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Research Paper

Predictive Value of UGT1A1*28 Polymorphism In Irinotecan-based Chemotherapy

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Abstract

The UGT1A1*28 polymorphism was suggested to be significantly connected with irinotecan-induced toxicity and response to chemotherapy. However, the results of previous studies are controversial. Hence we carried out a meta-analysis to investigate the effect of UGT1A1*28 polymorphism on severe diarrhea, neutropenia, and response of patients who had undergone irinotecan-based chemotherapy. The PubMed, Web of Science, Wanfang, and CNKI databases were searched for clinical trials assessing the association of UGT1A1*28 polymorphism with severe diarrhea, neutropenia, and response to irinotecan-based chemotherapy. The combined odds ratios (ORs) and 95% confidence intervals (CIs) were used to evaluate the relationship under a fixed- or random-effects model. Fifty-eight studies including 6087 patients with cancer were included. Our results showed that patients carrying the TA6/7 and TA7/7 genotypes had a greater prevalence of diarrhea and neutropenia than those with the TA6/6 genotype (TA6/7+TA7/7 vs. TA6/6: diarrhea, OR = 2.18, 95%CI = 1.68-2.83; neutropenia, OR = 2.15, 95%CI = 1.71-2.70), particularly patients with metastatic colorectal cancer. Stratified analysis showed that Asians with the TA6/7 and TA7/7 genotypes were more likely to have diarrhea and neutropenia, and Caucasians with the TA6/7 and TA7/7 genotypes were more likely to have neutropenia than other groups. However, patients with the TA6/7+TA7/7 genotypes showed a higher response than patients with TA6/6 genotype (OR = 1.20, 95%CI = 1.07–1.34), particularly Caucasians (OR = 1.23, 95%CI = 1.06–1.42) and patients with metastatic colorectal cancer (OR = 1.24, 95%CI = 1.05–1.48). Our data showed that the UGT1A1*28 polymorphism had a significant relationship with toxicity and response to irinotecan-based chemotherapy. This polymorphism may be useful as a monitoring index for cancer patients receiving irinotecan-based chemotherapy.

Key words: UGT1A1*28, diarrhea, neutropenia, response.

Introduction

According to the estimation, there are probably 1,658,370 people suffer from cancer and 589,430 people die of cancer in the United States in 2015[1]. In China, the corresponding data were 4,292,000 and 2,814,000 in 2015, respectively, which means cancer is an urgent problem to be solved [2]. Several methods such as surgery, radiotherapy, and chemotherapy are widely applied for the clinical treatment of cancer. Irinotecan-based chemotherapy is one of the most used chemotherapies for patients with advanced gastric cancer, ovarian cancer, metastatic colorectal cancer, and other cancers [3-5]. Irinotecan, a

camptothecin derivative, is mainly transported into liver by solute carriers and metabolized into ametabolite, SN-38, by a carboxylesterase [6]. In turn, SN-38 is glucuronidated by uridinediphosphate (UDP)-glucuronosyltransferases (UGTs) to an inactive form, SN-38G. Lower glucuronidation rates lead to higher SN-38 concentrations, resulting in irinotecan-induced severe toxicity [7]. Diarrhea and neutropenia are the most common side effects of irinotecan-based chemotherapy, limiting its application [8]. Recent studies have confirmed thatUDP UGT 1A1 play a vital role in the process of glucuronidation [9, 10].

The UGT1A1*28 polymorphism contains an extra TA repeat in the 5′-promoter region, whose mutant genotype is $A(TA)_7TAA$ (TA7/7) and has a wide genotype of $A(TA)_6TAA$ (TA6/6). Toffoli et al.[11] found that UGT1A1*28 TA7/TA7 genotype is related to a lower glucuronidation ratio. Previous studies investigated the relationship of UGT1A1*28 with neutropenia and diarrhea and have shown conflicting results. TA6/6 was reported to be a main predictive factor for diarrhea in a study of 56 advanced colorectal carcinoma (CRC) [12]. In contrast, some studies found that patients with the TA6/7 or TA7/7 genotypes are more inclined to suffer severe neutropenia and diarrhea [13-16]. However, no correlation was defined between the UGT1A1*28 polymorphism and neutropenia according to data from Hirata et al.[17] and Ferraldeschi et al.[18].

To clarify the predictive value of the UGT1A1*28 polymorphism in patients receiving irinotecan-based chemotherapy, we conducted this study to investigate the impact of the UGT1A1*28 polymorphism on tumor response and the common toxicities, diarrhea and neutropenia.

Materials and methods

Publication Search

Studies were selected by retrieving the Web of Science, PubMed, CNKI, and WanFang databases, up to June 2016. Similar keywords were used in different databases: “UGT1A1*28” and “diarrhea,” “UGT1A1*28” and “neutropenia,” “UGT1A1*28” and “response,” “UGT1A1*28” and “irinotecan,” “UGT1A1*28” and “CPT-11,” and related terms. No language restrictions were applied. All qualified studies were searched and a cross search was also used to identify the remaining relevant studies. When overlapping data exist in different reports, the most complete article was included. Disagreements between two authors will be settled by discussion and consensus.

Selection Criteria

Studies were included if they fulfilled the following criteria: (a) clinical trials; (b) evaluated the association of the UGT1A1*28 polymorphism with irinotecan-induced toxicities and chemotherapeutic effect; and (c) contained key information about the number of patients who have severe diarrhea, neutropenia and response to chemotherapy or not. Duplicate studies, review articles, letters, non-original studies, or case reports were excluded.

Data Extraction

Detailed information of included studies had been extracted and recorded in a standardized table by two reviewers. The following information was recorded: first author’s surname, year of publication, ethnicity, cancer subtype, methods of mutation detection, number of patients with and without response, severe diarrhea and neutropenia, genotypes were extracted. If these data were not reported, items were marked “NR” (not reported).

Data Synthesis

This meta-analysis was conducted according to the PRISMA guidelines [19]. We used the Newcastle-Ottawa-Scale (NOS) to assess the qualities of including studies and calculated the combined odd ratios (ORs) and 95% confidence intervals (CIs) to evaluate the strength of relationship between the UGT1A1*28 polymorphism and irinotecan-induced diarrhea or neutropenia under the four models (TA6/7 vs. TA6/6, TA7/7 vs. TA6/6, TA6/7+TA7/7 vs. TA6/6, and TA7/7 vs. TA6/6+TA6/7) [20]. The association between tumor response and the UGT1A1*28 polymorphism was calculated only in the dominant model (TA6/7+TA7/7 vs. TA6/6). Pooled ORs were tested by the Z test, and a P value <0.05 was considered significant. Chi-square test and Q test were used to examine the heterogeneity among the studies. We also performed stratified analysis depending on tumor types (advanced gastric cancer, metastatic non-small cell lung cancer, metastatic colorectal cancer, or others), ethnicity (Asian, Caucasian or mixed people) and study design (retrospective or prospective study). Publication bias were determined by Egger’s and Begg’s tests [21, 22]. Specific methods are described in our pervious study [23]. A trim and fill method of adjusting for publication bias was carried out when the P value of Egger’s test was less than 0.05 [24]. Trial sequential analysis (TSA) was conducted to calculate the required sample size to get a robust conclusion [20]. When P values of two-sided comparisons were less than 0.05, we considered the difference was significant. We performed all the statistical

calculations by STATA 12.0 (StataCorp LP, College Station, TX, USA).

