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ARTICLE



Association of *UGT1A1*6*, *UGT1A1*28*, or *ABCC2 c.3972C>T* genetic polymorphisms with irinotecan-induced toxicity in Asian cancer patients: Meta-analysis

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Abstract

Effects of *UGT1A1**6 and *UGT1A1**28 genetic polymorphisms on irinotecaninduced severe toxicities in Asian cancer patients are inconclusive. Also, *ABCC2 c.3972C>T* may affect toxicity of irinotecan. The aim was to assess the aggregated risk of neutropenia or diarrhea in Asian cancer patients taking irinotecan and inherited *UGT1A1*6*, *UGT1A1*28*, or *ABCC2 c.3972C>T* genetic variants. A PubMed literature search for eligible studies was conducted. Odds ratios (ORs) were measured using RevMan software where *p* values <0.05 were statistically significant. Patients that inherited both *UGT1A1*6* and *UGT1A1*28* genetic variants (heterozygous: *UGT1A1*1/*6*+*1/*28 and homozygous: *UGT1A1*6/*6*+*28/*28) were significantly associated with increased risk of neutropenia and diarrhea compared to patients with *UGT1A1*1/*1* (neutropenia: OR 2.89; 95% CI 1.97–4.23; *p*<0.00001; diarrhea: OR 2.26; 95% CI 1.71–2.99; *p*<0.00001). Patients carrying homozygous variants had much stronger effects in developing toxicities (neutropenia: OR 6.23;

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes. © 2022 The Authors. *Clinical and Translational Science* published by Wiley Periodicals LLC on behalf of American Society for Clinical Pharmacology and Therapeutics. 95% CI 3.11–12.47; p < 0.00001; diarrhea: OR 3.21; 95% CI 2.13–4.85; p < 0.00001) than those with heterozygous variants. However, patients carrying the *ABCC2* a 2072C T genetic variant were not similar the second with neutropartie (OR

than those with heterozygous variants. However, patients carrying the *ABCC2 c.3972C>T* genetic variant were not significantly associated with neutropenia (OR 1.67; 95% CI 0.98–2.84; p = 0.06) and were significantly associated with a reduction in irinotecan-induced diarrhea (OR 0.31; 95% CI 0.11–0.81; p = 0.02). Asian cancer patients should undergo screening for both *UGT1A1*6* and *UGT1A1*28* genetic variants to reduce substantially irinotecan-induced severe toxicities.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Cancer patients taking irinotecan and inheriting either UGT1A1*6 or UGT1A1*28 genetic polymorphisms or a combination of these variants (UGT1A1*6 + UGT1A1*28) are associated with severe toxicities such as neutropenia or diarrhea, but the aggregated risk is highly inconsistent, especially in Asian cancer patients. Also, the *ABCC2 c.3972C>T* genetic polymorphism is associated with irinotecan-induced toxicities.

WHAT QUESTION DID THIS STUDY ADDRESS?

Is the combination of *UGT1A1*6* and *UGT1A1*28* genetic polymorphisms or *ABCC2 c.3972C>T* genetic variant associated with severe neutropenia or diarrhea in Asian cancer patients?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Asian cancer patients, irrespective of the type of cancer, who carried both the UGT1A1*6 and UGT1A1*28 genetic variants were significantly associated with increased risk of neutropenia and diarrhea compared to patients with UGT1A1*1/*1, and the effects were even more striking in cancer patients with homozygous variants than those with heterozygous variants. In addition, dose-dependent analysis indicated that a high dose of irinotecan (>150 mg/m²) was significantly associated with diarrhea in cancer patients that carried both the UGT1A1*6 and UGT1A1*28 genetic variants compared to patients on medium and low doses of irinotecan. However, patients carrying the ABCC2 c.3972C>T genetic variant were not significantly associated with irinotecan-induced toxicities.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

The results presented in this meta-analysis will greatly enhance the clinical practice of irinotecan therapy considering *UGT1A1*6* and *UGT1A1*28* pharmacogenetics. The findings of this study will also assist clinicians in suggesting genotyping for *UGT1A1*6* and *UGT1A1*28* polymorphisms prior to administering irinotecan therapy as part of standard care and may advance the translation of irinotecan pharmacogenetics to the bedside.

INTRODUCTION

Irinotecan, an anticancer prodrug, is widely used for the treatment of solid cancers including colorectal, lung, and gastric cancers. It has been used either as monotherapy or in combination with 5-fluorouracil (5-FU)/leucovorin and is considered as first-line therapy in treating these cancers.¹ Severe neutropenia and diarrhea are the main toxicities associated with irinotecan treatment, resulting in treatment failure or even death.²

As an inhibitor of topoisomerase I, irinotecan is converted by carboxylesterase into 7-ethyl-10-hydroxycamptothecin (SN-38), which is 100–1000-fold more active than the parent drug.³ The active SN-38 causes cell death by preventing the DNA strand reannealing and interrupting DNA replication.⁴ The active form of irinotecan, SN-38, is glucuronidated by uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) to inactive SN-38 glucuronide (SN-38G) as part of the detoxification process and is eliminated further through biliary/urinary excretion.⁵ Therefore, the conjugating agent UGT1A1 encoded by the *UGT1A1* gene is an important enzyme that plays a pivotal role in the glucuronidation of SN-38.⁶

Since life-threatening diarrhea or neutropenia may be observed in ~25% of cancer patients taking irinotecan, these toxicities might be related to inter-individual UGT1A1 genetic variability.⁷ UGT1A1 is highly polymorphic, the most well-known polymorphism is UGT1A1*28 with seven TA repeats (A[TA]7TAA) in the promoter region leading to ~70% reduced expression and ~48% reduced function of the UGT1A1conjugating enzyme.⁸ Although several clinical studies have established the strong association of UGT1A1*28genetic polymorphisms with irinotecan-induced severe toxicity such as diarrhea and neutropenia especially in Caucasian cancer patients, the results of this association are still inconclusive and controversial, especially in Asian cancer patients.⁹⁻¹⁸

In addition to the *UGT1A1*28* genetic polymorphism, the other very important mutation of this gene is *UGT1A1*6* causing ~30–60% reduced activity of the UGT1A1-conjugating enzyme and leading to irinotecan-induced toxicity, especially diarrhea and neutropenia, in a considerable proportion of Asian cancer patients as evidenced in multiple studies.^{19–25} However, some studies did not find any significant association of *UGT1A1*6* genetic polymorphism and irinotecan-driven toxicities.^{18,26}

When patients inherit both of these polymorphisms (*UGT1A1*6* and *UGT1A1*28*), irinotecan toxicity may be exacerbated profoundly due to combined genetic effects as evidenced in some studies,^{14,26–28} although the results from other studies are again inconclusive and inconsistent.^{18,29–31} In these controversial clinical situations, it is also important to note that in addition to the UGT1A1 enzyme, irinotecan, SN-38, and SN-38G are transported out of the cell into bile by members of the ATP-binding cassette (ABC) transporter family, especially ABCC2 encoded by the *ABCC2* gene, especially the c.3972C>T single nucleotide polymorphism, are also suspected to influence interindividual variability of irinotecan which may also lead to toxicity.^{7,32–35}

Although there are some meta-analyses that have assessed the aggregated risk of neutropenia and diarrhea in cancer patients treated with irinotecan that have inherited either *UGT1A1*6* or *UGT1A1*28*, the results were highly conflicting and inconsistent even combined effects (*UGT1A1*6* + *28) in the majority of these analyses especially in Asian patients.^{16,18,20,36–40} Also, there is no meta-analysis in the literature that has assessed the association of the *ABCC2* c.3972C>T genetic polymorphism with irinotecan-induced toxicity. Therefore, the present study aimed to establish robust

evidence by assessing the aggregated risk of neutropenia or diarrhea in Asian cancer patients that have inherited either *UGT1A1*6*, *UGT1A1*28*, a combination of these variants (*UGT1A1*6* + *UGT1A1*28*), or *ABCC2* c.3972C>T genetic polymorphisms.

