

# Predictive Value of Clinical Toxicities to Chemotherapy with Fluoropyrimidines and Oxaliplatin in Colorectal Cancer by DPYD and GSTP1 Genes Polymorphisms

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## Research

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## Abstract

**Background:** Fluoropyrimidines and platinum are still widely used for colorectal cancer (CRC) management. Several studies have reported that mutations of dihydropyrimidine dehydrogenase (*DPYD*) and glutathione S-transferase pi-1 (*GSTP1*) polymorphisms are related to Chemotherapy-related adverse events. The present study was aimed to determine the role of *DPYD* and *GSTP1* variants on patient chemotherapy toxicity risk among the Hakka population, minimize adverse events and in order to maximize therapy outcome for individualized treatment.

**Methods:** Genotyping was examined in 104 patients diagnosed with CRC cases and receiving fluoropyrimidine and platinum drugs based chemotherapy regimen by direct sequencing of *DPYD* and *GSTP1* polymorphisms. Three *DPYD* variants including \*2A, \*5A, \*9A and *GSTP1* c.313A>G were analyzed and clinical outcomes were assessed.

**Results:** The data suggest that the incidence of *DPYD*\*5A, *DPYD*\*9A and *GSTP1* c.313A>G variants were 37.5%, 24% and 31.7%, respectively. *DPYD*\*2A variant was not found. A total of 38 patients (36.5%) suffered severe neutropenia and 23 patients (22.1%) suffered severe vomiting. *DPYD*\*5A polymorphism was found significantly associated with grade 3/4 ulceration ( $p = 0.001$ ). *GSTP1* was determined to be an independent risk factor for severe neutropenia and ulceration ( $p = 0.010$  and  $p = 0.034$ , respectively). Patients with *GSTP1* c.313A>G wild type contributed to higher risk for grade severe toxicity compared with A/G + G/G genotype ( $p = 0.024$ ). However, there was no significant difference between patients with *DPYD*\*9A T/T and T/C + C/C genotype for chemotherapeutic toxicity.

**Conclusions:** The results demonstrated that *DPYD*\*5A and *GSTP1* polymorphisms were useful predictors for severe events. Screening of single nucleotide polymorphisms of *DPYD* and *GSTP1* in colorectal cancer patients prior to chemotherapy may help to realize personalized therapy.

## Background

To date, malignant tumor has become responsible for the majority of global death, and its incidence has been increasing over recent decades. For both sexes combined, CRC is the second leading cause of cancer mortality in the world. CRC is the third most common cancer and the leading cause of cancer-related death in males and the second in female worldwide. Cancer is a major public health problem in China with increasing incidence and mortality. Among them, colorectal cancer is the fifth leading cause of cancer death in China and it is responsible for more than 191,000 death annually.

5-FU and capecitabine, an oral prodrug of 5-FU, are the backbone of therapeutic scheme for CRC and many other solid tumors either as a monotherapy or in combination with other chemotherapeutic drugs. Common combination regimens include FOLFOX [1]: (oxaliplatin combined with bolus/infusional 5-FU, and leucovorin); XELOX [2]: (capecitabine plus oxaliplatin); and FOLFIRI [3]: (fluorouracil, leucovorin, and irinotecan). Unfortunately, approximately from 10–30% of patients display varying degrees of adverse effects [4], most frequent manifestations include anemia, neutropenia, nausea, vomiting, diarrhea, and neurological toxicities, although clinical trials provided evidence of safety and efficacy of fluoropyrimidines. Various clinical studies revealed that dihydropyrimidine dehydrogenase (DPD), encoded by the *DPYD* gene, is the rate-limiting enzyme of pyrimidine catabolism and catabolizes more than 80% of the administered dose of fluoropyrimidines. Deficiency of the *DPYD* gene resulting in excess fluoropyrimidines accumulation in the blood, and increasing the risk of toxicity. A number of studies have reported that the polymorphism of the *DPYD* gene mutations results in a significantly decreased enzyme activity, such as well-known IVS14 + 1G > A (*DPYD*\*2A). The *DPYD* IVS14 + 1G > A alternate splicing in intron 14 resulting in the deletion of 55 amino acids and leading to the lack of normal DPD enzyme function. *DPYD* c.1627A > G (*DPYD*\*5A) and *DPYD* c.85T > C (*DPYD*\*9A) have been reported to be associated with low enzyme activity. The 85 T > C (*DPYD*\*9A) is the point mutation of T to C at the 85 position (codon 29) with an amino acid change from Cys to Arg, and *DPYD* 1627A > G substitution results in the *DPYD*\*5A allele due to the change in I543V. In different ethnic groups, *DPYD* genetic polymorphisms vary widely [5].

