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Dose-dependent association between UGT1A1*28 polymorphism and irinotecan-induced diarrhoea: A meta-analysis

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ABSTRACT

Life-threatening diarrhoea is observed in up to 25% of cancer patients receiving irinotecan. The associations between the UGT1A1*28 polymorphism and irinotecan-induced diarrhoea remains controversial because of conflicting data in the literature. Meta-analyses were performed on published data in terms of relationships between UGT1A1*28 and severe diarrhoea. We searched databases for relevant studies that were published in English or Chinese. Two reviewers extracted data and assessed methodological quality. UGT1A1*28 related odds ratios (ORs) were pooled by use of a fixed-effects model. The studies included were stratified into subgroups representing different races and irinotecan doses, and meta-regression analyses were performed to investigate the effect of study characteristics on the association between UGT1A1*28 and diarrhoea. Twenty trials including a total of 1760 cancer patients were included. The risk of severe diarrhoea at medium and high irinotecan doses was higher among patients with a UGT1A1*28/*28 genotype than among those with a UGT1A1*1/*1 genotype (OR = 3.69, 95% confidence interval [CI] = 2.00–6.83; $P < 0.001$). Considering the patients with a UGT1A1*1/*28 genotype, the risk of toxicity was also higher than among those with a wild-type genotype at medium and high doses (OR = 1.92, 95% CI = 1.31–2.82; $P = 0.001$). No association was observed between UGT1A1*28 and severe diarrhoea at low doses (<125 mg/m^2). In conclusion, patients carrying UGT1A1*28 allele(s) are at an increased risk of irinotecan-induced severe diarrhoea. This increased risk is only apparent in those who are administrated with medium or high irinotecan doses.

1. Introduction

Irinotecan is approved for first-line treatment of metastatic colorectal cancer.[1] The mechanism of action of irinotecan is associated with topoisomerase I inhibition by the active metabolite 7-ethyl-10-hydroxycamptothecin (SN-38). The main dose-limiting toxicities of irinotecan are delayed diarrhoea and neutropenia. Life-threatening diarrhoea is observed in up to 25% of patients receiving irinotecan.[2] Predicting individual patients' risk of severe toxicity could potentially improve the quality of care by allowing individualisation of treatment.[3]

SN-38 is eliminated predominantly by glucuronidation to SN-38 glucuronide. This glucuronidation reaction is mediated primarily by UDP-glucuronosyltransferase 1A1 (UGT1A1).[4] The UGT1A1*28 polymorphism is due to a change in the number of

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TA repeats in the TATA box of the UGT1A1 promoter from the wild-type 6 repeats to the variant 7 repeats. UGT1A1*28 was found to be associated with decreased activity and SN-38 glucuronidation in humans.[5–11] Besides being associated with reduced SN-38 glucuronidation in humans, the presence of UGT1A1*28 is assumed to be a risk factor for the occurrence of toxicity. Indeed, there are fairly strong evidences that individuals with UGT1A1*28/*28 genotype tend to have a higher prevalence of irinotecan-induced neutropenia.[12–17] However, the association between UGT1A1*28 polymorphism and severe diarrhoea is far less clear. For example, associations between the UGT1A1*28 genotype and diarrhoea were observed in several studies,[16,18–21] whereas no statistically significant association was found in other studies.[22–32]

In this meta-analysis, we assessed the associations between the irinotecan-induced diarrhoea and UGT1A1*28 polymorphism. We also stratified the participants into irinotecan dose- and race-matched groups, and then calculated the odds ratios (ORs) of severe diarrhoea for UGT1A1*28 mutation.

2. Materials and methods

2.1. Search strategy and selection criteria

We searched Medline, PubMed, Embase and Chinese Biological Medicine (from 1980 until November 30, 2009) databases using the Medical Subject Heading terms 'irinotecan', 'UGT1A1' and 'diarrhoea', and the individual corresponding free terms. Furthermore, we reviewed citations in the retrieved articles to search for additional relevant studies.

Studies were included if (1) they could be defined as clinical trials; (2) the exposure of interest was UGT1A1*28 genotype; (3) the outcome of interest was irinotecan-induced diarrhoea (grade III–IV) and (4) numbers of patients with and without diarrhoea were provided (or can be calculated by relevant data). We excluded studies that were not published as full reports; studies that included fewer than 10 patients who carried at least one UGT1A1*28 allele; studies that included children patients.

2.2. Data extraction

The following information were abstracted from included publications: study design, year, race, irinotecan dose, number of patients with and without diarrhoea (grade III–IV) in each genotype group (UGT1A1*1/*1, UGT1A1*1/*28 and UGT1A1*28/*28), mutation detection method and potential confounders. Two irinotecan-containing regimens were administered to patients in the study by Kweekel et al.,[17] and in our analyses, we analyzed the patients treated with each regimen as two separate samples. The patients treated with different regimens were analyzed as one sample if separate data was not available. If the patients in a trial received different irinotecan doses and only combined toxicity-related data was available, we calculated the average dose. In one study,[21] the number of chemotherapy cycles with diarrhoea in each genotype group was provided instead of the number of patients. We calculated the number of patients as $C \times tN/tC$, where C is the number of chemotherapy cycles with diarrhoea in each genotype group, tC is the total number of chemotherapy cycles with diarrhoea, tN is the total number of patients with diarrhoea.

2.3. Assessment of study quality

The use of quality scoring system in meta-analyses of observational studies is controversial. Thus, methodological components of study designs, rather than aggregate scores themselves, may be important.[33] Here, we did not assign a single grade or scores to represent the quality of a study. Instead, we focused on certain items that are reflective of methodological and reporting quality of the studies. Study design, number of patients, source of population, mutation detection method, races, tumour types, chemotherapy regimens and grade criteria for diarrhoea were considered in our evaluation of the quality of an included study (Table 1).