METHODS

Search strategy

A literature search was carried out using PubMed from its inception to the date May 22, 2021 following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines as described elsewhere⁴¹ by two authors (C.A. and N.V.), independently. Five keywords (i.e., "UGT1A1", "ABCC2" "Polymorphisms", "Irinotecan", and "Toxicity") were used to search for eligible studies in PubMed, with the search being restricted to Asian studies. Furthermore, the relevant references in retrieved articles were also searched and reviewed for the inclusion of eligible studies.

Inclusion and exclusion criteria

All eligible studies were selected using the following inclusion criteria: (1) clinical trials and observational studies conducted in Asian countries, (2) studies that explored the association between *UGT1A1*6* and/or *UGT1A1*28* or *ABCC2* and irinotecan-induced toxicities, (3) studies that included patients suffering from neutropenia, hematological toxicity, and diarrhea (grade III–IV), (4) studies that compared both homozygous and heterozygous versus wild-type, and (5) studies published in the English language.

Exclusion criteria were as follows: (1) non-English language papers, (2) reviews and case reports, (3) experiments involving animals, (4) studies without results on the toxicity of neutropenia or diarrhea, (5) studies with undefined genotypes, and (6) studies that simply focused on the allele frequency of either *UGT1A1*6*, *UGT1A1*28*, or *ABCC2* without any correlation with toxicity.

Data extraction and quality assessment of included studies

After the selection of eligible studies, the data extraction process was carried out by two authors (C.A. and N.V.) independently and was cross-checked at the end to remove any errors. General characteristics of included studies (e.g., author name with publication year, country, study design, sample size, age, gender, chemotherapy regimen, dose and schedule of irinotecan, genotyping method, etc.) and clinical outcome data (e.g., number of events with irinotecan-driven neutropenia/diarrhea corresponding to each genotype group) were extracted after reading the full texts in depth. Any disagreements were discussed until consensus between the two reviewers was reached.

Although the Thakkinstian et al.⁴² study suggested considering the Hardy–Weinberg equilibrium (HWE) test for molecular association studies, since the present meta-analysis was conducted based on published studies for the association of *UGT1A1*6* or *UGT1A1*28* genetic polymorphisms with irinotecan-induced toxicities, the HWE test was not performed for these genetic variants. Also previous meta-analyses did not employ the HWE test for *UGT1A1*6* or *UGT1A1*28* genetic variants.

The quality of included studies was assessed based on the Newcastle-Ottawa Scale (NOS) guidelines. With this scale, quality assessment scores range from '0' to '9' against '9' criteria set in NOS in which each criterion is given a star (*) corresponding to a score of '1'. Studies were considered to be of high quality if the NOS score was ≥ 6 and of moderate and low quality if the scores were '4–5' and '0–3', respectively.^{43,44}

Statistical analysis

Odds ratios (ORs) were calculated and forest plots were constructed using RevMan software (RevMan version 5.3 Windows; The Cochrane Collaboration, Oxford, UK) using either fixed or random effects models based on the level of heterogeneity. The level of heterogeneity in the forest plot was measured by the Cochrane chi-square-based Q-test and was considered significant if p < 0.1 as described elsewhere.⁴⁵ However, the I^2 statistic was used to test the heterogeneity of included studies in which $I^2 < 25\%$, $I^2 = 25-50\%$, and $I^2 > 50\%$ indicated low, moderate, and high levels of heterogeneity, respectively.⁴⁶ A random effects model was applied to estimate ORs if $I^2 > 50\%$ and if it was considered that the study had a high level of heterogeneity. In contrast, a fixed effects model was used to estimate ORs if $I^2 < 50\%$. Sensitivity analyses were carried out to assess the impact of any individual studies on measured pooled risk. Publication bias was detected by visual inspection of the funnel plot whereby symmetrical distribution of the plot indicated no publication bias.⁴⁷ All the calculated *p* values were considered statistically significant if they were <0.05.

RESULTS

General characteristics of included studies

In total, 300 articles were retrieved from PubMed following the search strategy, which were then screened to select studies of interest. Applying the exclusion criteria, 195 articles were removed and the remaining 105 full-text articles were assessed in depth in line with the predetermined eligibility criteria. Finally, 42 articles were included in the meta-analysis for assessing the associations of *UGT1A1*6/ UGT1A1*28* or *ABCC2* c.3972C>T with irinotecaninduced severe toxicities.^{12,14,21-24,26-31,34,35,48-75} The complete selection process for the articles following PRISMA guidelines is shown in Figure 1.

General characteristics of the included articles (e.g., author name, year of publication, where the study was undertaken, design of study, genotyping method, chemotherapy regimen, dose and schedule of irinotecan, toxicity assessed, etc.) are detailed in Table 1.

Outcomes of meta-analysis

Association of *UGT1A1*6* with irinotecaninduced severe toxicity

The associations of *UGT1A1*6* genetic polymorphism with irinotecan-induced neutropenia and diarrhea were assessed from 23 and 18 studies, respectively. After pooled estimation it was found that the aggregated risk of neutropenia was significantly higher in cancer patients with the inherited heterozygous and homozygous variants of *UGT1A1*6* (*UGT1A1*1/*6* and *UGT1A1*6/*6*) compared to the patients with the wild-type genotype (i.e., *UGT1A1*1/*1* [OR 2.00; 95% CI 1.64–2.44; p < 0.00001]) as shown in Figure 2a. However, the risk of neutropenia was much stronger in patients carrying the homozygous variant (i.e., *UGT1A1*6/*6* [OR 3.94; 95% CI 2.51–6.20; p < 0.00001]) compared to the patients carrying the heterozygous variant (i.e., *UGT1A1*1/*6* [OR 1.70; 95% CI 1.33–2.18; p < 0.0001]; Figure 2a).

It was also found that patients harboring the heterozygous and homozygous variants of *UGT1A1*6* (*UGT1A1*1/*6* and *UGT1A1*6/*6*) were significantly associated with increased risk of diarrhea compared to the patients with inherited wild-type genotype (i.e., *UGT1A1*1/*1* [OR 2.52; 95% CI 1.65–3.82; p < 0.0001]), that was derived from the patients with homozygous variant (i.e., *UGT1A1*6/*6* [OR 4.65; 95% CI 1.88–11.53; p = 0.009]), but not the patients with the heterozygous variant (i.e., *UGT1A1*1/*6* [OR 1.77; 95% CI 0.94–3.33; p = 0.08]) as shown in Figure 2b.