Results

Characteristics of the Studies Included

As shown in Figure 1, we performed the primary literature retrieval using the PubMed, Web of Science, Wanfang, and CNKI databases by the end of June 2016. First, 307 articles were included and 119 articles were excluded after searching for duplicates. Second, we read the titles and abstracts and excluded 78 articles because they were letters, case reports, reviews or reporting about other polymorphisms. Finally, after reading the full-text of all articles, 53 articles were excluded due to lacking of useful data or evaluation about other toxicities and 58 studies from 57 articles including 6087 patients with cancer were found to meet the inclusion criteria.

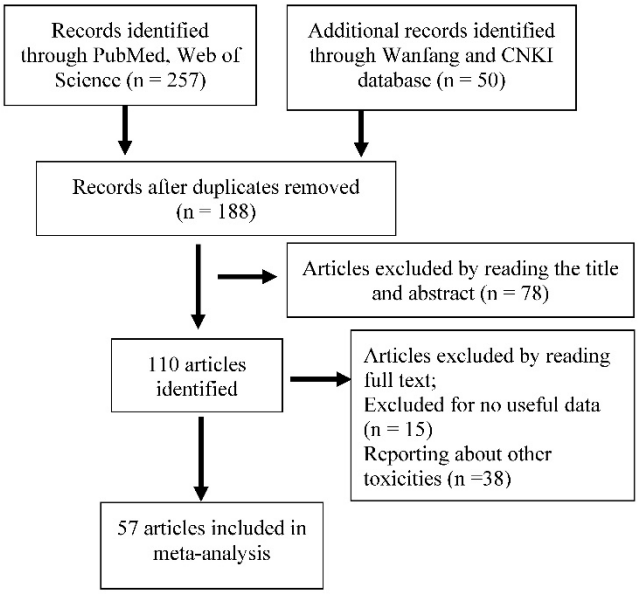

Figure 1. Flow diagram of included studies for the meta-analysis. CNKI = China National Knowledge Infrastructure

Among these studies, 16 studies investigated the associations in Caucasians [11-15, 18, 25-35], 40 in Asians [3, 9, 16, 17, 36-62], and two in mixed population or not reported [63, 64]. All studies were retrospective or prospective studies, including 29 metastatic colorectal cancer (mCRC) studies, five metastatic non-small cell lung cancer (mNSCLC), three advanced gastric cancer (GC) studies, two SCLC studies, and two advanced esophageal cancer studies and others. Table 1 summarized the basic information of the included studies.

Meta-Analysis of UGT1A1*28 Polymorphism and Severe Diarrhea

There were 44 studies of 4868 patients to evaluate the relationships between the UGT1A1*28 polymorphism and irinotecan-induced severe diarrhea. As shown in Table 2 and Figure 2, we found the UGT1A1*28 polymorphism was significantly related to severe diarrhea risk under all comparisons (TA 6/7 vs. TA6/6: OR = 1.56, 95%CI = 1.25-1.96; TA7/7 vs. TA6/6: OR = 3.97, 95%CI = 1.88-8.38; TA 7/7 vs. TA6/7+TA6/6: OR = 3.64, 95%CI = 2.01-6.58), regardless of the study design. By performing the subgroup analysis, we confirmed the relationship in the Asian group (TA6/7 vs. TA6/6: OR = 1.85, 95%CI = 1.37–2.50, P<0.001; TA7/7 vs. TA6/6: OR = 8.98, 95% CI = 5.21–15.47, P<0.001; TA6/7+TA7/7 vs. TA6/6: OR = 2.74, 95%CI = 2.21–3.40, P<0.001; TA 7/7 vs. TA6/6+TA6/7: OR = 8.64, 95%CI = 4.14–18.04, P<0.001) and in Caucasians (TA7/7 vs. TA6/6+TA6/7: OR = 1.62, 95%CI = 1.03–2.53). Stratified analysis according to cancer type was also carried out in this study. Individuals with mCRC carrying the TA7/7 or TA6/7 genotypes had a higher risk of getting diarrhea after irinotecan-based chemotherapy compared with the TA6/6 genotype (TA6/7 vs. TA6/6: OR = 1.60, 95%CI = 1.11–2.31, P = 0.011; TA7/7 vs. TA6/6: OR = 3.53, 95%CI = 1.54–8.09, P = 0.003). The same risk was also seen in SCLC patients (TA6/7+TA7/7 vs. TA6/6: OR = 3.95, 95%CI = 1.42–11.01, P = 0.009; TA7/7 vs. TA6/6+TA6/7: OR = 19.90, 95%CI = 2.57–154.1, P = 0.004).

Meta-Analysis of UGT1A1*28 Polymorphism and Severe Neutropenia

The relationships of the UGT1A1*28 polymorphism with irinotecan-induced severe neutropenia risk were investigated in 49 studies of 5232 patients. The UGT1A1*28 polymorphism was significantly related to an increased severe neutropenia incidence (Table 3 and Figure 3, TA 6/7 vs. TA6/6: OR = 1.71, 95%CI = 1.41-2.08; TA7/7 vs. TA6/6: OR = 5.34, 95%CI = 3.05-9.33; TA 7/7 vs. TA6/7+TA6/6: OR = 4.12, 95%CI = 2.36-7.20). Caucasians and Asians with at least one TA7 allele had a higher risk of neutropenia (Caucasians: TA6/7 or TA7/7 vs. TA6/6: OR = 1.84 and 5.67; Asians: TA6/7 or TA7/7 vs. TA6/6: OR = 1.56 and 4.77). In the analysis stratified by cancer type and study design, an association was also found in retrospective and prospective designs, with mCRC patients having the TA7/7 and TA6/7 genotypes (TA6/7 or TA7/7 vs. TA6/6: OR = 1.76 and 5.07) and solid tumor patients with the TA7/7 genotype (TA7/7 vs. TA6/6 or TA6/6+6/7: OR = 7.66 and 6.68).