2.4. Statistical analysis

The effect measures of interest were ORs, which was calculated by the number of patients with and without severe diarrhoea in each genotype group. Statistical heterogeneity among studies was evaluated using the χ^2 test, P values and I^2 statistics.[34] We considered both the presence of significant heterogeneity at the 10% level of significance and values of I^2 exceeding 56% as an indicator of significant heterogeneity. A fixed-effects model was used to obtain summary OR. We evaluated potential publication bias by visually examining for possible skewness in funnel plots and Egger test.[35] We also performed the Duval and Tweedie nonparametric 'trim and fill' procedure to further assess the possible effect of publication bias in our meta-analysis.[36] This method considers the possibility of hypothetical 'missing' studies that might exist, imputes their ORs and recalculates a pooled OR that incorporates the hypothetical missing studies as though they actually existed.

We stratified the participants into irinotecan dose- and race-matched groups, and then calculated the pooled OR of diarrhoea for UGT1A1*28 mutation. We also used meta-regression analyses to investigate the effect of irinotecan dose, age, sex ratio, study design and race on the association between UGT1A1*28 and severe diarrhoea. In order to facilitate the interpretation of the results, relative risk (RR) was calculated from OR as described in the Cochrane Handbook for Systematic Reviews of Interventions version 5.0.2 (http://www.cochrane-handbook.org). All statistical tests were two sided. Meta-analysis was done with Stata (version 10.1; Stata Corp, College Station, TX, United States of America).

3. Results

3.1. Study characteristics and methodological quality

61 potentially relevant studies were evaluated (Fig. 1 shows the number of studies evaluated at each stage). Twenty clinical trials including 1760 healthy volunteers were identified. Table 1 details the studies' characteristics and methodological quality. Sample sizes were small (ranging from 20[10] to 250[27]). Patients were predominantly Caucasian in 10 trials[10,11,15,17–19,23,26,27,29] and six trials were conducted

Table 1 – Characteristics and methodological quality of trials included in meta-analysis.

Study	Study design	No. of patients (male%)	Age (median or mean)	Source of population	Mutation detection methods[a]	Races[b]	Type of tumours[c]	Chemotherapy regimens[d]	Irinotecan dose (mg/m^2)/ schedule	Grade criteria[e]
Iyer et al.[10]	Prospective	20 (50)	Unknown	Single centre	SPR	C	Solid tumours	IRI alone	300/every 3 week	NCI
Innocenti et al.[11]	Prospective	61 (59)	60	Single centre	SPR	50C/10B/6O	Solid tumours	IRI alone	350/every 3 week	NCI
Cote et al.[15]	Prospective	89 (?)	Unknown	Multicentre	SPR	C	Stage III mCRC	FOLFIRI	180/biweekly	NCI
Liu et al.[16]	Retrospective	128 (67)	Unknown	Single centre	SPR	A	mCRC	FOLFIRI	180/biweekly	WHO
Kweekel et al.[17]	Retrospective	218 (63)	61	Multicentre	PYRS	C	mCRC	IRI or CAPIRI	250 or 350/every 3 week	NCI
Ferraldeschi et al.[18]	Prospective	92 (69)	63	Single centre	SPR	C	mCRC	FOLFIRI, CAPIRI, or IRI plus VEGF inhibitor	180/biweekly	NCI
Marcuello et al.[19]	Prospective	95 (63)	68	Unknown	SPR	C	mCRC	IRI alone, IRI plus Tomudex, or IRI plus 5FU or LV	80/weekly, 180/ biweekly or 350/ every 3 week	WHO
Yang et al.[20]	Unknown	66 (64)	58	Single centre	Sequencing	A	Solid tumours	FOLFIRI, IROX or CAPIRI	180/biweekly or 200/every 3 week	NCI
Massacesi et al.[21]	Prospective	56 (52)	64	Multicentre	Sequencing	Unknown	Advanced CRC	IRI plus RAL	80/weekly	NCI
Han[22]	Retrospective	81 (74)	58	Single centre	Sequencing	A	NSCLC	IP	80/weekly	NCI
de Jong et al.[23]	Retrospective	102 (51)	55	Multicentre	SPR	C	Solid tumours	IRI alone	350/every 3 week	NCI
Rouits et al.[24]	Unknown	44 (69)	60	Single centre	PYRS	Unknown	mCRC	FOLFIRI	180/biweekly	WHO
de Jong et al.[25]	Prospective	52 (60)	58	Multicentre	SPR	Unknown	Solid tumours	IRI alone	350/every 3 weeks	NCI
Rouits et al.[26]	Retrospective	73 (61)	62	Single centre	PYRS	C	mCRC	Modified FOLFIRI or FOLFIRI	85/weekly or 180 biweekly	NCI
Toffoli et al.[27]	Prospective	250 (65)	61	Multicentre	PYRS	C	mCRC	Modified FOLFIRI or FOLFIRI	180/biweekly	NCI
Font et al.[28]	Unknown	47 (89)	55	Single centre	Sequencing	Unknown	NSCLC	IRI plus DOC	70/weekly	NCI
Carlini et al.[29]	Prospective	64 (55)	61	Multicentre	SPR	55C/9B/2O	mCRC	CAPIRI	100 or 125/ weekly	NCI
Jada et al.[30]	Unknown	45 (56)	55	Single centre	SPR	A	Solid tumours	IRI alone	375/every 3 weeks	NCI
Wang et al.[31]	Prospective	70 (?)	Unknown	Multicentre	SPR	A	Advanced mCRC	Modified FOLFIRI or FOLFIRI	180/biweekly	NCI
Han et al.[32]	Retrospective	107 (77)	58	Single centre	SBE	A	NSCLC	IRI alone	65 or 80/weekly	NCI

[a] SPR, Sizing of PCR products (analysis of fragment size); SBE, Single base primer extension assay; PYRS, Pyrosequencing; Sequencing, other DNA sequencing methods.