Glutathione-S-transferase P1 (*GSTP1*) is a rate-limiting enzyme which catalyzes the detoxification pathway of platinum drugs, for the purpose of cell protection. *GSTP1* Ile105Val (rs1695, A > G) is a missense mutation and affects the activity of *GSTP1* enzyme. Oxaliplatin-related cumulative peripheral neuropathy was reported to be more frequent and severe in patients with heterozygous (AG) genotype, when compared to patients with wild type allele (AA) [6]. Wiese et al. [7] draw a conclusion that *GSTP1* c.313A > G polymorphism was associated with overall survival of patients treated with oxaliplatin-based therapy. From the above, we

hypothesize that *DPYD* and *GSTP1* polymorphisms could be linked to acute toxicity in patients undergoing 5-FU and oxaliplatin-based chemotherapy.

The aim of our study was to board the possible relationship between *DPYD* and *GSTP1* genomic variations and adverse reactions with 5-FU and Oxaliplatin-based treatment in Meizhou Hakka population, southern China, a unique Han Chinese ethnic group having its own civilization [8]. We performed a systematic retrospective pharmacogenetics study in a cohort of 104 Meizhou Hakka CRC patients for the first time to explore the associations.

## Patients And Methods

### Population study and data collection

One hundred and four registered patients with histologically confirmed CRC who received adjuvant chemotherapy regimen containing 5-FU, capecitabine or oxaliplatin between September 2016 and December 2017 at the Meizhou People's Hospital were investigated in this retrospective study. Patients had to follow the lists for inclusion criteria such as: (1) histopathologically proven colorectal cancers in any stage; (2) aged over 18 years; (3) patients received neoadjuvant, palliative or adjuvant chemotherapy containing 5-FU, capecitabine or oxaliplatin in any line of treatment and received at least 2 courses for treatment; (4) any previous chemotherapy completed half a year ago, without any other adjuvant chemotherapy or radiotherapy; (5) life expectancy > 4 months; (6) adequate hematological, liver or kidney functions. Patients were excluded from enrollment as follows: (1) patients with concomitant neoplastic disease other than colorectal cancer; (2) any non-compliance of the inclusion criteria of above; (3) severe renal or hepatic disorder, severe hematological disease prior to treatment; (4) less than 6 months of previous treatment unless appear greater than grade 3 adverse events. Patients who disagree to sign an informed consent form were excluded from the research. Written informed consent was provided from each patient prior to any procedure of this study. All participants were then followed up 18 months to obtain their detailed clinical response information, and recorded in a medical history sheet. The study protocol was approved by the institution's review and Human Ethics Committees of the Meizhou Peoples' Hospital (Huangtang Hospital), and Meizhou Hospital Affiliated to Sun Yat-sen University, Guangdong Province, China.

Clinical characteristics distribution of 55 men and 49 women clinically diagnosed with colorectal cancer patients were enrolled in this study. The demographic and clinical pathological characteristics of the patients were evaluated as summarized in Table 1. The median age at diagnosis was 56 (range 25–78).