Table 1. Characteristics of the Studies Included in the Meta-Analysis

Study	Year	Study design	Race	Cancer	Mutation detection methods	Regimen	IRI dose (mg/m2)/schedule	Population source	No. of patients	Age	ECOG	NOS
Yan[8]	2016	R	Asian	mixed tumors	PCR-Sanger sequence	FOLFIRI, IRI + CDDP, IRI + BEV	125, 150 or 180 mg/m2	S	157	53	NR	8
Xu[64]	2016	R	Asian	mCRC	Direct Sequencing	FOLFIRI, IRI+CAP	150mg/m2, every 2 or 3 weeks	S	183	NR	0-1	9
Gui[65]	2016	R	Asian	mCRC	SPR	FOLFIRI, IFL	180mg/m2, every 2 or 3 weeks	S	384	NR	0-2	8
Wang[5]	2016	P	Asian	Advanced GC	SPR	IRI+CDDP	80 or 125mg/m2	S	40	54	0-2	8
Li[4]	2016	P	Asian	mCRC	SPR	FOLFIRI, mCapeIRI, IRI	NR	M	160	50	0-2	9
Yang[63]	2015	R	Asian	pancreatic or biliary tract cancer	Direct Sequencing	FOLFIRI, IRI alone	180mg/m2, biweekly	S	48	56.2	0-1	7
Peng[60]	2015	P	Asian	mCRC	Sequencing	FOLFIRI; mFOLFIRI	180mg/m2, biweekly	S	208	59.8	0-3	7
Wu[59]	2015	P	Asian	Advanced esophageal cancer	NR	IRI+PLA	180mg/m2, every 3weeks	S	42	55	0-2	7
Xu[3]	2015	NR	Asian	advanced OC	PYRS	IRI+CDDP	60mg/m2 IRI (d1, 8) every 3 weeks	S	89	48	NR	7
Xiao[9]	2015	R	Asian	SCLC	PYRS	IRI+CDDP/CBP/LOB	60 mg/m2 (d1,8,15), every 4 weeks; 85mg/m2 (d1,8), every 3 weeks	S	67	NR	0-2	8
Shi[61]	2015	P	Asian	SCLC	Direct Sequencing	IRI+CDDP	65mg/m2 (d1, 8)	M	30	59	0-2	8
Atasilp[10]	2015	R	Asian	mCRC	PYRS	FOLFIRI, FOLFIRI+CET, FOLFIRI+BEV, mFOLFIRI, IRI alone, IRI+CET/CAP	180mg/m2, biweekly; 100mg/m2	S	44	6	0-2	7
Chen[62]	2015	P	Asian	mNSCLC	Sequencing	IRI+DDP	100mg/m2, every 3 weeks	S	86	63	0-2	8
Wang[35]	2015	P	Asian	mCRC	Sequencing	NR	NR	S	111	NR	0-1	7
Li[54]	2014	R	Asian	mCRC	PYRS	FOLFIRI, IRI + CET/BEV, IRI + RAL, IRI+ CAP	180 mg/m2, every 2 or 3 weeks	S	167	50	0-2	8
Hirata[17]	2014	P	Asian	mCRC	SPR	FOLFIRI	150mg/m2, biweekly	M	34	62	0-2	7
Zhao[55]	2014	P	Asian	SCLC	Direct sequencing	IRI+CDDP	60mg/m2 (d1,8,15), every 3 weeks	S	34	49	0-2	8
Song[56]	2014	P	Asian	Advanced OC	NR	IRI+PLA	60mg/m2 (d1,8), every 3 weeks	S	89	48	NR	8
Zhang[57]	2014	P	Asian	mCRC	Sequencing	FOLFIRI, XELIRI, IRIR	180mg/m2, biweekly; 200mg/m2, every 3weeks	S	102	55	NR	8
Xu[53]	2014	P	Asian	GC	Sequencing	NR	NR	S	67	62.7	0-2	8
Zhou[58]	2014	P	Asian	mCRC	SPR	IRI+5-FU/TMZ/CAP	180mg/m2	S	82	59	NR	8
Zhou[52]	2013	P	Asian	gastrointestinal cancer	Direct Sequencing	FOLFIRI	180mg/m2, biweekly	S	94	58.5	0-1	8
Hirasawa[50]	2013	R	Asian	cervical or ovarian cancer	Invader assay	IRI+CDDP, IRI alone	60 or 100mg/m2 (d1, 8, 15), every 4 weeks	S	53	48	NR	7
Gao[48]	2013	R	Asian	mCRC	Sanger Sequencing	FOLFIRI, IRI alone or IRI+CET/CAP	180mg/m2	S	276	55	NR	7
Gao[49]	2013	R	Asian	advanced GC	Sanger Sequencing	IRI+CDDP, FOLFIRI, IRI alone, IRI+CET	180mg/m2	S	42	53	NR	7
Gao[49]	2013	R	Asian	advanced esophageal cancer	Sanger Sequencing	IRI+CDDP, FOLFIRI, IRI alone, IRI+CET	130mg/m2; 180mg/m2	S	91	54	NR	7
Qin[51]	2013	R	Asian	advanced gastrointestinal carcinoma	Sequencing	IRI, IRI+CDDP, IRI+5-FU	NR	S	183	NR	NR	7
Wang[45]	2012	NR	Asian	mCRC	Direct Sequencing	FOLFIRI, IRI+LEU	180mg/m2, biweekly; 125mg/m2 (d1, 8, 15, 22), every 6 weeks	S	130	52	0-2	7
Zhang[46]	2012	P	Asian	mCRC	Direct Sequencing	FOLFIRI, IRI+LEU	180mg/m2, biweekly; 125mg/m2 (d1, 8, 15, 22), every 6 weeks	S	56	55.5	NR	8
Lamas[34]	2012	R	Caucasian	mCRC	Fluorescent DNA length fragment analysis	FOLFIRI, FOLFIRI-CET, FOLFIRI-BEV, IRI+CET	180mg/m2, biweekly	S	101	67	0-2	7
Wang[47]	2012	P	Asian	mCRC	Sequencing	IFL, FOLFIRI	125mg/m2, weekly;180mg/m2,biweekly	S	180	54	0-2	7
Shulman[33]	2011	R	Caucasian	mCRC	SPR	FOLFIRI, IFL, TEGAFIRI, XELIRI	U	M	214	63.1	NR	8
Okuyama[43]	2011	P	Asian	mCRC	SPR	FOLFIRI	150mg/m2	S	39	64	0-2	7
Nakamura[42]	2011	P	Asian	mNSCLC	Polyacrylamide gel electrophoresis	IRI+PAC, IRI+GEM	50mg/m2 (d1, 8 and 15), every 4 weeks; 100mg/m2 (d1 and 8), every 3 weeks	S	77	NR	0-1	8
Park[44]	2011	P	Asian	mGC	Sequencing	S-1+IRI+OXA	150mg/m2, every 3 weeks	S	44	54	0-2	7
Mcleod[32]	2010	P	Caucasian	mCRC	PYRS	IRI+FU+LEU, IRI+OXA	100-125mg/m2 (d1, 8, 15 and 22), every 6 weeks; 200mg/m2, every 3 weeks	M	212	61	0-2	8
Ji[41]	2010	R	Asian	mCRC	Sequencing	FOLFIRI	180mg/m2, biweekly	S	64	NR	0-2	7