FIGURE 1 Flowchart of eligible studies included in the meta-analysis.



Association of *UGT1A1*28* with irinotecan-induced severe toxicity

A total of 27 studies assessed the risk of neutropenia in cancer patients taking irinotecan and carrying the *UGT1A1*28* genetic polymorphism. It was found that the aggregated risk of neutropenia was significantly higher in patients with the inherited heterozygous and homozygous variants of *UGT1A1*28* (*UGT1A1*1/*28* and *UGT1A1*28/*28*) compared to patients with the wild-type genotype (i.e., *UGT1A1*1/*1* [OR 1.86; 95% CI 1.52–2.27; p < 0.00001]), that was mainly derived from the patients that carried the homozygous variant (i.e., *UGT1A1*28/*28* [OR 3.11; 95% CI 1.71– 5.63; p = 0.0002]) than the heterozygous variant (i.e., *UGT1A1*1/*28* [OR 1.53; 95% CI 1.18–2.00; p = 0.001]) as shown in Figure 3a.

When the estimated pooled risk for diarrhea was calculated from 20 studies, it was found that the patients that had inherited the heterozygous and homo-zygous variants of the *UGT1A1*28* (*UGT1A1*1/*28* and *UGT1A1*28/*28*) were significantly associated with increased risk of diarrhea (OR 2.74; 95% CI 2.14–3.50; p < 0.00001) compared to the patients with the wild-type

genotype (*UGT1A1*1/*1*) as shown in Figure 3b. Further analysis indicated that the risk of diarrhea was far more significant in patients carrying the homozygous variant (i.e. *UGT1A1*28/*28* [OR 5.70; 95% CI 3.10–10.50; p < 0.00001]) compared to the patients with the heterozygous variant (i.e., *UGT1A1*1/*28* [OR 2.18; 95% CI 1.58–3.02; p < 0.00001]) (Figure 3b).

Effects of combined *UGT1A1*6* and *UGT1A1*28* genetic polymorphisms with irinotecan-induced severe toxicity

In total, 27 and 20 studies investigated the combined effects of *UGT1A1*6* and *UGT1A1*28* genetic polymorphisms with irinotecan-induced neutropenia and diarrhea, respectively. After pooled estimation, it was found that patients carrying both *UGT1A1*6* and *UGT1A1*28* variants (heterozygous: *UGT1A1*1/*6* + *UGT1A1*1/*28* and homozygous: *UGT1A1*6/*6* + *UGT1A1*28/*28*) were significantly associated with increased risk of neutropenia compared to patients with wild-type genotype (i.e. *UGT1A1*1/*1* [OR 2.89; 95% CI 1.97–4.23; p < 0.00001]) as shown in Figure S1A. Patients with homozygous variants

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TABLE 1 Baseline characteristics of included studies

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Author	Country	Study design	Type of cancer	Patients (n)
Hirasawa et al. 2013 ²⁸	Japan	Retrospective	Gynecologiccancer	53
Ando et al. 2017 ⁴⁹	Japan	Prospective	Colorectal cancer	35
Atasilp et al. 2015 ¹⁴	Thailand	Retrospective	Colorectal cancer	44
Atasilp et al. 2020 ¹⁴	Thailand	Retrospective and prospective	Colorectal cancer	66
Bai et al. 2017 ³¹	China	Retrospective	Lung cancer, colorectal cancer, esophageal cancer	81
Bandyopadhyay et al. 2021 ⁵⁰	India	observational cohort	SCLC	213
Yang et al. 2015 ²⁷	China	Retrospective	Pancreatic cancer	48
Choi et al. 2012 ⁵¹	Korea	Retrospective	Colorectal cancer	29
Liu et al. 2007 ¹²	China	Retrospective	Colorectal cancer	128
Deng et al. 2017 ⁵²	China	Retrospective	Malignanttumor	115
Gao et al. 2013 ⁴⁸	China	Retrospective	Gastric cancer, esophageal cancer	133
Gao et al. 2013 ²¹	China	Retrospective	Colorectal cancer	276
Han et al. 2007 ³⁴	Korea	Prospective	NSCLC	107
Han et al. 2009 ²⁴	Korea	Prospective	NSCLC	107
Minami et al. 2006 ⁵³	Japan	Retrospective	Lung, colon, stomach and others	55 62
Horikawa et al. 2015 ³⁰	Japan	Retrospective	Cervical cancer	103 23
Kimura et al. 2018 ²⁹	Japan	Retrospective	Rectal cancer	46
Liu et al. 2017 ⁵⁴	China	Retrospective	Colorectal cancer	661
Onoue et al. 2009 ²²	Japan	Prospective	Lung, gastric, colorectal and others	133



Regimen	Irinotecan dose (mg/m ²)/schedule	Toxicity assessment	Genotyping method
Irinotecan + cisplatin or irinotecan alone	60/(days 1, 8, and 15 every 4 weeks) or 100/(days 1, 8, and 15 every 4 weeks)	Neutropenia, diarrhea	Invader UGT1A1 Molecular Assay kit
XELIRI	200/biweekly	Neutropenia, diarrhea	N/A
FOLFIRI or FOLFIRI + cetuximab or FOLFIRI + bevacizumab or modified FOLFIRI or single irinotecan or irinotecan + cetuximab/capecitabine	180/biweekly, 100/day 1	Neutropenia	Pyrosequencing
FOLFIRI or FOLFIRI + cetuximab or FOLFIRI + bevacizumab or modified FOLFIRI or single irinotecan or irinotecan + cetuximab or irinotecan + capecitabine	180/biweekly or 180/every 3 weeks or 100/(day 1)	Neutropenia	Pyrosequencing, real time-PCR
Single irinotecan or irinotecan + cisplatin or irinotecan + bevacizumab or irinotecan + cisplatin + bevacizumab or FOLFIRI or FOLFIRI + bevacizumab/cetuximb	60 (days 1, 8, and 15 for every 4 weeks) or 130 (day 1 for every 3 weeks) or 180/biweekly or 180 (day 1 for every 3 weeks) or 150/biweekly	Neutropenia, diarrhea	DFMH using fluorescent probes
Irinotecan + cisplatin	100 (day 1 of a 3-week cycle) or 65 (days 1 and 8 of a 3-week cycle)	Neutropenia, diarrhea	PCR-RFLP
FOLFIRI	180/biweekly	Neutropenia	Direct sequencing
CPT-11 + S-1	225/every 3 weeks	Neutropenia, diarrhea	Direct sequencing
FOLFIRI	180/biweekly	Neutropenia, diarrhea	Direct sequencing
FOLFIRI	180/biweekly	Neutropenia, diarrhea	Direct sequencing
Irinotecan + cisplatin or FOLFIRI or single irinotecan or irinotecan + cetuximab	180 mg/m ²	Neutropenia	Direct sequencing
FOLFIRI or single irinotecan or irinotecan + capecitabine	180 mg/m ²	Neutropenia, diarrhea	Direct sequencing
Single irinotecan or irinotecan + cisplatin	65 or 80/every 3 weeks	Neutropenia and diarrhea	Sequencing
Single irinotecan or irinotecan + cisplatin	65 or 80/every 3 weeks	Neutropenia, diarrhea	Sequencing
Single irinotecan	100/weekly	Neutropenia	Pyrosequencing
Irinotecan + cisplatin	150/biweekly		
IROX	200/every 3 weeks		
CPT-11 + NDP every 3 weeks	60 (day 1 and 8)	Neutropenia, diarrhea	Direct sequencing
Irinotecan-based regimen	80/day S-1 (days 1–5, 8–12, 22–26, and 29–33), 60 (days 1, 8, 22, and 29), and 45 Gy radiation (1.8 Gy/day, 5 days per week for 5 weeks)	Neutropenia, diarrhea	Invader UGT1A1 Molecular Assay kit
Single irinotecan or irinotecan + target treatment or irinotecan + 5-FU (5-FU, capecitabine, S-1, or tegafur) or FOLFOXIRI	180 mg/m ² or 150 mg/m ²	Neutropenia, diarrhea	Direct sequencing
Single irinotecan or irinotecan + platinum or irinotecan + other anticancer agents or FOLFIRI	<100 or 101–150, or 151–200 or >200 mg/m ² weekly or biweekly or every 3 or 4 weeks	Neutropenia	Direct sequencing