[b] A: Asian; B: Black; C, Caucasian; O, other races. The accompanying number represents the number of subjects belonging to each group.

[c] Solid tumours, Multiple solid tumour types; NSCLC, non–small-cell lung cancer; mCRC, Metastatic colorectal cancer.

[d] IRI, irinotecan; CAP, capecitabine; OXA, oxaliplatin; 5FU, 5-fluorouracil; LV, leucovorin; DOC, docetaxel; RAL, raltitrexed; IP, irinotecan plus cisplatin; CAPIRI, capecitabine plus irinotecan; FOLFIRI, irinotecan plus 5FU and leucovorin; IROX, irinotecan plus OXA.

[e] NCI, National Cancer Institute common toxicity criteria; WHO, World Health Organisation criteria.

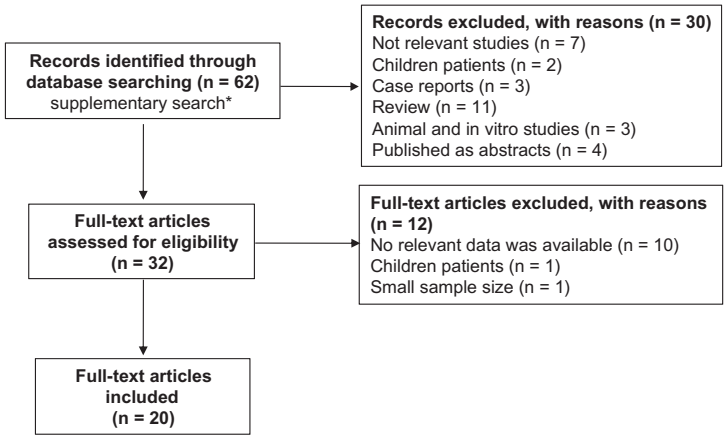

Fig. 1 – Studies evaluated at each stage of the meta-analysis (*Supplementary search includes: reference lists, contacting authors).

in East Asian patients.[16,20,22,30–32] Four trials did not clearly report the race of the participants.[21,24,25,28] However, the race was assumed to be Caucasian because the trials were conducted in Europe and the frequency of UGT1A1*28 allele was similar to the frequency of Caucasian. Ten trials were investigated prospectively,[10,11,15,18,19,21,25,27,29,31] six of which were also multicentre trials.[15,21,25,27,29,31] Eight trials use DNA sequencing as the method for detecting the UGT1A1*28 mutation.[17,20–22,24,26–28] Single chemotherapy regimen was employed in 13 trials[10,11,15,16,21–25,28–30,32] while the chemotherapy regimens varied among patients in other trials.[17–20,26,27,31] The patients in the same trial received the same irinotecan dose in 13 trials[10,11,15,16,18,21–25,27,28,30,31] while the doses varied among patients in other trials.[17,19,20,26,29,32] Among these trials with multiple irinotecan dose groups, only one trial[17] provided detailed data regarding individual dose group while the other trials[19,20,26,29,32] provided the combined data. Toxicities were evaluated on the basis of National Cancer Institute Common Toxicity Criteria in 17 trials[10,11,15,17,18,20–23,25–32] while three studies[16,19,24] used World Health Organisation criteria.

There may be publication bias in two subgroups from both the funnel plot (Fig. 2, other subgroups without publication bias are not shown) and Egger test (Table 2). The results of meta-analysis are summarised in Table 2.

3.2. *UGT1A1*1/*28 or UGT1A1*28/*28 versus UGT1A1*1/*1*

Relevant data for the comparison of the risk of severe diarrhoea between patients with a UGT1A1*1/*28 or UGT1A1*28/*28 genotype and those with a UGT1A1*1/*1 genotype was available in 20 included trials.[10,11,15–32] Pooled data from all studies showed that the risk of toxicity was higher among patients with a UGT1A1*1/*28 or UGT1A1*28/*28 genotype than among those with a UGT1A1*1/*1 genotype (OR = 1.81, 95% confidence interval [CI] = 1.38–2.39; $P < 0.001$). No statistical heterogeneity was detected across all studies ($I^2 = 0$, $P = 0.688$). Hoskins et al. reported that the risk of experiencing irinotecan-induced neutropenia for patients with a UGT1A1*28/*28 genotype was a function of the irinotecan dose administered.[13] It is noteworthy that ethnic differences do exist in the UGT1A1*28 polymorphism.[37] Based on these facts, we carried out stratified analyses according to race and dose irrespective of the observed absence of statistical heterogeneity across studies. 125 mg/m^2 of irinotecan dose was set as the cutoff value between low and medium or high dose. In Asians, the risk of toxicity at medium and high doses was higher among patients with at least one UGT1A1*28 allele than among those with a wild-type genotype (OR = 3.02, 95% CI = 1.42–6.44; $P = 0.004$) (Fig 3). Similar results were observed in Caucasians (OR = 1.93, 95% CI = 1.38–2.70; $P < 0.001$) (Fig 3). Pooled data from trials conducted in Asians and Caucasians also showed an increased risk of toxicity at medium and high doses (OR = 2.06, 95% CI = 1.51–2.80; $P < 0.001$) (Fig 3). By contrast, risk was similar at low doses in both Caucasians and Asians (Fig 3).

