyte ratio (PLR)	180.50 ± 128.04	205.66 ± 145.34	156.14 ± 103.22	<0.001*
Platelet distribution width (fL)	11.50 ± 3.23	11.69 ± 3.21	11.32 ± 3.24	0.146
Red blood cell count, $\times 10^{12}$ cells/L	4.35 ± 0.87	4.24 ± 0.88	4.46 ± 0.85	0.002*
Red blood cell distribution width (fL)	45.28 ± 6.79	46.25 ± 7.40	44.34 ± 6.00	<0.001*
Mean hemoglobin concentration, g/L	326.94 ± 16.96	323.98 ± 18.78	329.82 ± 14.43	<0.001*

*indicates statistical significance (*P* < 0.05) for the difference between the digestive tract cancer patient group and control group. Ranges represent mean ± standard deviation.

(*P* = 0.001) (Table 2). There were no statistically significant differences in the *ALDH2* rs671 genotype and allele distributions between the patients with different types of digestive tract cancer (Table 3).

Clinical characteristics of digestive tract cancer patients stratified by ALDH2 variants

The laboratory test results of digestive tract cancer patients stratified by *ALDH2* variants were compared. The neutrophil counts of digestive tract cancer patients with G/G, G/A, and A/A genotypes were 6.27 ± 3.54, 7.21 ± 4.87, and 9.44 ± 6.42 ($\times 10^9$ cells/L), respectively, which had statistically significant differences (*P* = 0.006). The NLRs in digestive tract cancer patients with G/G, G/A, and A/A genotypes were 5.26 ± 4.61, 6.56 ± 10.03, and 11.31 ± 14.87, respectively, which also showed statistically significant differences (*P* = 0.009) (Table 4).

Table 2. Prevalence of *ALDH2* Glu504Lys (rs671) variants in digestive tract cancer patients and controls.

	Total (n (%))	Cases with digestive tract cancer (n (%))	Controls (n (%))	P-value
Genotype				
G/G	340 (54.5)	147 (47.9)	193 (60.9)	0.003*
G/A	252 (40.4)	140 (45.6)	112 (35.3)	
A/A	32 (5.1)	20 (6.5)	12 (3.8)	
G/G + G/A	592 (94.9)	287 (93.5)	305 (96.2)	
G/A + A/A	284 (45.5)	160 (52.1)	124 (39.1)	
Allele				
G	932 (74.7)	434 (70.7)	498 (78.5)	0.001*
A	316 (25.3)	180 (29.3)	136 (21.5)	

*indicates statistical significance ($P < 0.05$) for the differences in genotype and allele distributions between the digestive tract cancer patient group and control group.

Table 3. Prevalence of *ALDH2* rs671 variants in cases based on digestive tract cancer type.

	Colorectal cancer (n = 180) (n (%))	Gastric cancer (n = 75) (n (%))	Esophageal cancer (n = 52)* (n (%))	P-value[#]
Genotypes				
G/G	87 (48.3)	34 (45.3)	26 (50.0)	0.676
G/A	80 (44.4)	35 (46.7)	25 (48.1)	
A/A	13 (7.2)	6 (8.0)	1 (1.9)	
Allele				
G	254 (70.6)	103 (68.7)	77 (74.0)	0.644
A	106 (29.4)	47 (31.3)	27 (26.2)	

*, includes esophageal cancer patients and gastric cancer combined with esophageal cancer patients.
#, P-values represent the comparison of differences in genotype and allele distributions among patients with different types of digestive tract cancer.

Logistic regression analysis of risk factors associated with digestive tract cancer

The associations between the *ALDH2* rs671 genotypes and digestive tract cancer were studied using three genetic modes: co-dominant mode (G/A vs. G/G; A/A vs. G/G), dominant mode (G/A plus A/A vs. G/G), and recessive mode (A/A vs. G/G plus G/A). Logistic regression analyses were performed to determine the independent risk factors for digestive tract cancer. Multiple logistic regression analysis indicated that there was a significantly high risk of digestive tract cancer in the presence of alcohol drinking history (Present vs. Absent: odds ratio (OR) 2.966, 95% confidence interval (CI): 1.618–5.440, $P < 0.001$), low NLR (≤ 3.690 vs. > 3.690: OR 1.824, 95% CI: 1.228–2.709, $P = 0.003$), and high PLR (> 161.255 vs. ≤ 161.255: OR: 2.249, 95% CI: 1.538–3.287, $P < 0.001$). The *ALDH2* G/A genotype (G/A vs. G/G) (adjusted OR 1.839, 95% CI: 1.294–2.615, $P = 0.001$) and A/A genotype (A/A vs. G/G) (adjusted OR 2.229, 95% CI: 1.024–4.852, $P = 0.043$) in the co-dominant mode were significant risk factors for digestive tract cancer susceptibility. Additionally, the *ALDH2* G/A plus A/A genotypes (G/A plus A/A vs. G/G) (adjusted OR 1.878, 95% CI: 1.334–2.634, $P < 0.001$) in the

Table 4. Clinical characteristics of digestive tract cancer patients stratified by *ALDH2* variants.