Table 1  
Demographic and Clinical Characteristics of Treated Patients

Characteristics	Overall patients, n (%)	≥Grade 3 AE	
		no, n (%)	yes, n (%)
Age (years)			
Range	25–78	40–74	25–78
Median	56	61.5	54
≤ 56	50(48.1)	7(35.0)	47(56.0)
≠56	54(51.9)	13(65.0)	37(44.0)
Gender			
Male	55(52.8)	18(90.0)	37(44.0)
Female	49(47.1)	2(20.0)	47(56.0)
Smoking status			
Smoker	8(7.6)	3(15.0)	5(6.0)
Non-smoker	96(92.3)	17(85.0)	79(94.0)
Alcohol intake			
Yes	4(3.8)	2(10.0)	2(10.0)
No	100(96.1)	18(90.0)	82(90.0)
Anatomic site			
Rectum	39(37.5)	10(50.0)	31(36.9)
Colon	65(62.5)	10(50.0)	53(63.1)
Histopathological Type			
Adenocarcinoma	104(100)	20(100)	84(100)
Squamous cell carcinoma	0(0)	0(0)	0(0)
Adenocarcinoma Histology			
Poorly differentiated	1(1)	0	1
Moderately differentiated	57(54.8)	11	46
Mucinous adenocarcinoma	3(2.9)	1	2
Undefined	43(41.3)	6	37
Grade of tumor			
I	0(0)	0	0
II	30(28.8)	6	24
III	46(44.2)	10	36
IV	28(27)	4	24
Clinical T-stage			
1	2(1.9)	0	2
2	3(2.9)	0	3

Characteristics	Overall patients, n (%)	≥Grade 3 AE	
		no, n (%)	yes, n (%)
3	65(62.5)	14	51
4	34(32.7)	6	28
Clinical N-stage			
0	33(31.7)	6	27
1	42(40.4)	8	34
2	28(26.9)	6	22
3	1(1)	0	1
Clinical M-stage			
0	76(73)	16	60
1	28(27)	4	24

## Genotyping

Genomic DNA from each enrolled patient was extracted from EDTA peripheral blood using the DNA Isolation Kit for Blood/Bone Marrow/Tissue (TIANGEN BIOTECH (BEIJING) CO., LTD) according to the manufacturer's protocol. DNA concentration and purity were evaluated using a NanoDrop2000 (Thermo Scientific). The primer sequences and the restriction enzymes used were provided by SINOMD GENE (BEIJING) CO., LTD. Genomic DNA was used for the cyclic condition consisted of initial denaturation at 95°C for 3 min, followed by 45 cycles of denaturation at 94°C for 15 s, annealing at 63°C for 1 min and extension at 72°C for 1 min. Final elongation at 72°C for 10 min. PCR products were purified with ExoSap-It (ABI PCR Product Cleanup Reagent). Single nucleotide polymorphisms were analyzed using ABI 3500 Dx Genetic Analyzer (ABI Terminator v3.1 Cycle Sequencing kit) and Sequencing Analysis v5.4 (Life Technologies, CA, USA). We looked for the following SNPs: *DPYD\*2A*, *DPYD\*5A*, *DPYD\*9A*, and *GSTP1*.

## Toxicity Grading and Statistical Analysis

All adverse drug reactions and toxicity experienced in the first 6 cycles of chemotherapy in each patient were monitored and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 (CTCAE). All quantitative variables such as age, gender, smoking, alcohol intake, tumor location, neoplasms histologic type, grade and stage of the tumor were analyzed. Toxicity including hematopoietic toxicity (anemia, leucopenia, neutropenia and thrombocytopenia), gastrointestinal toxicity (mucositis, vomiting and diarrhea) and dermatologic toxicity (ulceration and hand-foot syndrome) were grouped by four classes. Association between *DPYD* and *GSTP1* variants status with response and different toxicity was evaluated by Fisher's exact test. The Hardy-Weinberg equilibrium (HWE) of *DPYD* and *GSTP1* genotypes was assessed using the  $\chi^2$  test. A *p* value less than 0.05 was considered to be significant in all analyses. All tests were carried out by the Statistical Package for the Social Sciences software version 21.0 (SPSS, Chicago, USA)

## Results

### Histopathological type and clinical stage

As shown in Table 1, colon cancer was more predominant than rectum cancer (62.54 and 37.5%, respectively) about tumor location. All histopathological type was adenocarcinoma. Seventy-four (46.9%) patients were affected by stage III–IV tumors. According to the American Joint Committee on Cancer's (AJCC) Cancer Staging 6th edition 2002 TNM grading systems, there were 28.8% of stage II, 44.2% of stage III and 27% of stage IV about grade of tumor, but none of stage I.

## Chemotherapy toxicity

Toxicity of chemotherapy in the study participants is shown in Table 2. Treatment of fluoropyrimidine and platinum combination chemotherapy was made at the time of the first diagnosis of CRC. All patients received chemotherapy regimens for at least one cycle and were evaluated for adverse events outcome. Of the total 104 cases, 84 patients (80.8%) develop severe chemotherapy-related toxicities, including 11.5% suffered from anemia, 12.5% for leukopenia, 36.5% for neutropenia, 8.7% for thrombocytopenia, 7.7% for mucositis, 8.7% for diarrhea, 22.1% for vomiting, and 8.6% for dermatological toxicities.