With regard to the subgroup of Caucasian patients administrated with medium and high doses, visual inspection of the funnel plot revealed asymmetry (Fig. 2 A1). This raises the possibility of publication bias. Because of this, we undertook a sensitivity analysis using the trim and fill method,[36] which imputes hypothetical negative unpublished studies to mirror the positive studies that cause funnel plot asymmetry. The imputed studies produce a symmetrical funnel plot (Fig. 2 B1). The pooled analysis incorporating the hypothetical studies continued to show a statistically significant high risk of toxicity in patients with at least one UGT1A1*28 allele (OR = 1.78, 95% CI = 1.28–2.49; $P = 0.001$).

3.3. *UGT1A1*1/*28 versus UGT1A1*1/*1*

Fifteen included trials compared the risk of severe diarrhoea between patients with a UGT1A1*1/*28 genotype and those with a wild-type genotype.[10,11,15,17–22,26–30,32] Overall analyses suggest an increased risk of severe diarrhoea in patients with a UGT1A1*1/*28 genotype as compared with those with a wild-type genotype (OR = 1.73, 95% CI = 1.25–2.40; $P = 0.001$). No statistical heterogeneity was detected ($I^2 = 0$, $P = 0.885$). Analyses were further stratified by race and dose. Considering the Asian patients administrated with medium and high doses of irinotecan, a trend towards increased risk of severe diarrhoea was observed in patients

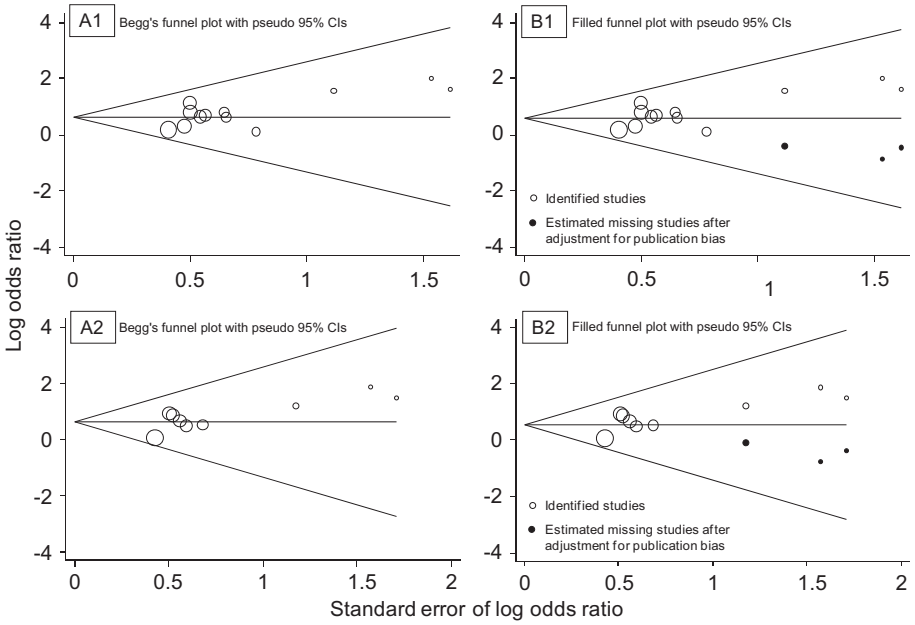

Fig. 2 – Funnel plots with and without trim and fill. A1 (without trim and fill) and B1 (with trim and fill) represent the subgroup for the comparison of the toxicity at medium and high doses between Caucasian patients with at least one UGT1A1*28 allele and those with a wild-type genotype. A2 (without trim and fill) and B2 (with trim and fill) represent the subgroup for the comparison of toxicity at medium and high doses between Caucasian patients with a UGT1A1*1/*28 genotype and those with a wild-type genotype. The dashed line represents 95% confidence intervals. Circles represent individual studies (size of the circles reflects the study-specific statistical weight).

Table 2 – Summary of meta-analysis.

Compared genotype (UGT1A1*1/*1 as reference genotype)	No. of trials	No. of participants	Stratified analysis		Odds ratios (ORs)	P	Test for heterogeneity		Egger test
			Race	Irinotecan doses			P	I^2 (%)	P
UGT1A1*1/*28	4	309	Asian	Medium and high	3.02 (1.42, 6.44)[c]	0.004[a]	0.227	30.8	ne
or UGT1A1*28/*28	11	1096	Caucasian	Medium and high	1.93 (1.38, 2.70)	<0.001[a]	0.916	0	0.044[b]
	15	1405	Total	Medium and high	2.06 (1.51, 2.80)	<0.001[a]	0.730	0	0.248
	2	188	Asian	Low	0.71 (0.15, 3.28)	0.663	0.882	0	ne
	3	167	Caucasian	Low	1.17 (0.58, 2.36)	0.666	0.477	0	ne
	5	355	Total	Low	1.06 (0.57, 1.99)	0.851	0.772	0	ne
	20	1760	Total	Total	1.81 (1.38, 2.39)	<0.001[a]	0.688	0	0.575
UGT1A1*1/*28	2	111	Asian	Medium and high	2.48 (0.80, 7.74)	0.117	0.148	52.1	ne
	8	819	Caucasian	Medium and high	1.87 (1.25, 2.81)	0.002[a]	0.901	0	0.055[b]
	10	930	Total	Medium and high	1.92 (1.31, 2.82)	0.001[a]	0.820	0	0.117
	2	188	Asian	Low	0.71 (0.15, 3.28)	0.663	0.882	0	ne
	3	147	Caucasian	Low	1.47 (0.71, 3.07)	0.300	0.570	0	ne
	5	335	Total	Low	1.27 (0.67, 2.42)	0.470	0.768	0	ne
	15	1265	Total	Total	1.73 (1.25, 2.40)	0.001[a]	0.885	0	0.414
UGT1A1*28/*28	8	494	Caucasian	Medium and high	3.69 (2.00, 6.83)	<0.001[a]	0.453	0	0.278
	3	99	Caucasian	Low	0.43 (0.11, 1.74)	0.237	0.505	0	ne
	11	593	Caucasian	Total	2.23 (1.31, 3.81)	0.003[a]	0.162	28.9	0.956
UGT1A1*28/*28[d]	8	898	Caucasian	Medium and high	2.49 (1.42, 4.36)	0.001[a]	0.460	0	0.660
	3	167	Caucasian	Low	0.36 (0.09, 1.40)	0.140	0.648	0	ne
	11	1065	Caucasian	Total	1.62 (0.98, 2.67)	0.057	0.171	27.9	0.437