Balibrea[31]	2010	P	Caucasian	mCRC	Sequencing	IRI+ 5-FU, IRI+5FU/LV	80mg/m2, weekly; 180mg/m2, biweekly	M	149	NR	0-2	8
Han[39]	2009	P	Asian	mNSCLC	SBE	IRI+CDDP	65 or 80mg/m^2 (d1 and 8), every 3 weeks	S	107	58	0-2	7
Onoue[40]	2009	P	Asian	Mixed tumors	Direct Sequencing	IRI alone; IRI+plat; IRI+ other anticancer agents, FOLFIRI	60-100mg/m2	S	133	NR	0-1	7
Ferraldeschi[18]	2009	P	Mixed	mCRC	SPR	IRI, FOLFIRI, IRI+VEGF inhibitor	350mg/m2, every 3 weeks; 180mg/m2, biweekly	S	92	62.9	NR	8
Rouits[29]	2008	R	Caucasian	mCRC	PYRS	FOLFIRI	180mg/m2, biweekly	S	44	60	0-2	8
Parodi[28]	2008	P	Caucasian	mCRC	SPR	FOLFIRI, mIFL, CapeIRI	125 or 180mg/m2, biweekly; 250mg/m2, every 3 weeks	M	110	NR	0-2	8
Liu[16]	2008	R	Asian	mCRC	SPR	FOLFIRI	180mg/m2, biweekly	S	128	NR	0-2	8
Kweekel[15]	2008	R	Caucasian	mCRC	PYRS	IRI+CAP+OAX	250 or 350mg/m2 (d1), every 3 weeks	M	218	NR	0-2	8
Wang[38]	2007	P	Asian	mCRC	SPR	FOLFIRI	180mg/m2, biweekly	M	70	NR	0-3	8
Ruzzo[30]	2007	P	Caucasian	mCRC	SPR	FOLFIRI	180mg/m2, biweekly	M	146	61	NR	7
Jada[37]	2007	NR	Asian	Mixed tumors	SPR	IRI	375 mg/m2, every 3 weeks	S	45	55	0-2	7
Cote[14]	2007	P	Caucasian	stage III colon cancer	SPR	LV5FU2+IRI	180 mg/m2 (d1), every 2 weeks	M	89	NR	NR	8
Toffoli[11]	2006	P	Caucasian	mCRC	PYRS	mFOLFIRI or FOLFIRI	180mg/m2 (d1), every 2 weeks	M	250	60.6	0-2	8
Massacesi[12]	2005	P	Caucasian	mCRC	Sequencing	IRI+RAL	80 weekly (d1, 8, 15 and 22), every 5 weeks	M	56	64	0-2	7
Jong[13]	2006	P	Caucasian	Mixed tumors	SPR	IR+NEO	350mg/m2, every 3 weeks	M	52	58	0-2	8
Han[36]	2006	P	Asian	mNSCLC	Direct Sequencing	IRI+CDDP	80mg/m2 (d1 and 8), every 3 weeks	S	81	NR	0-2	8
Rouits[27]	2004	R	Caucasian	mCRC	PYRS	IRIFUFOL, FOLFIRI	85mg/m2, weekly; 180mg/m2, biweekly	S	73	62	0-2	8
Marcuello[26]	2004	P	Caucasian	mCRC	SPR	IRI alone, IRI+TOM, IRI+5-FU, IRI+5-FU+leuc	80mg/m2, weekly; 180mg/m2, biweekly;3 50mg/m2, every 3 weeks	S	95	68	0-2	8
Innocenti[67]	2004	P	Mixed	Mixed tumors	SBE	IRI	350mg/m2, every 3 weeks	S	59	60	NR	7
Font[66]	2003	NR	NR	mNSCLC	Sequencing	IRI+DOC	70mg/m2 (d1, 8 and 15), every 4 weeks	S	47	55	0-2	7
Iyer[25]	2002	P	Caucasian	Mixed tumors	SPR	IRI	300mg/m2, every 3 weeks	S	20	NR	NR	8

R, analysis was planned retrospectively; P, analysis was planned prospectively; NR, Not reported; mCRC, metastatic colorectal cancer; GC, gastric cancer; SCLC, small-cell lung cancer; NSCLC, non-small-cell lung cancer; SPR, Sizing of PCR products (analysis of fragment size); PYRS, Pyrosequencing; SBE, Single base prime extension assay; IRI, irinotecan; CDDP, cisplatin; BEV, bevacizumab; OXA, oxaliplatin; CET, cetuximab; PLA, platinum; IFL, FU+IRI; CAP, capecitabine; CBP, carboplatin; LOB, lobaplatin; RAL, raltitrexed; 5-FU, 5-fluorouracil; LV, leucovorin; GCB, gemicitabine; TOM, toumdex; DOC, docetaxel; PAC, paclitaxel; IFL, IRI+5-FU/LV; FOLFIRI, FOL stands for folinic acid, F for fluorouracil, IRIR for irinotecan+5-FU; S, single center; M, multicenter; ECOG, Estern Cooperative Oncology Group; NOS: Newcastle-Ottawa Scale.

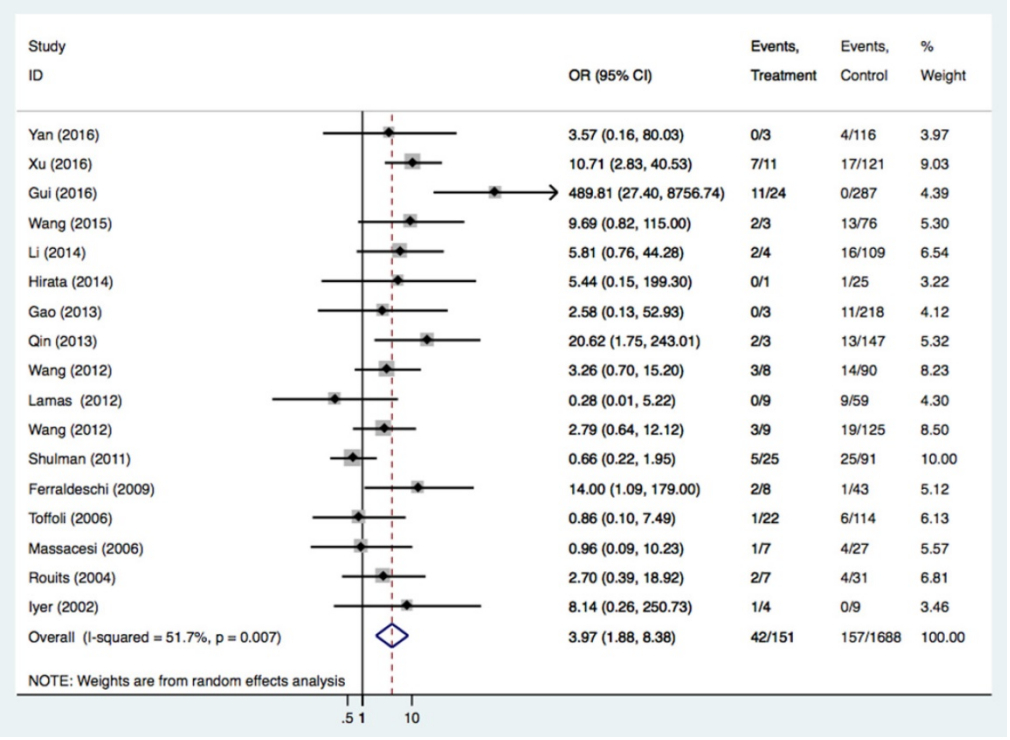

Figure 2. Forest plot of diarrhea risk related to UGT1A1*28 polymorphism under the homozygous model.

Table 2. Meta-analysis Results for diarrhea.