1620

TABLE 1 (Continued)

Author	Country	Study design	Type of cancer	Patients (n)
Matsuoka et al. 2020 ⁵⁵	Japan	Retrospective	Cervical cancer	51
Li et al. 2014 ⁵⁶	China	Retrospective	Colorectal cancer	167
Moriya et al. 2014 ²³	Japan	Retrospective	Gynecological cancer	44
Nakamura et al. 2011 ⁵⁷	Japan	Randomized phase II trial	NSCLC	77
Okuyama et al. 2011 ²⁶	Japan	Prospective	Colorectal cancer	39
Park et al. 2010 ⁵⁸	Korea	Retrospective	Gastric cancer	44
Peng et al. 2017 ⁵⁹	China	Retrospective	Gastrointestinal cancer, lung cancer	106
Satoh et al. 2011 ⁶⁰	Japan	Prospective	Gastrointestinal cancer	73
Shi et al. 2015 ⁶¹	China	Retrospective	SCLC	29
Chen et al. 2020 ⁶²	China	Retrospective	Colorectal cancer	86
Sunakawa et al. 2010 ⁶³	Japan	Retrospective	Colorectal cancer	42
Takahara et al. 2013 ⁶⁴	Japan	Prospective	Pancreatic cancer	44
Takano et al. 2009 ⁶⁵	Japan	Prospective	Gynecologic cancer	30
Yamaguchi et al. 2019 ⁶⁶	Japan	Retrospective	Gastric cancer	74
Wang et al. 2012 ⁶⁷	China	Retrospective	Colorectal cancer	130
Wang et al. 2017 ⁶⁸	China	Retrospective	Lung, colon, rectum, esophagus, stomach and others	206
Xiao et al. 2015 ⁶⁹	China	Retrospective	E-SCLC	67
Xu et al. 2016 ⁷⁰	China	Retrospective	Colorectal cancer	183
Xu et al. 2020 ⁷¹	China	Retrospective	Pulmonary neuroendocrine tumors	68
Xu et al. 2015 ⁷²	China	Retrospective	Ovarian cancer	89
Yamamoto et al. 2009 ⁷³	Japan	Prospective	NSCLC	36
Lu et al. 2014 ⁷⁴	China	Retrospective	Lung and gastrointestinal cancer	89
Yun et al. 2014 ⁷⁵	China	Retrospective	SCLC	31

Abbreviations: 5-FU, 5-fluorouracil; CPT-11, irinotecan; CTCAE, Common Terminology Criteria for Adverse Events; DFMH, digital fluorescence molecular hybridization; E-SCLC, extensive-stage small cell lung cancer; FLIRI, irinotecan + 5-FU + folic acid; FOLFIRI, irinotecan + 5-FU + leucovorin; IFL, irinotecan + 5-FU; IROX, irinotecan + oxaliplatin; Lv5FU2-IRI, irinotecan + 5-FU + folic acid; N/A, not available; NCI-CTC, National Cancer Institute Common Toxicity Criteria; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NDP, nedaplatin; NSCLC, non-small cell lung cancer; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; SCLC, small cell lung cancer; XELIRI, irinotecan + capecitabine + bevacizumab.



Regimen	Irinotecan dose (mg/m ²)/schedule	Toxicity assessment	Genotyping method
Irinotecan + NDP	60/(days 1 and 8) or 60/(days 1 and 15)	Neutropenia, diarrhea	Direct sequencing
FOLFIRI or irinotecan + cetuximab/bevacizumab or irinotecan + raltitrexed or irinotecan + capecitabine	180/biweekly or 180/every 3 weeks	Neutropenia, diarrhea	Pyrosequencing
Irinotecan + cisplatin or irinotecan + mitomycin C	40–60/(days 1, 8, and 15) or 70–150/(days 1 and 15 or on days 1, 8, and 15)	Neutropenia	Direct sequencing
Irinotecan + paclitaxel or irinotecan + gemcitabine	50 (days 1, 8, and 15 for every 4 weeks) or 100 (days 1 and 8 for every 3 weeks)	Neutropenia	Direct sequencing
FOLFIRI	$150 \text{mg/m}^2 \text{ or } 100 \text{mg/m}^2$	Neutropenia	PCR-RFLP
Irinotecan + oxaliplatin	150/every 3 weeks	Neutropenia	Direct sequencing
FOLFIRI or single irinotecan or irinotecan + cisplatin or irinotecan + capecitabine	180 mg/m ² or 90 mg/m ²	Neutropenia, diarrhea	Direct sequencing
Single irinotecan	$150 \text{ mg/m}^2 \text{ or } 100 \text{ mg/m}^2 \text{ or } 75 \text{ mg/m}^2$	Neutropenia, diarrhea	Invader UGT1A1 Molecular Assay kit
Irinotecan + cisplatin	$65 \mathrm{mg/m^2}$	Diarrhea	Direct sequencing
FOLFIRI	180/biweekly	Neutropenia, diarrhea	Pyrosequencing
FOLFIRI	180/biweekly	Neutropenia, diarrhea	Direct sequencing
Single irinotecan	100 (days 1, 8, and 15 for every 4 weeks)	Neutropenia	Direct sequencing
Irinotecan + cispatin	60 (day 1, 8, 15 for every 4 weeks)	Neutropenia, diarrhea	Invader UGT1A1 Molecular Assay kit
Irinotecan-based regimen	150/biweekly	Neutropenia, diarrhea	Invader UGT1A1 Molecular Assay kit
FOLFIRI or IFL	180/biweekly or 125/every 6 weeks	Neutropenia, diarrhea	Direct sequencing
Irinotecan + antitumor platinum drugs or irinotecan + 5-FU or irinotecan + capecitabine or single irinotecan	300–350/every 3 weeks or 250/every 3 weeks or 180/biweekly or 180/every 3 weeks	Neutropenia, diarrhea	Direct sequencing
CPT-11 + appropriate platinum drug (cisplatin, carboplatin, or lobaplatin)	60 (day 1, 8, 15 for every 4 weeks) or 85/ every 3 weeks	Neutropenia, diarrhea	Pyrosequencing
FOLFIRI or irinotecan + capecitabine	150/biweekly or 150/every 3 weeks	Neutropenia, diarrhea	Direct sequencing
Single irinotecan or irinotecan + cisplatin	60 (days 1, 8, and 15 for every 4 weeks)	Neutropenia, diarrhea	Quantitative fluorescent PCR
Irinotecan + cisplatin	60 (days 1 and 8 for every 3 weeks)	Neutropenia, diarrhea	Pyrosequencing
Single CPT-11	100 (days 1 and 8 for every 3 weeks)	Neutropenia	Direct sequencing
Irinotecan + cispatin, NDP, carboplatin or lobaplatin; modified FOLFIRI; irinotecan + platinum, 5-FU, pemetrexed, or raltitrexed	100–175/biweekly or 100–175/every 3 weeks	Neutropenia, diarrhea	Direct sequencing
Single irinotecan	80 (days 1 and 8 for every 3 weeks)	Neutropenia, diarrhea	Direct sequencing