ne, Egger test was not done if less than six studies were included in the analysed subgroup.

[a] The risk of toxicity was significantly higher among patients with UGT1A1*28 mutation than among those with a reference genotype.

[b] Publication bias may exist in these subgroups.

[c] Values in parentheses are 95% confidence intervals.

[d] UGT1A1*1/*1 or UGT1A1*1/*28 was considered as reference genotype.

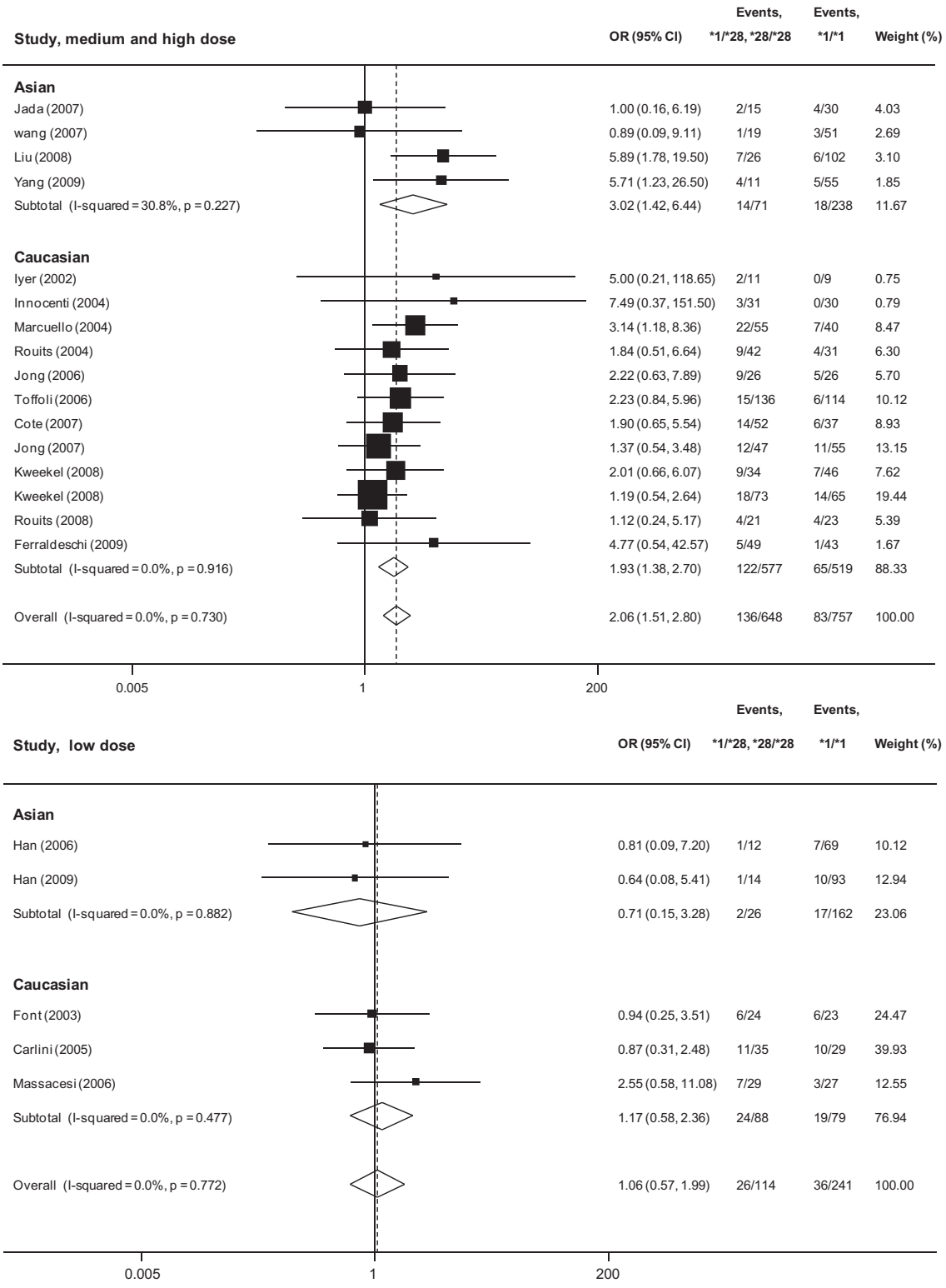

Fig. 3 – Summary odds ratio (OR) of severe diarrhoea for UGT1A1*1/*28 or UGT1A1*28/*28 versus UGT1A1*1/*1 (upper panel, medium and high dose of irinotecan; lower panel, low dose). A fixed-effects model was used for all analyses. Squares represent study-specific estimates (size of the square reflects the study-specific statistical weight); Horizontal lines represent 95% confidence intervals (CIs); Diamonds represent summary estimates with corresponding 95% CIs.