Compared genotype	Group	No. of studies	No. of participants	OR (95%CI)	P	Test for heterogeneity	
						P	I^2
TA6/7 vs. TA6/6	All	28	3435	1.56 (1.25-1.96)	<0.001	0.175	19.9%
	mCRC	16	2563	1.60 (1.11-2.31)	0.011	0.034	43.3%
	SCLC	3	131	2.40 (0.74-7.74)	0.144	0.208	36.3%
	mNSCLC	3	235	0.92 (0.34-2.54)	0.879	0.883	0.0%
	Asian	18	2270	1.85 (1.37-2.50)	<0.001	0.334	10.1%
	Caucasian	9	1118	1.28 (0.91-1.80)	0.117	0.136	35.3%
	Retrospective	13	2123	1.70 (1.09-2.66)	0.020	0.032	46.8%
	Prospective	12	1090	1.69 (1.13-2.52)	0.010	0.495	0.0%
TA7/7 vs. TA6/6	All	17	2610	3.97 (1.88-8.38)	<0.001	0.007	51.7%
	mCRC	14	1172	3.53 (1.54-8.09)	0.003	0.004	57.5%
	Asian	10	1805	8.98 (5.21-15.47)	<0.001	0.152	32.0%
	Caucasian	7	805	1.09 (0.56-2.13)	0.807	0.259	22.3%
	Retrospective	9	1737	4.84 (1.32-17.69)	0.017	<0.001	71.7%
	Prospective	7	743	2.86 (1.30-6.30)	0.009	0.555	0.0%
TA6/7+7/7 vs. TA6/6	All	44	4868	2.18 (1.68-2.83)	<0.001	0.003	40.8%
	SCLC	3	131	3.95 (1.42-11.01)	0.009	0.115	53.8%
	mNSCLC	4	321	1.24 (0.58-2.65)	0.582	0.560	0.0%
	Advanced OC	2	178	7.09 (2.91-17.26)	<0.001	1.00	0.0%
	mCRC	25	3477	1.96 (1.42-2.70)	<0.001	0.005	47.3%
	Asian	32	3607	2.74 (2.21-3.40)	<0.001	0.132	22.2%
	Caucasian	11	1214	1.39 (0.84-2.32)	0.202	0.038	47.9%
	Retrospective	16	2359	2.17 (1.36-3.49)	0.001	0.001	62.0%
	Prospective	24	2198	2.12 (1.62-2.79)	<0.001	0.263	14.3%
TA7/7 vs. TA6/7+TA6/6	All	24	3175	3.64 (2.01-6.58)	<0.001	<0.001	57.6%
	SCLC	2	64	19.90 (2.57-154.1)	0.004	0.832	0.0%
	mCRC	17	2656	3.16 (1.61-6.19)	0.001	<0.001	64.1%
	Asian	13	1917	8.64 (4.14-18.04)	<0.001	0.092	36.3%
	Caucasian	10	1211	1.62 (1.03-2.53)	0.035	0.188	27.8%
	Retrospective	11	2003	2.06 (1.23-3.44)	0.006	0.168	32.5%
	Prospective	11	995	2.92 (1.64-5.21)	<0.001	0.219	26.2%

mCRC, metastatic colorectal cancer; mNSCLC, metastatic non-small-cell lung cancer.

Meta-Analysis of UGT1A1*28 Polymorphism and Response

Eighteen studies with 2024 patients were assessed to determine the association of the UGT1A1*28 polymorphism with tumor response to irinotecan-based chemotherapy (Table 4 and Figure 4). A partial or complete remission was grouped as a response, while stable tumor or progression was considered no response. A response occurred in patients with at least one mutation allele but not in patients with the wide genotype (TA6/7+TA7/7 vs. TA6/6: OR = 1.20, 95%CI = 1.07–1.34, P = 0.016). The association was significant in Caucasians (OR = 1.23, 95%CI = 1.06–1.42, P = 0.006), retrospective study designs (OR = 1.54, 95%CI = 1.06–2.23, P = 0.022), and mCRC patients (OR = 1.24, 95%CI = 1.05–1.48, P = 0.014).

Heterogeneity Analysis

There was high heterogeneity among studies evaluating severe diarrhea under the homozygous and recessive comparisons (TA7/7 vs. TA6/6: P = 0.007, I^2= 51.7%; TA7/7 vs. TA6/6+TA6/7: P<0.001, I^2= 57.6%). We performed meta-regression to explore the sources of heterogeneity. The data indicated that ethnicity and year of publication accounted for 76% and 26% of heterogeneity under the homozygous model and 54% and 41% under the recessive model, respectively (data not shown). There was high heterogeneity among studies of neutropenia under recessive comparison (P<0.001, I^2= 60.7%). The meta-regression results only revealed that the number of patients represented 25% of the heterogeneity and no other factors were found (data not shown).

Table 3. Meta-analysis Results for neutropenia.

Compared genotype	Group	No. of studies	No. of participants	OR (95%CI)	P	Test for heterogeneity	
						P	I^2
TA6/7 vs. TA6/6	All	32	3948	1.71 (1.41-2.08)	< 0.001	0.104	24.8%
	mCRC	19	2801	1.76 (1.40-2.23)	<0.001	0.434	1.8%
	mNSCLC	2	188	1.35 (0.55-3.34)	0.518	0.920	0.0%
	Asian	21	2547	1.56 (1.07-2.27)	0.020	0.011	46.0%
	Caucasian	10	1342	1.86 (1.34-2.60)	<0.001	0.991	0.0%
	Retrospective	14	1468	1.90 (1.43-2.53)	<0.001	0.201	23.3%
	Prospective	15	1448	1.53 (1.15-2.05)	0.004	0.882	0.0%
TA7/7 vs. TA6/6	All	27	3575	5.34 (3.05-9.33)	<0.001	0.003	48.7%
	mCRC	19	2801	5.07 (2.56-10.02)	<0.001	0.001	59.3%
	Asian	15	2154	4.77 (1.71-13.22)	0.003	0.001	62.6%
	Caucasian	11	1362	5.39 (3.43-8.47)	<0.001	0.342	10.7%
	Retrospective	12	1914	5.61 (3.58-8.82)	<0.001	<0.001	69.3%
	Prospective	14	1531	5.81 (3.57-9.47)	<0.001	0.291	14.8%
TA6/7+7/7 vs. TA6/6	All	49	5232	2.15 (1.71-2.70)	<0.001	0.003	39.5%
	mCRC	26	3473	2.47 (1.86-3.27)	<0.001	0.013	42.1%
	Advanced esophageal cancer	2	133	1.20 (0.48-3.05)	0.697	0.691	0.0%
	Advanced GC	4	193	1.40 (0.64-3.06)	0.402	0.759	0.0%
	mNSCLC	4	351	1.79 (0.97-3.33)	0.064	0.432	0.0%
	Asian	35	3715	2.11 (1.54-2.89)	<0.001	<0.001	53.9%
	Caucasian	13	1458	2.29 (1.69-3.08)	<0.001	0.992	0.0%
	Retrospective	18	2318	2.52 (1.64-3.88)	<0.001	<0.001	59.3%
	Prospective	29	2739	1.90 (1.53-2.35)	<0.001	0.530	0.0%
TA7/7 vs. TA6/6+6/7	All	28	3668	4.12 (2.36-7.20)	<0.001	<0.001	60.7%
	mCRC	20	2894	3.70 (1.88-7.30)	<0.001	<0.001	69.4%
	Asian	15	2154	4.16 (1.44-11.99)	0.008	<0.001	68.9%
	Caucasian	12	1455	3.39 (1.92-5.98)	<0.001	0.057	42.7%
	Retrospective	12	1914	3.59 (1.05-12.28)	0.042	<0.001	76.4%
	Prospective	15	1624	4.10 (2.36-7.12)	<0.001	0.088	35.1%

mCRC, metastatic colorectal cancer; GC, gastric cancer; mNSCLC, metastatic non-small-cell lung cancer.