(a)	UGT1A	1*6	*1/*	1		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.1.1 *6/*6+*1/*6vs *1/*	1						
Ando 2017	3	9	5	22	1.5%	1.70 [0.31, 9.37]	
Atasilp 2015	2	7	1	37	0.2%	14,40 [1,10, 189,33]	→
Atasilp 2020	4	12	6	54	1.1%	4.00 (0.92, 17, 40)	<u> </u>
Bai 2017	3	19	11	62	3.3%	0.87 (0.22, 3.51)	
Bandyonadhyay 2021	3	12	13	aa	1.6%	2 21 [0 53 9 22]	
Chen 2020	8	20	10	88	2.1%	3 73 [1 22 11 44]	
Dong 2017	2	20	2	77	2.1%	2 52 (0 56, 22 06)	
Delig 2017	0		15		0.9%	5.52 [0.50, 22.00]	
Gao 10010	20	39	15	94	3.3%	0.04 [2.40, 12.79]	
Gao J 2013	29	98	21	1/8	10.3%	2.35 [1.29, 4.27]	
Hirasawa 2013	8	16	10	31	2.3%	2.70 [0.80, 9.14]	
Li 2014	9	55	12	112	5.0%	1.63 [0.64, 4.14]	T
Liu 2017	57	230	79	431	31.5%	1.47 [1.00, 2.16]	
Ma 2020	2	17	4	51	1.3%	1.57 [0.26, 9.42]	
Nakamura 2011	8	19	9	58	2.0%	3.96 [1.25, 12.57]	
Okuyama 2011	6	13	11	26	3.0%	1.17 [0.31, 4.46]	
Onoue 2009	20	54	9	79	3.5%	4.58 [1.88, 11.11]	
Park 2010	4	16	0	28	0.2%	20.52 [1.03, 410.69]	_
Peng 2017	9	23	6	83	1.2%	8.25 [2.54, 26.84]	
Wang 2012	4	53	8	77	4.6%	0.70 [0.20, 2.47]	
Wang 2017	6	34	9	67	3.8%	1.38 [0.45, 4.26]	
Xu 2016	7	54	18	129	7.0%	0.92 [0.36, 2.34]	
Xu Q 2015	11	25	37	64	8.9%	0.57 [0.23, 1.46]	
Yang 2015	10	14	12	34	1.5%	4.58 [1.18, 17, 79]	
Subtotal (95% CI)		874		1965	100.0%	2.00 [1.64, 2.44]	♦
Total events	236		314				
Hotorogeneitr Chiz - 42	200 25 df-	22 (P -	0.0063-14	2 - 49%			
Test for overall effect: 7		22 (F -	0.000), 1	- 40%	,		
Testion overall ellect. 2-	- 10.00 (F	< 0.000	501)				
1 1 2 *1/*6.00 *1/*1							
1.1.2 1/ 005 1/ 1		-		~ 7			
Atasiip 2015	2		1	37	0.2%	14.40 [1.10, 189.33]	,
Bai 2017	3	17	11	62	4.3%	0.99 [0.24, 4.06]	
Gao 2013	16	34	15	94	4.6%	4.68 [1.96, 11.18]	
Gao J 2013	21	79	27	178	13.3%	2.02 [1.06, 3.86]	
Li 2014	7	48	12	112	6.7%	1.42 [0.52, 3.87]	
Liu 2017	43	198	79	431	42.5%	1.24 [0.81, 1.88]	
Ma 2020	1	14	4	51	1.7%	0.90 [0.09, 8.80]	
Okuyama 2011	5	12	11	26	4.4%	0.97 [0.24, 3.90]	
Onoue 2009	17	48	9	79	4.8%	4.27 [1.71, 10.62]	
Pena 2017	7	21	6	83	1.8%	6.42 [1.88, 21.96]	
Wang 2012	4	48	8	77	6.1%	0.78 (0.22, 2.76)	
Xu 2016	7	51	18	129	9.6%	0.98 (0.38, 2.51)	
Subtotal (95% CI)		577		1359	100.0%	1.70 [1.33, 2.18]	♦
Total events	133		201				, T
Heterogeneity Chi ² = 23	12 df=	11 (P =	0.02) 12:	= 52%			
Test for overall effect: 7	- A 22 /P	< 0.000	0.02),1 -	- 52 %			
restion overall effect. 2	- 4.22 (r	~ 0.000	517				
1.1.3 *6/*6vs *1/*1							I
Rai 2017	0	2	4.4	60	6.0%	0.00 0.04 40.04	
Dai 2017		2	15	02	0.9%	0.90 [0.04, 19.94]	
Gao 2013	4	5	15	94	2.0%	21.07 [2.20, 201.84]	
Gao J 2013	8	19	21	1/8	20.3%	4.07 [1.50, 11.04]	
Li 2014	2		12	112	6.8%	3.33 [0.58, 19.10]	
Liu 2017	14	32	79	431	41.4%	3.47 [1.65, 7.26]	
Ma 2020	1	3	4	51	2.0%	5.88 [0.43, 79.77]	
Okuyama 2011	1	1	11	26	2.7%	4.04 [0.15, 108.57]	_
Onoue 2009	3	6	9	79	4.3%	7.78 [1.36, 44.50]	
Peng 2017	2	2	6	83	0.5%	59.62 [2.58, 1377.45]	│
Wang 2012	0	5	8	77	7.5%	0.74 [0.04, 14.65]	
Xu 2016	0	3	18	129	6.5%	0.86 [0.04, 17.36]	
Subtotal (95% CI)	-	85		1322	100.0%	3.94 [2.51, 6.20]	◆
Total events	35		200				
Heterogeneity: Chi ² = 8	88. df = 1	0 (P = 1).54): I ² =	0%			
Test for overall effect: 7	= 5.95 (P	< 0.00	001)	* .*			I
. cottor official elleve Z.	0.00 (1	0.000	,				
							0.01 0.1 1 10 100
						96	Wild type (*1/*1) UGT1A1*6 Carriers
						~	

FIGURE 2 (a) Forest plot of the UGT1A1*6 versus UGT1A1*1/*1 for irinotecan-induced neutropenia. (b) Forest plot of the UGT1A1*6 versus UGT1A1*1/*1 for irinotecan-induced diarrhea.