Table 2  
Toxicity of chemotherapy in the study participants

Toxicities	Grade 0–2 n (%)	Grade 3–4 n (%)
Hematological toxicity		
Anemia	92(88.5)	12(11.5)
Leucopenia	91(87.5)	13(12.5)
Neutropenia	66(63.5)	38(36.5)
Thrombocytopenia	95(91.3)	9(8.7)
Gastrointestinal toxicity		
Mucositis	96(92.3)	8(7.7)
Vomiting	81(77.9)	23(22.1)
Diarrhea	95(91.3)	9(8.7)
Dermatology toxicity		
Ulceration	100(96.2)	4(3.8)
hand-foot skin reaction	99(95.2)	5(4.8)

## Dihydropyrimidine Dehydrogenase and Glutathione S-transferase pi-1 Genotypes

In our cohort all patients were genotyped for *DPYD\*2A*, *DPYD\*5A*, *DPYD\*9A* and *GSTP1* variants. The *DPYD* [IVS] 14 + 1G > A mutation was not identified in any of this study patients. In case of *DPYD\*5A* polymorphism, *DPYD* c.1627A > G was present in 32 (30.8%) patients in heterozygosis and in 7 (6.7%) in homozygosis. And there were 76% wild types and 24% heterozygote mutants with respect to *DPYD* c.85T > C. The results also show that distribution of *GSTP1* A/A, *GSTP1* A/G and *GSTP1* G/G was 68.3%, 28.8% and 2.9%, respectively (Table 3). Determined SNPs were found to be in Hardy-Weinberg Equilibrium.

Table 3  
DPYD and GSTP1 genes frequency in the study patients.

Gene	Genotypes	No. of patients	Percentage (%)
DPYD*2A	WT(GG)	104	100.0
	HET(GA)	0	0.0
	HOM(AA)	0	0.0
DPYD*5A	WT(AA)	65	62.5
	HET(AG)	32	30.8
	HOM(GG)	7	6.7
DPYD*9A	WT(TT)	79	76.0
	HET(TC)	25	24.0
	HOM(CC)	0	0.0
GSTP1	WT(AA)	71	68.3
	HET(AG)	30	28.8
	HOM(GG)	3	2.9
WT = Wild type. HET = Heterozygote. HOM = Homozygote.			

## Adverse events

The frequency of grade 0–2 and grade 3–4 toxicity in patients with *DPYD* and *GSTP1* wild type and mutant was shown in Table 4 and Table 5, respectively. Among patients screened for *DPYD* mutant (n = 54), 43 patients had *DPYD* c.1627A > G (*DPYD*\*5A) variant while *DPYD* c.85T > C (*DPYD*\*9A) variant was seen in 19 patients. Therein 8 patients had double heterozygous status for *DPYD*\*5A and *DPYD*\*9A variants. The most commonly experienced grade 3 or grade 4 toxicity in both *DPYD* wild type and mutant patients was neutropenia in hematological and vomiting in gastrointestinal toxicity. (Table 4) The same results were found in patients with *GSTP1* wild type and mutants. (Table 5)

Table 4  
The frequency of all grade toxicities in patients with *DPYD* wild type and mutants.

Toxicities	DPYD Wild Type (n = 50)		DPYD Mutant (n = 54)			
	G 0-2	G 3-4	DPYD*5A (n = 43*)		DPYD*9A (n = 19*)	
	G 0-2	G 3-4	G 0-2	G 3-4	G 0-2	G 3-4
Hematological toxicity						
Anemia	42(84)	8(16)	39(90.7)	4(9.3)	19(100)	0(0)
Leucopenia	44(88)	6(12)	39(90.7)	4(9.3)	15(78.9)	4(21.1)
Neutropenia	26(52)	24(48)	22(51.2)	21(48.8)	9(47.4)	10(52.6)
Thrombocytopenia	47(94)	3(6)	37(86)	6(14)	16(84.2)	3(15.8)
Gastrointestinal toxicity						
Mucositis	44(88)	6(12)	41(95.3)	2(4.7)	19(100)	0(0)
Vomiting	37(74)	13(26)	34(79.1)	9(20.9)	15(78.9)	4(21.1)
Diarrhea	43(86)	7(14)	40(93)	3(7)	17(89.5)	2(10.5)
Dermatology toxicity						
Ulceration	49(98)	1(2)	40(93)	3(7)	19(100)	0(0)
hand-foot skin reaction	48(96)	2(4)	38(88.4)	5(11.6)	19(100)	0(0)
Data are presented as n (%).						
*8 patients had double heterozygous status for DPYD*5A and DPYD*9A variants.						