Table 4. Meta-analysis Results for response.

Group	No. of studies	No. of participants	OR (95%CI)	P	Test for heterogeneity	
					P	I^2
All	18	2024	1.20 (1.07-1.34)	0.016	0.082	33.6%
mCRC	12	1691	1.24 (1.05-1.48)	0.014	0.060	42.2%
SCLC	2	64	0.87 (0.57-1.33)	0.514	0.458	0.0%
mNSCLC	3	202	1.08 (0.71-1.63)	0.726	0.127	51.5%
Asian	12	2270	1.08 (0.82-1.42)	0.168	0.019	51.7%
Caucasian	5	1118	1.23 (1.06-1.42)	0.006	0.669	0.0%
Retrospective	4	538	1.54 (1.06-2.23)	0.022	0.060	59.5%
Prospective	12	1292	1.07 (0.93-1.22)	0.343	0.511	0.0%

mCRC, metastatic colorectal cancer; mNSCLC, metastatic non-small-cell lung cancer

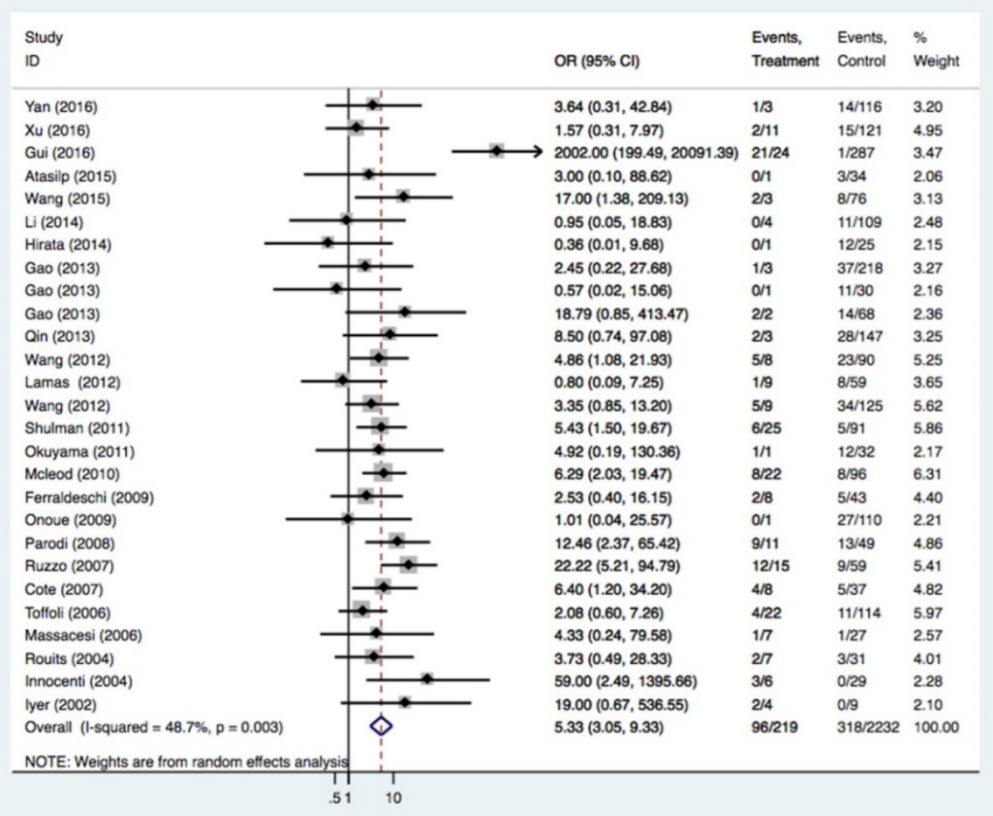

Figure 3. Forest plot of neutropenia risk related to UGT1A1*28 polymorphism under the homozygous model.

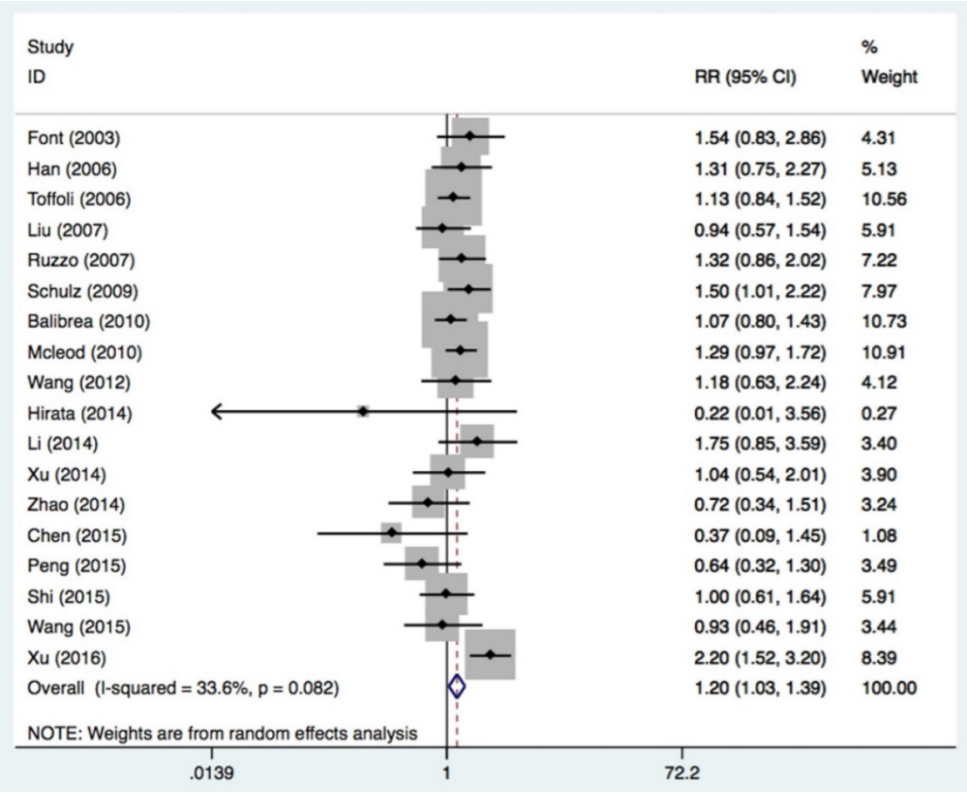

Figure 4. Forest plot of response related to UGT1A1*28 polymorphism under the homozygous model.

Table 5. P values for Begg's funnel plot and Egger's test for diarrhea and neutropenia.