(b)	UGT1A	1*6	* 1/*	1		Odds Ratio	Odds Batio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Random, 95% CL	M-H. Bandom, 95% Cl
1.1.1 *6/*6+*1/*6vs *1/*	1	Total	Liento	Total	roigin	in the training of the trainin	
Ando 2017	2	9	4	22	34%	1 29 (0 19 8 67)	
Bai 2017	3	22	3	65	4 1 %	3 26 [0.61 17 52]	· · · · · · · · · · · · · · · · · · ·
Bandyonadhyay 2021	5	12	17	99	5.7%	3 45 [0 98 12 16]	
Chen 2020	ğ	20	6	66	5.9%	8 18 [2 42 27 62]	
Deng 2017	ő	35	2	77	1.6%	0.10 [2.42, 21.02]	
Gan 2013	6	98	10	178	6.8%	1 10 (0 30 3 11)	
Gao.12013	29	98	27	178	9.5%	2 35 [1 29 4 27]	
Hirasawa 2013	4	16	1	37	2.6%	12 00 [1 22 118 10]	
1 i 2014	16	55	18	112	8.4%	2 14 0 99 4 63	
Liu 2014	17	230	42	431	9.6%	0.74 [0.33, 4.03]	
Ma 2020	2	17	2	51	3.1%	3 27 10 42 25 211	
Ma 2020 Pong 2017	2	22	10	02	1 1 96	0.70 (0.42, 23.21)	
Chi 2015	4	25	10	21	2 4 96	16 00 [1 45 176 45]	· · · · · · · · · · · · · · · · · · ·
Mana 2012	13	53	10	77	7.6%	2 19 (0 97 5 42)	
Wong 2012	10	24	0	67	6.0%	2.10 [0.07, 5.42]	
Viang 2017	10	34	2	45	4.00%	0.00 (1.00, 0.73)	
Xia0 2015	24	22	3	45	4.9%	8.00 [1.80, 34.39]	
Xu 2016	31	14	12	109	8.5%	5.83 [2.73, 12.42]	
XU Q 2015 Subtetel (05% CI)	3	25	5	1793	4.6%	1.61 [0.35, 7.30]	
Subiotal (95% CI)		652		1/02	100.0%	2.52 [1.05, 5.82]	
l otal events	164	~~ **	181				
Heterogeneity: I au- = 0.	39; Chin=	= 38.43	at = 17	(P = 0.0	102); 1*= ;	06,00	
Test for overall effect: Z =	= 4.32 (P	< 0.000)1)				
112 *1/*6.00 *1/*1							
				05	0.40	0.05 10.07 40.70	
Bai 2017	3	20	3	05	8.4%	3.65 [0.67, 19.72]	
Gao 2013	4	19	10	1/8	11.9%	0.90 [0.27, 2.95]	
LI 2014	12	48	18	112	15.3%	1.74 [0.76, 3.97]	
Liu 2017	14	198	42	431	17.1%	0.70 [0.38, 1.32]	
Ma 2020	0	14	2	51	3.5%	0.68 [0.03, 15.04]	
Peng 2017	2	21	10	83	8.9%	0.77 [0.16, 3.81]	
Shi 2015	3	8	1	21	5.0%	12.00 [1.02, 141.34]	· · · · · · · · · · · · · · · · · · ·
Wang 2012	11	48	10	77	14.1%	1.99 [0.77, 5.13]	
Xu 2016	27	68	12	109	15.8%	5.32 [2.46, 11.52]	
Subtotal (95% CI)		504		1127	100.0%	1.77 [0.94, 3.33]	-
Total events	/6	24.50	108		C). 17 - C'	201	
Heterogeneity: Taur = 0.	51; Chi*=	= 21.56	, df = 8 (F	' = 0.0U	16); 1* = 63	3%	
l est for overall effect: Z =	= 1.76 (P	= 0.08)					
1.1.3 *6/*6vs *1/*1							
Poi 2017		2	2	65	6.20	2 67 10 1 4 00 621	
Gao 2012	2	10	10	170	15.0%	1 00 0 40 0 771	
040 2013	2	19	10	110	15.0%	1.90 [0.40, 9.77] 6 06 (1 40, 00 70)	
Li 2014	4		10	112	10.1%	0.90[1.45, 55.79]	
Liu 2017	3	32	42	431	18.5%	0.96 [0.28, 3.28]	
Ma 2020	2	3	2	51	1.1%	49.00 [3.02, 794.52]	
Peng 2017	0	2	10	83	0.5%	1.40 [0.06, 31.22]	
Shi 2015	1	1	1	21	5.2%	41.00 [1.12, 1507.26]	
wang 2012	2	5	10	11	12.5%	4.47 [0.66, 30.12]	
Xu 2016 Subtetel (05% Ch	4	6	12	109	13.3%	16.17 [2.67, 97.82]	
Subtotal (95% CI)		11		1127	100.0%	4.05 [1.88, 11.53]	-
i otal events	18		108			u	
Heterogeneity: Tau ² = 0.	11; Chi*=	= 14.03	, df = 8 (F	' = 0.08); I*= 439	8	
l est for overall effect: Z =	= 3.32 (P	= 0.000	18)				
							0.01 0.1 1 10 100
							Wild type (*1/*1) UGT1A1*6 Carriers

FIGURE 2 (Continued)

had much stronger effects for developing neutropenia (OR 6.23; 95% CI 3.11–12.47; p < 0.00001) than the patients with heterozygous variants (OR 2.04; 95% CI 1.28–3.27; p = 0.003; Figure S1A).