Table 5  
The frequency of all grade toxicities in patients with *GSTP1* wild type and mutants.

Toxicities	GSTP1 Wild Type (n = 71)		GSTP1 Mutant (n = 33)	
	G 0-2	G 3-4	G 0-2	G 3-4
Hematological toxicity				
Anemia	64(90.1)	7(9.9)	28(84.9)	5(15.1)
Leucopenia	60(84.5)	11(15.5)	31(93.9)	2(6.1)
Neutropenia	34(47.9)	37(52.1)	19(57.6)	14(42.4)
Thrombocytopenia	65(91.5)	6(8.5)	30(90.9)	3(9.1)
Gastrointestinal toxicity				
Mucositis	64(90.1)	7(9.9)	32(97)	1(3)
Vomiting	57(80.3)	14(19.7)	22(66.7)	11(33.3)
Diarrhea	63(88.7)	8(11.3)	31(93.9)	2(6.1)
Dermatology toxicity				
Ulceration	70(98.6)	1(1.4)	30(90.9)	3(9.1)
hand-foot skin reaction	67(94.4)	4(5.6)	30(90.9)	3(9.1)
Data are presented as n (%).				

# Association between SNPs and toxicities

At least one of three toxicity groups (hematopoietic, gastrointestinal and dermatologic toxicity) was observed in all patients. We further examined the association between these SNPs and adverse event in all individuals. *DPYD\*5A* polymorphism was significantly associated with grade 3 and grade 4 5-FU and capecitabine related toxicity. This polymorphism is significantly associated with grade 3 and grade 4 ulceration when G/G genotype was compared to wild type ( $p = 0.001$ ) outline in Table 6. We did not find such a correlation between the mutant *DPYD* c.85T > C allele and 5-FU and capecitabine related toxicities, although there was a statistical trend for more anemia in the patients when carrying the mutant *DPYD\*9A* T/C genotype. The existence of the *GSTP1* c.313A > G polymorphism was associated with platinum related several toxicities such as neutropenia and ulceration. ( $p = 0.010$  and  $p = 0.034$ , respectively) We also found that patients with the AA genotype for *GSTP1* presented higher rates of neutropenia (81.6%) than patients with the AG and GG genotype (13.2% and 5.2%, respectively,  $p = 0.024$ ). In most of the cases, toxicity occurred after the first or second cycle of chemotherapy. Hand-foot syndrome and gastrointestinal toxicity were low grade and could not be demonstrated statistically significant association was observed with *DPYD* and *GSTP1* genotype in our study.

Table 6  
Association between polymorphisms of *DPYD* and *GSTP1* genes and toxicity of chemotherapy.

Genotype	Anemia			Neutropenia			Thrombocytopenia			Ulceration			
	Grade 0-2	Grade 3-4	P	Grade 0-2	Grade 3-4	P	Grade 0-2	Grade 3-4	P	Grade 0-2	Grade 3-4	P	
<i>DPYD*5A</i> (c.1627A > G)	WT	41	8	Ref.	28	21	Ref.	46	3	Ref.	48	1	Ref.
	HET	26	3	0.463	13	16	0.394	23	6	0.052	28	1	0.704
	HOM	5	1	0.983	5	1	0.216	6	0	0.533	4	2	<b>0.001</b>
	HET + HOM	31	4	0.527	18	17	0.604	29	6	0.107	32	3	0.166
<i>DPYD*9A</i> (c.85T > C)	WT	57	12	Ref.	40	29	Ref.	63	6	Ref.	65	4	Ref.
	HET	15	0	0.081	6	9	0.205	12	3	0.200	15	0	0.339
	HOM	0	0	-	0	0	-	0	0	-	0	0	-
	HET + HOM	15	0	0.081	6	9	0.205	12	6	0.200	15	0	0.339
<i>GSTP1</i> (c.313A > G)	WT	51	7	Ref.	27	31	Ref.	52	6	Ref.	57	1	Ref.
	HET	18	5	0.269	18	5	<b>0.010</b>	20	3	0.727	20	3	<b>0.034</b>
	HOM	3	0	0.522	1	2	0.654	3	0	0.557	3	0	0.819
	HET + HOM	21	5	0.386	19	7	<b>0.024</b>	23	3	0.870	23	3	0.051