	Begg	Egger
Diarrhea		
TA6/7 vs. TA6/6	0.635	0.244
TA7/7 vs. TA6/6	0.365	0.166
TA6/7+TA7/7 vs. TA6/6	0.927	0.282
TA7/7 vs. TA6/6+TA6/7	0.215	0.697
Neutropenia		
TA6/7 vs. TA6/6	0.284	0.088
TA7/7 vs. TA6/6	0.755	0.999
TA6/7+TA7/7 vs. TA6/6	0.044	0.027
TA7/7 vs. TA6/6+TA6/7	0.782	0.617

Publication Bias

To detect publication bias in studies that evaluated diarrhea and neutropenia, we performed the Begg and Egger tests (Table 5). As shown in Table 5, publication bias was found only among the studies of neutropenia under the dominant model (P = 0.027). Next, a trim and fill method was applied and the results (OR = 1.80, 95%CI = 1.37–2.36, P<0.001) showed no statistical difference compared from the results described above (OR = 2.15, 95%CI = 1.71–2.70, P<0.001). There was also no publication bias in studies evaluating response (P = 0.082). Thus, publication bias did not appear to affect our results.

Sensitivity Analysis

Statistical analysis was conducted as described previously [23]. As shown in Figure 5, 6, and 7, the results were not affected by omitting individual studies in this meta-analysis, indicating that our results are reliable.

Trial Sequential analysis

We used the dominant model as an example to perform the TSA, which included eighteen trials with 2024 patients. The results showed the required information size was 1078, which meant our sample size was enough to get a robust conclusion about the UGT1A1*28 polymorphism and chemotherapy response (Figure 8). The required sample sizes for determining the associations between UGT1A1 and diarrhea and neutropenia under the dominant model were 763 and 1162, respectively (data were not shown).

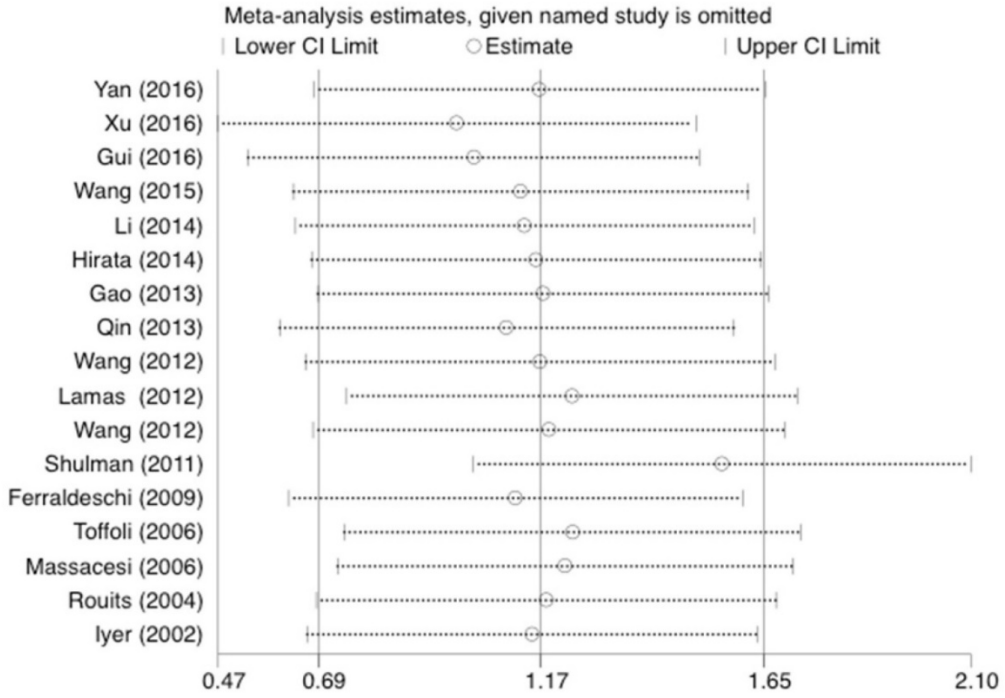

Figure 5. Sensitivity analysis of the studies about diarrhea under the homozygous model.

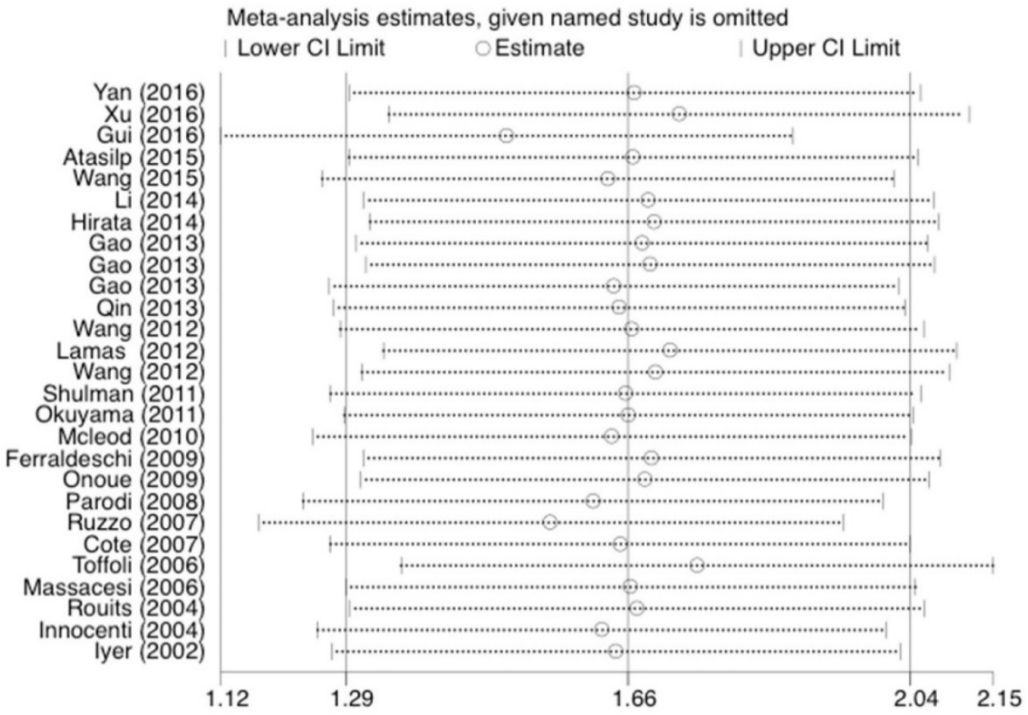

Figure 6. Sensitivity analysis of the studies about neutropenia under the homozygous model.