Clinical characteristics	G/G (n = 147)	G/A (n = 140)	A/A (n = 20)	P-value
Age (years)				
≤65, n (%)	73 (49.7)	62 (44.3)	3 (15.0)	0.013*
>65, n (%)	74 (50.3)	78 (55.7)	17 (85.0)	
Sex				
Male, n (%)	111 (75.5)	112 (80.0)	11 (55.0)	0.052
Female, n (%)	36 (24.5)	28 (20.0)	9 (45.0)	
History of smoking				
Never, n (%)	101 (68.7)	104 (74.3)	15 (75.0)	0.552
Ever or Current, n (%)	46 (31.3)	36 (25.7)	5 (25.0)	
History of alcohol drinking				
Never, n (%)	102 (69.4)	125 (89.3)	18 (90.0)	<0.001*
Ever or Current, n (%)	45 (30.6)	15 (10.7)	2 (10.0)	
Neutrophil count, ×10^9 cells/L	6.27 ± 3.54	7.21 ± 4.87	9.44 ± 6.42	0.006*
Monocyte count, ×10^9 cells/L	0.58 ± 0.26	0.61 ± 0.34	0.59 ± 0.33	0.735
Lymphocyte count, ×10^9 cells/L	1.58 ± 0.85	1.56 ± 0.68	1.37 ± 0.55	0.540
Neutrophil to lymphocyte ratio (NLR)	5.26 ± 4.61	6.56 ± 10.03	11.31 ± 14.87	0.009*
Lymphocyte to monocyte ratio (LMR)	3.09 ± 1.80	3.17 ± 2.37	3.03 ± 2.04	0.929
Platelet count, ×10^9 cells/L	261.67 ± 114.11	251.34 ± 96.65	265.15 ± 88.47	0.665
Platelet to lymphocyte ratio (PLR)	208.74 ± 148.18	198.62 ± 145.23	232.26 ± 126.42	0.589
Platelet distribution width (fL)	11.70 ± 3.27	11.56 ± 3.23	12.45 ± 2.49	0.513
Red blood cell count, ×10^{12} cells/L	4.27 ± 0.84	4.25 ± 0.91	3.96 ± 0.93	0.331
Red blood cell distribution width (fL)	46.31 ± 7.65	46.15 ± 7.30	46.50 ± 6.52	0.972
Mean hemoglobin concentration, g/L	325.01 ± 19.52	323.89 ± 17.26	317.05 ± 22.67	0.206

*indicates statistical significance ($P < 0.05$) for the differences in clinical features between digestive tract cancer patients with different genotypes. Ranges represent mean ± standard deviation.

dominant mode was a significant risk factor for digestive tract cancer susceptibility (Table 5).

Discussion

The digestive tract has a high incidence of malignant tumor development. Digestive tract cancers are the majority of malignant tumor cases in China. Gastric cancer, colorectal cancer, and esophageal cancer are common gastrointestinal malignancies observed in Chinese individuals.[26] Increasing studies have found that cancer is a complex disease caused by interactions of genetic and environmental factors.[27,28] Significant regional and population differences can be seen in the incidence of certain cancers in China.[29,30] Therefore, it is of great clinical significance to explore the clinical characteristics and genetic differences between people with and without

cancer to help improve cancer prevention and screening methods.

Studies have shown that blood cell parameters show significant differences between cancer patients and individuals without cancer. An elevated NLR is a useful marker of tumor recurrence and can independently predict poorer disease-free and overall survival rates among patients with adenocarcinoma of the esophagogastric junction.[31] NLR is associated with metabolic tumor volume in esophageal squamous cell cancer patients,[32] and NLR and PLR are both associated with tumor progression in individuals with esophageal cancer.[33] Other studies have described relationships between hematological parameters and gastric cancer. Platelet count, mean platelet volume, red blood cell distribution width, NLR, and PLR are diagnostic markers of gastric cancer.[34] The lymphocyte-to-leukocyte ratio

Table 5. Logistic regression analysis of risk factors associated with digestive tract cancer.

Variables	Genotypes	Unadjusted values		Adjusted values	
		OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Age (>65/≤65 years)		1.217 (0.888–1.667)	0.221	1.266 (0.899–1.781)	0.177
Sex (Male/Female)		1.311 (0.917–1.874)	0.138	1.199 (0.804–1.787)	0.374
History of smoking (Yes/No)		1.926 (1.312–2.827)	0.001*	1.161 (0.711–1.896)	0.549
History of alcohol drinking (Yes/No)		2.718 (1.677–4.405)	<0.001*	2.966 (1.618–5.440)	<0.001*
Neutrophil to lymphocyte ratio (NLR) (≤3.690/>3.690)		1.128 (0.821–1.552)	0.457	1.824 (1.228–2.709)	0.003*
Lymphocyte to monocyte ratio (LMR) (≤2.155/>2.155)		1.351 (0.962–1.897)	0.083	1.266 (0.846–1.896)	0.251
Platelet to lymphocyte ratio (PLR) (>161.255/≤161.255)		1.965 (1.426–2.708)	<0.001*	2.249 (1.538–3.287)	<0.001*
Genetic model of *ALDH2* gene					
Co-dominant					
	G/G	1.000 (reference)			
	G/A	1.641 (1.182–2.279)	0.003*	1.839 (1.294–2.615)	0.001*
	A/A	2.188 (1.037–4.619)	0.040*	2.229 (1.024–4.852)	0.043*
Dominant					
	G/G	1.000 (reference)			
	G/A + A/A	1.694 (1.233–2.328)	0.001*	1.878 (1.334–2.634)	<0.001*
Recessive					
	G/G + G/A	1.000 (reference)			
	A/A	1.771 (0.850–3.689)	0.127	1.675 (0.783–3.580)	0.183