It was also found that the aggregated risk of diarrhea was significantly higher in cancer patients that carried both *UGT1A1*6* and *UGT1A1*28* variants (heterozygous: *UGT1A1*1/*6* + *UGT1A1*1/*28* and homozygous: *UGT1A1*6/*6* + *UGT1A1*28/*28*) compared to the patients with wild-type genotype (i.e., *UGT1A1*1/*1* [OR 2.26; 95% CI 1.71–2.99; p < 0.00001]) as shown in Figure S1B. Further analysis indicated that the risk of

(a)	LIGT1A	1*28	* 1/*	1		Odds Batio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.1.1 *28/*28+*1/*28vs	*1/*1						
Ando 2017	3	4	5	22	0.3%	10.20 (0.86, 120.96)	
Atasilp 2015	1	10	2	34	0.6%	1.78 [0.14, 21.91]	
Atasilp 2020	4	15	6	51	1.5%	2.73 [0.65, 11.36]	
Bai 2017 Banduana dhuau 2024	3	20	11	61	3.6%	0.80 [0.20, 3.22]	
Chen 2020	10	26	0	42	4.0%	1.20 [0.40, 3.60]	
Deng 2017	ů	20	9	85	2.970	2.52 [0.64, 7.52]	
Gao 2013	10	35	25	98	7.3%	1.17 [0.49, 2.77]	_
Gao J 2013	19	58	37	218	8.1%	2.38 [1.24, 4.58]	_
Hirasawa 2013	2	9	3	44	0.6%	3.90 [0.55, 27.74]	
Li 2014	10	58	11	109	4.9%	1.86 [0.74, 4.67]	+
Liu 2017	46	160	90	501	24.0%	1.84 [1.22, 2.78]	
Liu CY 2007	14	26	5	102	0.7%	22.63 [6.93, 73.97]	
Lu 2014	4	22	8	67	2.5%	1.64 [U.44, 6.08]	
Ma 2020 Nakamura 2011	4	19	12	49	2.1%	0.27 [1.04, 37.09]	
Okuvama 2011	5	6	12	32	0.5%	8 33 [0.87 80 11]	
Onoue 2009	2	23	27	110	6.6%	0.29 [0.06, 1.33]	
Park 2010	1	193	0	113	0.5%	1.77 [0.07, 43.79]	
Peng 2017	5	25	10	81	2.9%	1.77 [0.54, 5.79]	
Wang 2012	5	40	7	90	2.9%	1.69 [0.50, 5.70]	
Wang 2017	6	19	9	86	1.7%	3.95 [1.20, 12.96]	
Xiao 2015	2	11	4	56	0.8%	2.89 [0.46, 18.17]	
Xu 2016 Xu 0 2016	10	62	15	121	6.6%	1.36 [0.57, 3.23]	
Xu Q 2015 Vang 2015	13	10	40	20	0.3%	0.97 [0.37, 2.00]	
Yun 2014	3	6	10	25	1 2%	2.00 [0.50, 8.55]	
Subtotal (95% CI)	0	987	Ŭ	2420	100.0%	1.86 [1.52, 2.27]	•
Total events	201		385				
Heterogeneity: Chi ² = 39	.03, df = 2	26 (P =	0.05); l² =	33%			
Test for overall effect: Z =	= 5.99 (P	< 0.000	01)				
1.1.2 *1/*28vs *1/*1							
Atasilp 2015	1	9	2	34	0.9%	2.00 [0.16, 24.92]	
Bai 2017	2	16	11	61	4.7%	0.65 [0.13, 3.28]	
Gao 12013	19	32	20	219	10.9%	0.97 [0.39, 2.44]	
Li 2014	10	54	11	109	7.0%	2.00 [1.22, 4.03]	
Liu 2017	42	152	90	501	35.8%	1.74 [1.14, 2.66]	
Ma 2020	3	15	2	49	0.9%	5.88 [0.88, 39.21]	
Okuyama 2011	4	6	12	32	1.5%	3.33 [0.53, 21.03]	
Onoue 2009	2	22	27	110	9.7%	0.31 [0.07, 1.40]	
Peng 2017	3	19	10	81	3.8%	1.33 [0.33, 5.40]	
Wang 2012	2	32	7	90	4.1%	0.79 [0.16, 4.02]	
Xu 2016 Subtotal (95% CI)	8	51 463	15	121	8.9%	1.31 [0.52, 3.33]	
Total events	102	405	240	1504	100.0%	1.55 [1.18, 2.00]	•
Hotorogonoity Chi ² = 12	14 df = 1	1 (P =	245 	0.96			
Test for overall effect: Z =	= 3.19 (P =	= 0.001)	5.0			
1.1.3 *28/*28 vs *1/*1							
Atasilp 2015	0	1	2	34	2.1%	4.33 [0.14, 136.43]	
Bai 2017	1	4	11	61	10.5%	1.52 [0.14, 15.97]	
Gao 2013	2	3	25	98	5.1%	5.84 [0.51, 67.21]	
Gao J 2013	1	3	37	218	6.9%	2.45 [0.22, 27.68]	
LI 2014 Liu 2017	0	4	11	109	9.3%	0.95 [0.05, 18.83]	
Ma 2020	1	4	2	49	2 3 96	7 83 [0 54 113 02]	,
Okuyama 2011	1	1	12	32	3.7%	4.92 [0.19, 130.36]	
Onoue 2009	O	1	27	110	7.5%	1.01 [0.04, 25.57]	
Peng 2017	2	6	10	81	9.5%	3.55 [0.57, 21.95]	
Wang 2012	3	8	7	90	7.4%	7.11 [1.40, 36.17]	│ ──
Xu 2016	2	11	15	121	21.1%	1.57 [0.31, 7.97]	
Subtotal (95% CI)		54		1504	100.0%	3.11 [1.71, 5.63]	
i otal events	17	10- 0	249	200			
Test for overall effect: 7 -	20,01 = 11 3 72 /P	- 0.000	.90); I* = 1 2)	7,20			
restion overall effect. Z =	- 9,19 (P -	- 0.000	-)				
							0.01 0.1 1 10 100 Wild type (*1/*1) UGT1A1*28 Carriers

FIGURE 3 (a) Forest plot of the UGT1A1*28 versus UGT1A1*1/*1 for irinotecan-induced neutropenia. (b) Forest plot of the UGT1A1*28 versus UGT1A1*1/*1 for irinotecan-induced diarrhea.