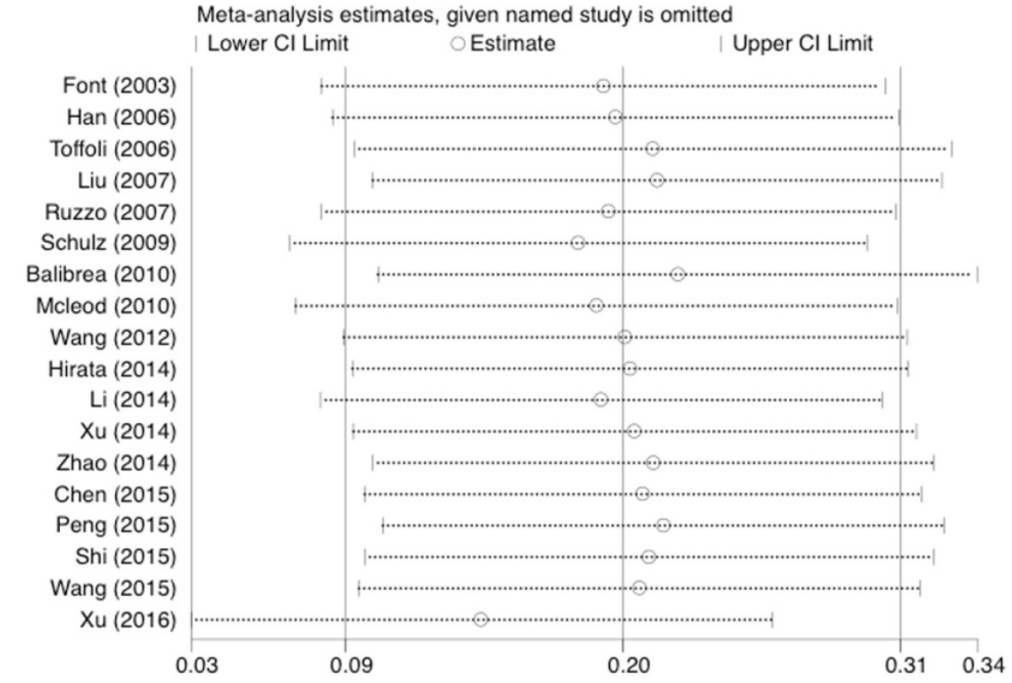

Figure 7. Sensitivity analysis of the studies about response under the dominant model.

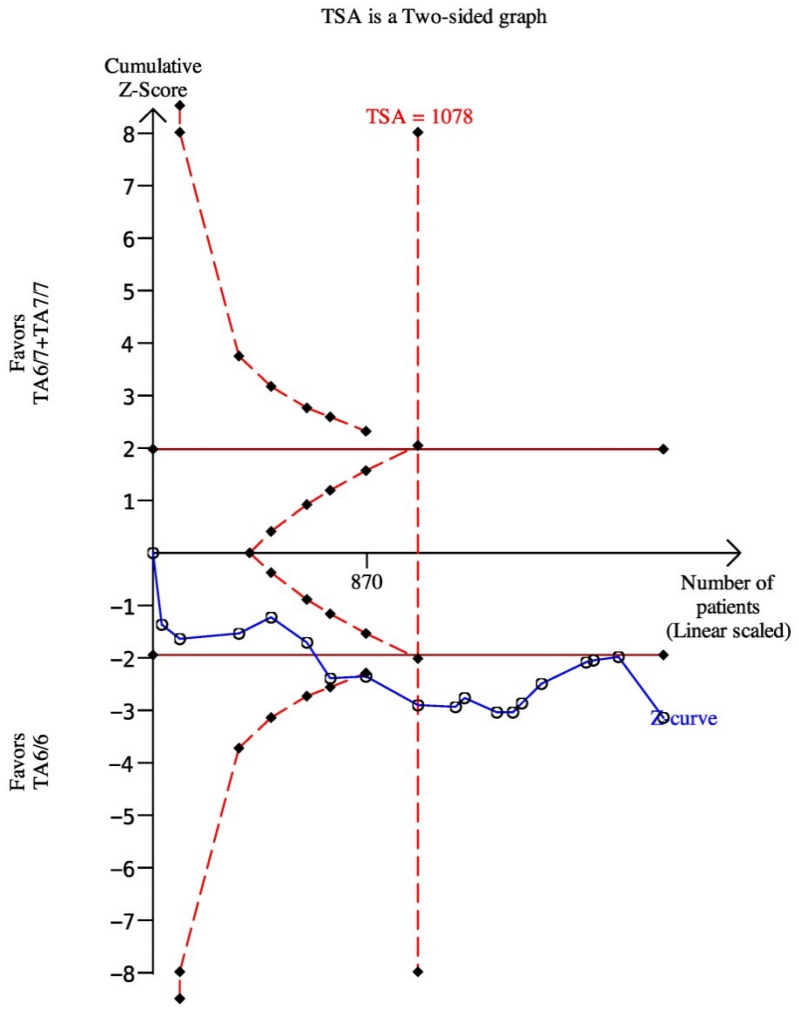

Figure 8. The required sample size to demonstrate the relationship between UGT1A1*28 polymorphism and chemotherapy response. The solid line represents the cumulative z-curve. The dashed curve represents the trial sequential monitoring boundary.

Discussion

A couple of meta-analyses have investigated the relationships between the UGT1A1*28 polymorphism and irinotecan-induced toxicity, severe diarrhea, and neutropenia. A study by Chen *et al*. in 2014 included six articles and found no statistically significant association between the UGT1A1*28 polymorphism and neutropenia in Asians (OR = 1.67, 95%CI = 0.94–2.97) [65]. Liu et al.[66] conducted a meta-analysis of 16 articles and found that mCRC patients carrying the TA7/7 genotype had a higher risk of neutropenia and diarrhea in Caucasians. In contrast to previous studies, we evaluated 58 articles including 6087 cancer patients and performed stratified analyses based on ethnicity, study design, and cancer type. Statistical difference between the UGT1A1*28 polymorphism and diarrhea was confirmed in Asian patients and mCRC patients under the five models. Individuals with at least mutation allele had a 1.71- and 5.34-fold greater risk of neutropenia than individuals carrying the wide genotype. Mutated genotypes of the UGT1A1*28 polymorphism may lower the glucuronidation rates of SN-38 and lead to greater susceptibility to severe toxicities [25, 36].

Patients evaluated in this study, particularly mCRC patients with the TA6/7 and TA7/7 genotypes, may have severe diarrhea and neutropenia after irinotecan-induced chemotherapy. However, the UGT1A1*28 TA6/6 and TA7/7 genotypes may show an increased treatment response according to our results. In contrast to our results, Xu *et al*.[67] observed different clinical responses in Ugyur patients with different UGT1A1*28 polymorphism genotypes, but not in the Han population. Although the reduction of irinotecan was greater in patients with the TA7/7 or TA6/7 genotypes than the TA6/6 genotype, no difference in overall or progression-free survival between the two group patients were found by Dias *et al*.[68]. These results indicate that if the patients with mutant genotypes could tolerate the

toxicities, irinotecan-based chemotherapy is a good choice for treatment. Additional studies of the treatment response should be carried out.

Previous meta-analyses included few than 20 studies and only focused on toxicities or chemotherapy response. In comparison with these studies, we included more research (58 studies) and investigated the associations of UGT1A1*28 polymorphism with toxicities and chemotherapy effect. We also got a novel conclusion that patients with a higher risk of chemotherapy toxicities have a tendency to better response to chemotherapy. However, there were some limitations to our study. First, the number of studies of SCLC, mNSCLC, advanced GC, solid tumors, and other cancers were limited, and thus, larger sample sizes for a single tumor are needed to validate our results. Second, high heterogeneity existed among studies related to severe neutropenia under the recessive comparison. Although the number of patients could explain 25% of the heterogeneity, other influencing factors were not identified. Third, the studies we including selected different irinotecan doses in the chemotherapies, which may lead to some bias.

Conclusions

In conclusion, we detected a significant relationship between the UGT1A1*28 polymorphism and irinotecan-induced toxicity and response to irinotecan-based chemotherapy. This polymorphism may be useful as a detective index for cancer patients receiving irinotecan-based chemotherapy.

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Competing Interests

The authors have declared that no competing interest exists.

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