OR, odds ratio; CI, confidence interval.
*indicates statistical significance (P < 0.05).

and monocyte-to-leukocyte ratio are prognostic markers of gastric cancer.[35,36] NLR values were significantly increased in gastric cancer patients, suggesting that this parameter may be a predictive marker of gastric cancer.[37] High PLR values are associated with metastatic gastric cancer.[38] In addition, some reports have demonstrated relationships between hematological parameters and colorectal cancer. Th whole blood count can provide valuable information for the diagnosis and prognosis of colorectal cancer.[39] Red blood cell distribution width is a marker for predicting colorectal cancer occurence,[40] its metastasis,[41] and patient overall survival rates.[42] PLR, NLR, and lymphocyte-to-white blood cell ratio were prognostic markers in colorectal cancer patients who received neoadjuvant chemotherapy.[43] The ratio of mean platelet volume to platelet count was a marker for diagnosing colorectal cancer.[19] Overall, our work and previous studies have demonstrated that hematological indicators may be useful biomarkers for the diagnosis and prognosis of digestive tract malignant tumors.

In this study, the digestive tract cancer patients had significantly higher monocyte count, platelet count, PLR, red blood cell distribution width, and mean hemoglobin concentration values, as well as significantly lower lymphocyte count, LMR, and red blood cell count values compared with the control group. Additionally, logistic regression analysis indicated that there was a significantly increased risk of digestive tract

malignant tumor development with a high PLR. Our data suggest that PLR may be a potential diagnostic marker of digestive tract cancers. In addition, blood markers of inflammation, such as neutrophil count and NLR values, were higher in digestive tract cancer patients with the *ALDH2* SNP rs671 variant than in patients with WT *ALDH2*. One study found that the A allele in the *ALDH2* gene is associated with elevated plasma levels of high-sensitivity C-reactive protein (hs-CRP) after the onset of acute myocardial infarction (AMI).[44] ALDH2 can suppress oxidative stress-elicited DNA damage in gastric mucosa cells.[45] However, patterns of inflammatory indicators in the blood of patients with different *ALDH2* SNP rs671 genotypes have not been reported in other studies. Therefore, a prospective study with a larger sample size is needed to confirm our results.

Other work has reported that the *ALDH2* polymorphism is potentially associated with the susceptibility to some cancers. Previous studies on the correlations between *ALDH2* gene polymorphisms and cancer mainly focused on a single cancer type, with relatively few studies on the major cancers of the digestive tract. A meta-analysis showed that the *ALDH2* rs671 polymorphism is associated with overall cancer risk in Asians.[46] Alcohol consumption is associated with cancer of the upper digestive tract, with the *ALDH2* rs671 polymorphism increasing this risk.[47] *ALDH2* rs671 A allele carriers have an increased risk of developing multiple primary tumors in the upper digestive tract.[48] The *ALDH2* rs671 polymorphism was significantly associated with upper aerodigestive tract cancer in a Japanese population.[49] The results of this study show that subjects with the *ALDH2* rs671 G/A and A/A genotypes have an increased risk of digestive tract cancers. Our results here are consistent with those of the abovementioned studies.

In recent years, the biological functions of ALDH2 have attracted more attention from clinicians and researchers. The role and mechanism of ALDH2, as well as its related metabolites and their associated signaling pathways in tumor development, are gradually being clarified. Whether *ALDH2* gene variations can be used as diagnostic markers, prognostic markers, or therapeutic targets for related tumors remains to be further confirmed. In this study, we found that *ALDH2* rs671 A allele carriers have an increased risk of digestive tract cancers. However, this work does have some limitations. First, because this was a retrospective study, the medical records of some subjects may be incomplete, and other influencing factors that may be related to the occurrence of digestive tract cancer were not considered. Second, this work involved subjects from a healthcare facility, making selection bias inevitable. Third, this study did not analyze the clinical characteristics and prognosis of patients with digestive tract cancer and their relationships with *ALDH2* gene polymorphisms. Future studies should include a larger sample size and consider additional potential influencing factors.

Conclusion

ALDH2 rs671 A allele (G/A and/or A/A genotypes) carriers may have an increased risk of digestive tract cancers among the Hakka people in southern China. Our study is the first report on the relationship between an *ALDH2* polymorphism and the risk of gastrointestinal tumors in this population. Our work provides a valuable reference for the early screening and prevention of gastrointestinal tumors.

Author contributions

Data availability statement

Declaration of conflicting interests

Funding

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