with a UGT1A1*1/*28 genotype. However, the trend did not reach statistical significance (OR = 2.48, 95% CI = 0.80–7.74; P = 0.117) (Fig 4). It is noteworthy that only two trials were included in this subgroup. In Caucasians, the risk of severe diarrhoea at medium and high irinotecan doses was higher among patients with a UGT1A1*1/*28 genotype than among

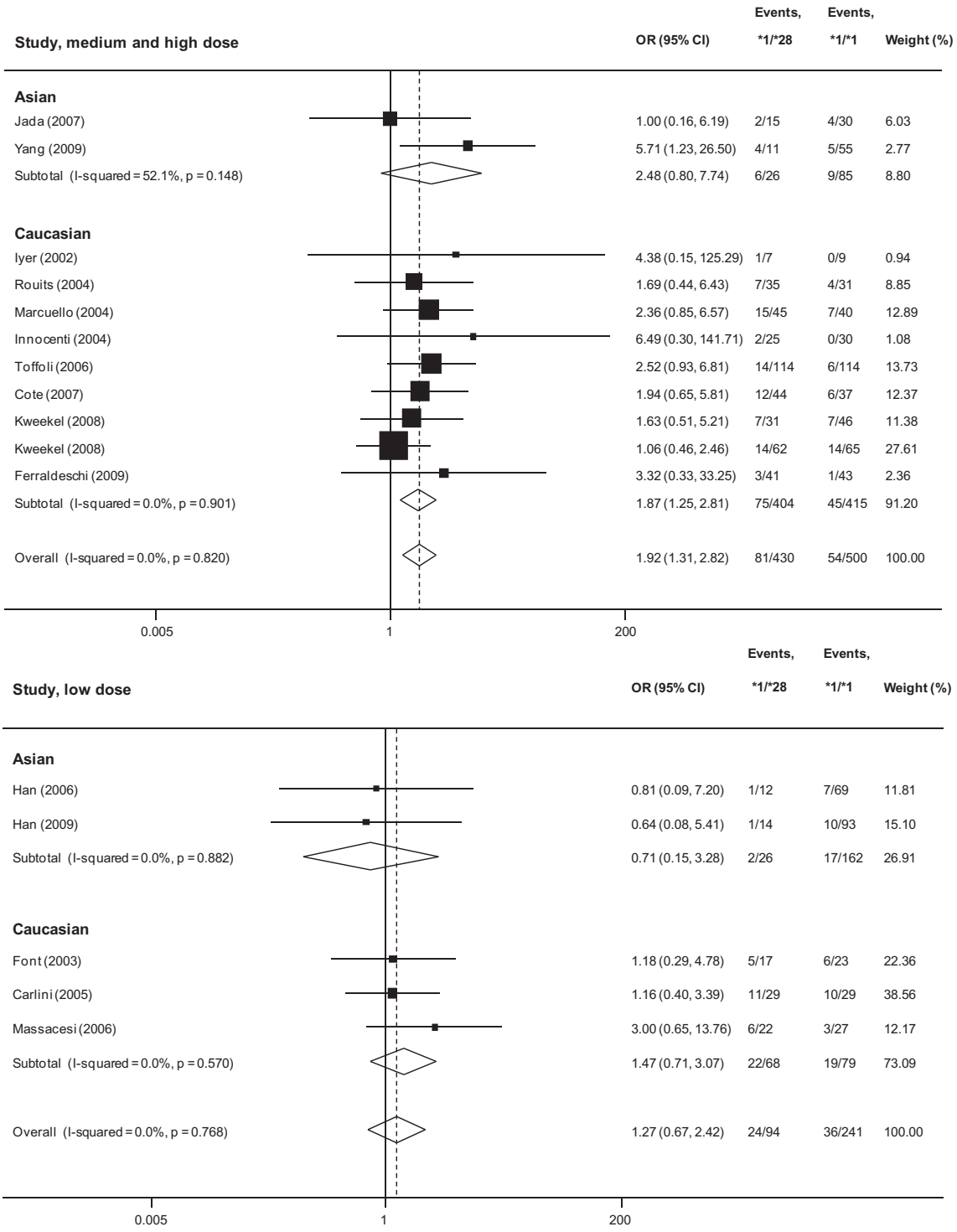

Fig. 4 – Summary odds ratio (OR) of severe diarrhoea for UGT1A1*1/*28 versus UGT1A1*1/*1 (upper panel, medium and high dose of irinotecan; lower panel, low dose). A fixed-effects model was used for all analyses. Squares represent study-specific estimates (size of the square reflects the study-specific statistical weight); Horizontal lines represent 95% confidence intervals (CIs); Diamonds represent summary estimates with corresponding 95% CIs.

those with a UGT1A1*1/*1 genotype (OR = 1.87, 95% CI = 1.25–2.81; $P = 0.002$) (Fig 4). Pooled data from trials conducted in Asians and Caucasians also showed an increased risk of toxicity at medium and high doses (OR = 1.92, 95% CI = 1.31–2.82; $P = 0.001$) (Fig 4). By contrast, risk was similar at low doses in both Caucasians and Asians (Fig. 4).