## Discussion

Fluorouracil (FU) is the most common component of chemotherapy agents for malignant tumors like leukemia, lung, breast, gastric and colorectal cancers, majority followed three chemotherapy treatments including FOLFOX [9], XELOX and FOLFIRI, added to oxaliplatin or irinotecan in combination regimens [10]. Fluorouracil-Based treatment is generally well tolerated, except about 5–10% patient who suffers grade > 3 toxicity, which even impact on quality of life [11]. Intolerance of 5-FU is usually because of decreased activity of the fluoropyrimidines detoxifying enzyme dihydropyrimidine dehydrogenase (DPD) [12]. DPD is known to be the initial and rate-limiting enzyme catalyze degradation more than 85% of the given 5-FU. Activity levels vary caused by variable phenotypes and genetic alterations [13]. Single-nucleotide polymorphisms (SNPs) in its encoding gene *DPYD* is the most common cause of deficient in DPD enzyme activity [14]. Analyzing the impact of *DPYD* genotype in serum levels of 5-FU and correlative toxicity is vital to achieving good curative effect and prevent adverse events.

In this research, we looked for adverse events related to fluoropyrimidines and platinum drugs-based treatment and association with *DPYD* and *GSTP1* gene polymorphisms. Neutropenia and ulceration were the most chemotherapy related toxicity observed in our study.

The allelic variant (A > G) at position 1627 amino acid in exon 13 of *DPYD* gene results in an exchange of isoleucine to valine at codon 543 of *DPYD\*5A*. There is wide interethnic and inter geographical difference about gene polymorphism and frequency of *DPYD\*5A*. In our cohort the frequency of the mutation allele was 37.5%, which is apparently higher than that in African-Americans (22.7%) [15] and Caucasian subjects (28%) [16], and similar to that in Japanese (35%) [17]. Some early studies showed that the mutation may be linked to 5-FU toxicity. In our study a significant association was found between 1627A > G (*DPYD\*5A*) mutation and ulceration ( $p = 0.001$ ), strengthening its role as a toxicity predictive biomarker of chemotherapy drugs. The enzymatic activity of DPD is reduced with the A1627G polymorphism, resulted in patients with this polymorphism is more likely to undergo adverse reactions to 5-fu treatment, as showed in the above.

Dihydropyrimidine dehydrogenase gene (*DPYD*)\*9A genotype is regarded as one of the common *DPYD* variants. The prevalence of TT and TC genotype of *DPYD\*9A* in our enrolled patients was 76% and 24%, respectively, whereas the homozygous *DPYD\*9A* genotype was not found. Relationship about *DPYD\*9A* genotype and fluoropyrimidines-associated toxicity has been reported in previously studies. Khushman et al. [18] showed that *DPYD* c.T85C mutant variant was associated with diarrhea ( $p = 0.0055$ ). Joerger [19] reported that the correlation between *DPYD\*9A* genotype and DPD deficiency in clinical phenotype was noticeable in patients who experienced severe diarrhea. ( $p = 0.033$ ). However, several other studies showed no correlation. Maarten [20], Amirfallah [21] and McLeod et al. [22] revealed that *DPYD* heterozygous for 85T > C was not associated with a decreased risk for grade 3 to 4 toxicity. In our study cohort, we not found a statistically significant relationship between *DPYD\*9A* polymorphism and grade 3/4 toxicities, owing to the limited size of cohort in our study, and different allele frequency of these gene variants among different populations in different regions