Although there is some asymmetry in the funnel plot (Fig. 2 A2, subgroup of Caucasian patients at medium and high doses), suggesting the possibility of publication bias, adjustment for the likely effect of bias using 'trim and fill' gave a pooled OR of 1.74 (95% CI = 1.16–2.59; $P = 0.007$), which is only a slight change from our estimate of 1.87.

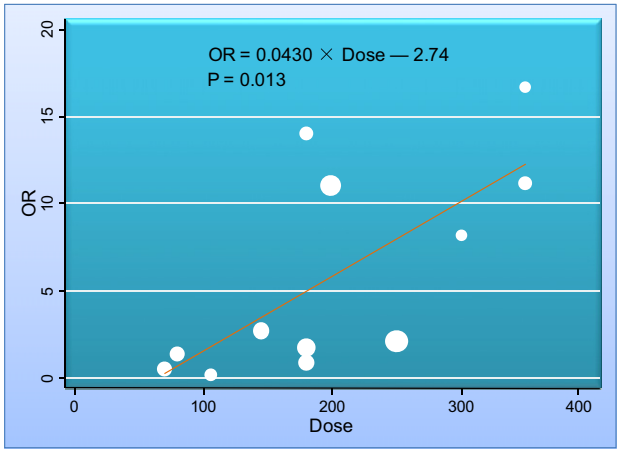

Fig. 5 – Meta-regression of odds ratios (ORs) of severe diarrhoea against dose of irinotecan (UGT1A1*28/*28 versus UGT1A1*1/*1). Size of circle is proportional to the study-specific statistical weight.

3.4. *UGT1A1*28/*28 versus UGT1A1*1/*1*

Eleven trials compared the risk of severe diarrhoea between patients with a UGT1A1*28/*28 genotype and those with a wild-type genotype.[10,11,15,17–19,21,26–29] Patients were predominantly Caucasian in these trials. The pooled OR was 2.23 (95% CI = 1.31–3.81; $P = 0.003$) for all studies. Heterogeneity was not statistically significant across all studies ($I^2 = 28.9\%$, $P = 0.162$). I^2 ranging from 30% to 60% may represent moderate heterogeneity (Cochrane Handbook for Systematic Reviews of Interventions version 5.0.2, http://www.cochrane-handbook.org). Hence, we did meta-analysis to explore which study characteristics are a significant source of the observed heterogeneity across studies. The results of meta-regression indicated that study design, age or sex ratio was not a significant source of heterogeneity across studies ($P = 0.496$, 0.393 and 0.745, respectively). Not unexpectedly, meta-regression showed that irinotecan dose was a significant source of heterogeneity ($P = 0.013$), and accounted for about 44% of the variance across all studies (Fig 5). Furthermore, the meta-analysis gave an increased OR of 4.30 (95% CI = 1.12–7.49) per 100 mg/m^2 dose increase, with an estimated relative increase in the incidence of severe diarrhoea of 37% per 100 mg increase of dose. Analyses stratified by dose suggest an increased risk of severe diarrhoea in patients with a UGT1A1*28/*28 genotype as compared with patients with a wild-type genotype at medium and high doses (OR = 3.69, 95% CI = 2.00–6.83; $P < 0.001$) (Fig 6). As expected, we failed to find significant difference in the risk of severe diarrhoea at low doses (Fig 6).

3.5. *UGT1A1*28/*28 versus UGT1A1*1/*1 or UGT1A1*1/*28*

Eleven trials were included for this analysis.[10,11,15,17–19,21,26–29] Heterogeneity among studies was not important ($I^2 = 27.9\%$, $P = 0.171$). Meta-regression showed that irinotecan dose was

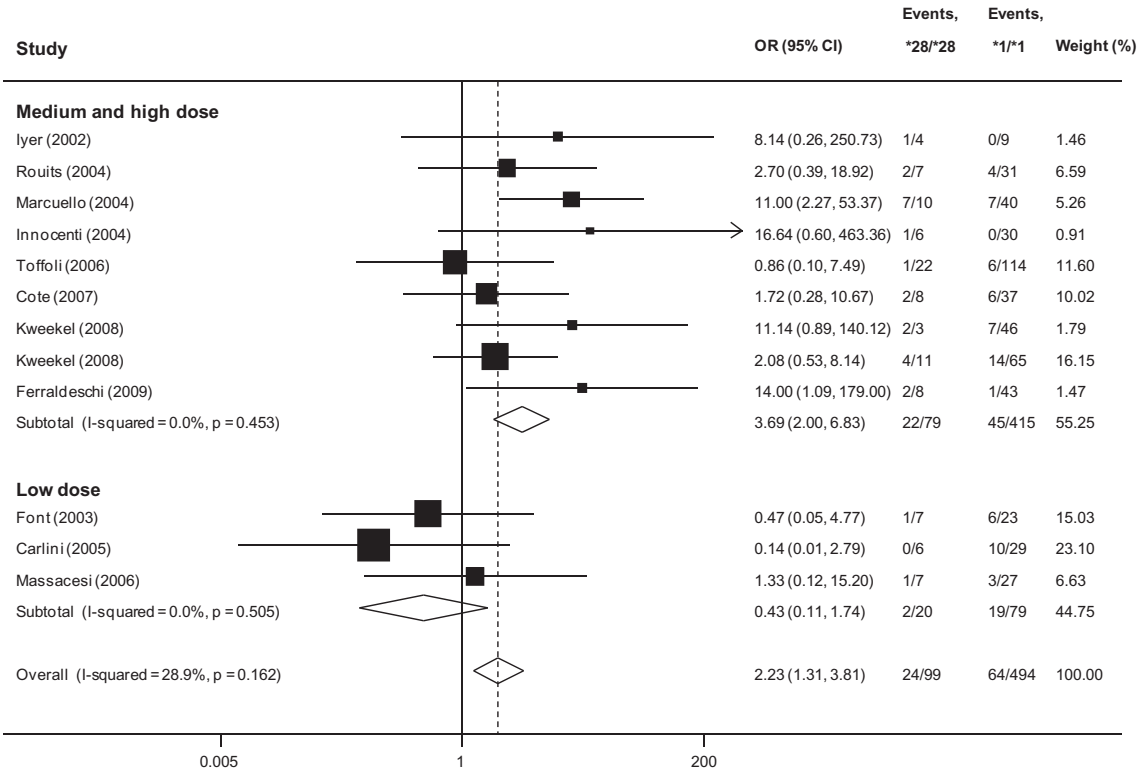

Fig. 6 – Summary odds ratio (OR) of severe diarrhoea for UGT1A1*28/*28 versus UGT1A1*1/*1. A fixed-effects model was used for all analyses. Squares represent study-specific estimates (size of the square reflects the study-specific statistical weight); Horizontal lines represent 95% confidence intervals (CIs); Diamonds represent summary estimates with corresponding 95% CIs.

a significant source of heterogeneity ($P = 0.014$). An increased risk of severe diarrhoea was observed at medium and high doses (OR = 2.49, 95% CI = 1.42–4.36; $P = 0.001$), but risk was similar at low doses group.

4. Discussions

This report is the first published meta-analysis examining the effect of UGT1A1*28 polymorphism on the risk of irinotecan-induced diarrhoea. The primary finding of this study is that patients carrying UGT1A1*28 allele(s) are at an increased risk of severe diarrhoea. This increased risk is only apparent in those who are administrated with medium or high doses of irinotecan. Secondary finding is that there was a significant linear correlation between irinotecan doses and ORs of severe diarrhoea. But this association was only observed in the comparison of the risk of diarrhoea between patients with a UGT1A1*28/*28 genotype and those carrying wild-type allele(s). The last finding is that there was no ethnic difference in the association between UGT1A1*28 and diarrhoea.

It is important to note that three additional important trials were not included in this meta-analysis. These are FOCUS trial,[3] N9741 in metastatic CRC[12] and PETACC-3[14] in the adjuvant setting. FOCUS trial was excluded because no data were provided concerning the association between UGT1A1*28 mutation and incidence of diarrhoea. The other two trials were excluded because both studies were published as abstract and the data were not presented in detail. However, taking these results into consideration will not change the result of our meta-analysis. For example, the results from N9741 trial showed that there was no association between UGT1A1 and diarrhoea. More than half of the patients received a low dose of irinotecan (100 or 125 mg/m^2 weekly). The rest received a dose of 200 mg/m^2 every 3 weeks, which was assumed to be lower than the medium dose of 180 mg/m^2 biweekly. As a result, the results from trial N9741 do not contradict the result of our meta-analysis, but confirmed our results that there was no association between UGT1A1 and diarrhoea at lose doses. Surprisingly, the results from PETACC-3 trial showed that the rate of severe diarrhoea was decreased in patients who carried UGT1A1*28/*28 genotype. There was substantial heterogeneity between this study and other included trials (e.g. $I^2 = 59.1\%$, $P = 0.009$), which means that the true underlying effect varies between this study and all the other trials. However, inclusion of this study in the meta-analysis did not change the general result (although the strength of the association was attenuated). For example, patients with a UGT1A1*28/*28 (OR = 2.98, 95% CI = 1.18–7.57; $P = 0.021$) or UGT1A1*1/*28 (OR = 1.84, 95% CI = 1.23–2.75; $P = 0.020$) genotype still have an increased risk of severe diarrhoea compared with those with a wild-type genotype at medium and high doses.

Limitations of this meta-analysis must be considered. First, the possibility of information and selection biases cannot be completely excluded because some of the included studies were retrospective. Second, it was premature to decide irinotecan dose of 125 mg/m^2 as a rational cutoff value discriminating increased or unchanged risk of toxicity. Third, the funnel plot analysis and Egger test showed the possibility of publication bias at two subgroups. The trim and fill sensitivity analysis did not change the general result, suggesting that the result is not an artefact of unpublished negative studies. Nevertheless, that possibility is not fully excluded by this method. Fourth, we restricted our search strategy to articles published in English or Chinese. Articles with potentially high-quality data that were published in other languages were not included because of anticipated difficulties in obtaining accurate medical translation.

In contrast to the rarity of UGT1A1*28, it was demonstrated that the UGT1A1*6 polymorphism was very frequent in Asian populations.[22,30–32] Pooled OR from four trials[22,30–32] conducted in Asians showed higher risk of severe diarrhoea in patients with UGT1A1*6/*6 genotype compared with those with at least one wild-type allele (OR = 3.54, 95% CI = 1.16–10.77; $P = 0.026$).

Until now, there are many strong evidences that individuals with UGT1A1*28/*28 genotype tend to have a higher prevalence of irinotecan-induced neutropenia.[12–17] Our findings also provide direct evidence that people carrying UGT1A1*28 allele(s) are at an increased risk of irinotecan-induced diarrhoea at medium and high doses. As a result, the influence of UGT1A1*28 on the irinotecan-induced diarrhoea and neutropenia is clear. All of these evidences support the assessment of UGT1A1*28 in routine clinical practice. It is noteworthy that UGT1A1*6 genotypes should also be taken into consideration in Asians.

Conflict of interest statement

None declared.

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