As a part of the Phase II detoxification system, Glutathione S-transferase (GST) superfamily members detoxifies cisplatin by the formation of glutathione conjugates, conversion to less toxic and increases its excretion from the body, result in the detoxification [23]. It is important to note that polymorphisms in GSTs are linked to the occurrence and development of various tumors by way of altering biological pathways and affecting protein expression [24]. Genes encoding GSTs, including *GSTP1*, are classified into seven families and four main classes, contain lots of polymorphic loci, hypothesis that these polymorphisms could impact the ability to detoxify exogenous and endogenous toxic species. Extensive research has been carried out to revealed the 313A > G(*GSTP1*) mutation found in this study is the point mutation of A to G at the 313 position (codon 105) with an amino acid change from Ile to Val which results in decreases enzymatic activity, and highly linked for causing platinum treatment-related toxicity in different cancers.

In previous studies, Santric [25] reported a significant association between *GSTP1* Ile105Val polymorphism and oxaliplatin-related toxicity. Kudhair [26] analyzed allelic variations in *GSTP1* amongst 123 lung cancer patients and 129 controls in Arab populations showed the results suggest that smoking WP tobacco and carrying *GSTP1* c.313A > G polymorphisms are risk factors for lung cancer. Conversely, Sophonnithprasert [27] reported for no significant association between *GSTP1* Ile105Val polymorphism and oxaliplatin-induced toxicity. Our research showed *GSTP1* c.313A > G polymorphism was linked to acute toxicity in colorectal cancer patients undergoing neutropenia and ulceration. We also found that those participants having heterozygotes and homozygotes genotype showed a lower risk of high grade severe toxicity compared to the wild type of *GSTP1*, in line with the study of Mir reported [28]. According to the research of Watson suggested that GST enzyme activities were significantly reduced among individuals with Val-containing [29]. Ambrosone et al. [30] found that in a patient decrease in activity of GST enzymes may have a serious impact on disease recurrence as hepatic carcinoma and breast cancer. In addition, lower activity toward chemotherapy drug tolerance [31], which conflicting with our results. Different by tumor types and chemotherapy regimens in the above studies. This may lead to different results between our findings and those of other clinical studies. There are some limitations to our study. First, the present study is mainly limited by its small sample size. Second, we did not investigate other SNPs of GST associated with oxaliplatin related toxicities. The third limitation of this study is that we focus on only three out of more than 30000 variants reported *DPYD* variants [32]. Moreover, there is a difference of chemotherapy regimens. Future analysis will enroll larger cohort and reveal the potential associations between more mutations combinations of *DPYD* and GST variants and severe toxicities.

## Conclusions

In brief, ulceration and neutropenia were the major dose-limiting toxicity of fluoropyrimidine and platinum based regimen in our study cohort. A significant association was observed between *DPYD\*5A* and *GSTP1* polymorphisms and toxicity like neutropenia and ulceration strengthening *DPYD* and *GSTP1* polymorphisms as predictors of severe events. Screening of genetic polymorphisms of *DPYD* and *GSTP1* in colorectal cancer patients prior to chemotherapy could contribute to effectively decrease the occurrence of serious adverse toxicity, improve the predictive specificity for severe event. We indicate that detection of *DPYD* and *GSTP1* phenotypes may become a routine laboratory test item. This may enable clinicians to implement the optimal therapeutic schedule to achieve satisfactory efficacy and minimize toxic and side effects, and then, lead to a personalized therapy. Further studies should focus on validating results in a larger sample size, ascertain of possible interactions between more other *DPYD* and *GST* polymorphisms and clinical outcome.

## List Of Abbreviations

CRC: colorectal cancer; *DPYD*: dihydropyrimidine dehydrogenase; *GSTP1*: glutathione S-transferase pi-1; SNP: single-nucleotide polymorphisms

## Declarations

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## Author Contributions

Xunwei Deng performed data collection, analyzed the data, interpretation of the results and wrote this paper. All of the authors designed this study, and gave final approval of the submitted version.

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## Availability of data and materials

Not applicable

## Ethics approval and consent to participate

The study protocol was approved by the institution's review and Human Ethics Committees of the Meizhou Peoples' Hospital (Huangtang Hospital), and Meizhou Hospital Affiliated to Sun Yat-sen University, Guangdong Province, China.

## Consent for publication

Not applicable

## Competing interests

The authors declare that they have no conflict of interest.

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