(b)	LICTAN	41:20	*4/2			Oddo Datia	Odda Patia
Study or Subgroup	Events	Total	Events	Total	Weight	M H Fixed 95% CL	M H Eived 95% Cl
1.1.1 *28/*28+*1/*28vs	*1/*1	Total	Lycins	Total	weight	M-11, 11Xeu, 35% CI	M-11, 11Xed, 35% CI
Ando 2017	2	4	4	22	0.9%	4 50 (0 48 42 25)	
Bai 2017	2	20	4	61	2.6%	1 58 0 27 9 371	
Bandyopadhyay 2021	17	43	6	42	5.4%	3.92 [1.36, 11.31]	
Chen 2020	9	26	7	60	4.0%	4.01 [1.30, 12.39]	
Deng 2017	2	29	0	85	0.3%	15.55 [0.72, 333.75]	
Gao 2013	5	58	11	218	6.2%	1.78 [0.59, 5.33]	
Hirasawa 2013	2	9	3	44	1.2%	3.90 [0.55, 27.74]	
Li 2014	18	58	16	109	11.2%	2.62 [1.21, 5.64]	
Liu 2017	19	160	40	501	24.9%	1.55 [0.87, 2.77]	
Liu CY 2007	7	29	6	101	3.0%	5.04 [1.54, 16.48]	
Lu 2014	5	22	4	67	2.2%	4.63 [1.12, 19.16]	
Ma 2020	1	19	3	49	2.3%	0.85 [0.08, 8.74]	
Peng 2017	10	25	2	81	0.8%	26.33 [5.24, 132.46]	→
Shi 2015	3	10	2	20	1.4%	3.86 [0.53, 28.24]	
Wang 2012	9	40	14	90	9.8%	1.58 [0.62, 4.02]	
Wang 2017	2	19	16	86	7.6%	0.51 [0.11, 2.46]	
Xiao 2015	1	11	6	56	2.6%	0.83 [0.09, 7.70]	
Xu 2016	26	62	17	121	9.8%	4.42 [2.15, 9.07]	
Xu Q 2015	8	22	5	67	2.3%	7.09 [2.01, 24.95]	
Yun 2014	2	6	4	25	1.5%	2.63 [0.35, 19.51]	
Subtotal (95% CI)		672		1905	100.0%	2.74 [2.14, 3.50]	
Total events	150		170	000			
Heterogeneity: Chi* = 28	1.00, df = 1	19 (P = 1	0.08); 1* =	32%			
Test for overall effect: Z:	= 7.98 (P -	< 0.000	01)				
1 1 2 *1/*28vs *1/*1							
Rai 2017	2	16	4	61	2 206	2 0.4 (0 24 12 26)	
Gao 2013	5	55	11	218	0.1%	1 88 (0 63 5 66)	
112014	16	54	16	109	16.8%	2 45 [1 11 5 39]	
Liu 2017	18	152	40	501	37.0%	1 55 [0 86 2 79]	
Ma 2020	1	15	3	49	3.0%	1 10 0 11 11 381	
Peng 2017	6	19	2	81	1.2%	18.23 [3.32, 100,24]	· · · · · · · · · · · · · · · · · · ·
Shi 2015	1	7	2	20	2.0%	1.50 [0.11, 19.64]	
Wang 2012	6	32	14	90	13.4%	1.25 [0.44, 3.60]	
Xu 2016	19	51	17	121	14.3%	3.63 [1.69, 7.81]	
Subtotal (95% CI)		401		1250	100.0%	2.18 [1.58, 3.02]	•
Total events	74		109				
Heterogeneity: Chi ² = 10	.60, df = 8	B(P = 0)	23); 2 =	25%			
Test for overall effect: Z :	= 4.72 (P	< 0.000	01)				
4 4 2 420 220 - 4424							
1.1.3 -28/-28VS -1/*1	1	÷.					
Bai 2017	0	4	4	61	10.2%	1.42 [0.07, 30.74]	
Gao 2013	U	3	11	218	6.1%	2.58 [0.13, 52.93]	and the second sec
Li 2014	2	4	16	109	9.6%	5.81 [0.76, 44.28]	
Liu 2017	1	8	40	501	18.6%	1.65 [0.20, 13.72]	
Ma 2020	0	4	3	49	9.7%	1.48 [0.07, 33.34]	
Peng 2017	4	0	2	81	1.6%	19.00 [8.73, 714.67]	
Sill 2015 Wang 2012	2	3	14	20	2.9%	2 26 (0 20 45 20)	
Vu 2016	3 7	0 44	14	104	17 40	3.20 [0.70, 15.20]	
Subtotal (95% CI)	(51	17	1250	100.0%	5.70 [3.10 10.50]	
Total evente	10	51	100	12.50	100.070	5110 [5110, 10.50]	•
Heterogeneity Chi2 - 10	157 df - 9	R (P - 0	23) 12-	74%			
Test for overall effect: 7	= 5 59 /P	< 0.000	01)	24 /0			
reaction overall ellect. Z.	0.00 (1	0.000	.,				
							U.UT U.T T 10 100 Wild type (*1/*1) UGT141*28 Carriers
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FIGURE 3 (Continued)

diarrhea was much greater in patients carrying homozygous variants (i.e. UGT1A1*6/*6 + UGT1A1*28/*28[OR 3.21; 95% CI 2.13-4.85; p < 0.00001]) compared to patients with heterozygous variants (i.e., UGT1A1*1/*6 + UGT1A1*1/*28 [OR 1.83; 95% CI 1.31-2.55; p = 0.0004]; Figure S1B). Subgroup analysis for combined effects of *UGT1A1*6* and *UGT1A1*28* with irinotecan-induced severe toxicity

To assess the effects of the combined *UGT1A1*6* and *UGT1A1*28* variants in different Asian ethnicities, this

study undertook subgroup analysis for the toxicities reported in at least two studies in the respective country. Subgroup analysis revealed that patients carrying both $UGT1A1^*6$ and $UGT1A1^*28$ variants were significantly associated with increased risk of neutropenia in Chinese (OR 2.29; 95% CI 1.20–4.37; p = 0.01), Japanese (OR 2.81; 95% CI 1.85–4.28; p < 0.00001), and Thai patients (OR 10.51; 95% CI 3.56–31.05; p < 0.0001) as shown in Figure 4a.

However, patients carrying both *UGT1A1*6* and *UGT1A1*28* genetic variants were associated with significantly increased risk of diarrhea in only Chinese patients (OR 3.34; 95% CI 1.67–6.71; p = 0.0007) but not in Japanese patients (OR 1.74; 95% CI 0.85–3.55; p = 0.13; Figure 4b).

Since different studies used irinotecan to treat different types of cancer (e.g., colorectal, lung, stomach, cervical, ovarian, esophageal, pancreatic, pulmonary neuroendocrine tumor, and sometimes a combination of these cancers), the present study undertook subgroup analysis to investigate the impacts of these cancers on the development of toxicities. In this study, patients were grouped as colorectal cancer versus other cancers, where the other cancers group included lung, stomach, cervical, ovarian, esophageal, pancreatic, pulmonary neuroendocrine tumor, and a combination of these cancers. Following analysis it was found that the patients with either colorectal or other cancers carrying both UGT1A1*6 and UGT1A1*28 variants were associated with significantly increased risk of neutropenia (colorectal cancer: OR 2.85; 95% CI 1.42–5.73; *p* = 0.003; other cancers: OR 2.86; 95% CI 1.90-4.32; p < 0.00001; Figure S2A).

Similar trends were also found for diarrhea (colorectal cancer: OR 2.47; 95% CI 1.24–4.91; p = 0.01; other cancers: OR 2.71; 95% CI 1.26–5.81; p = 0.01; Figure S2B).

Because different irinotecan dosing schedules were applied in treating different types of cancer, the present study also undertook subgroup analysis to assess whether these dosing schedules affected the development of toxicities. In this analysis, dose was categorized as low, medium, and high corresponding to <150, 150, and >150 mg/m², respectively.⁷⁶ It was found that patients carrying both *UGT1A1*6* and *UGT1A1*28* variants were associated with significantly increased risk of neutropenia for only high and low doses (high dose: OR 3.21; 95% CI 1.77–5.84; p = 0.0001; low dose: OR 3.35; 95% CI 1.78–6.32; p = 0.0002) but not for medium doses (OR 1.34; 95% CI 0.46–3.87; p = 0.59; Figure 5a).

However, patients carrying both *UGT1A1*6* and *UGT1A1*28* variants were associated with significantly increased risk of diarrhea only for high doses (high dose: OR 2.01; 95% CI 1.19–3.38; p = 0.009) but not for medium and low doses (medium dose: OR 3.38; 95% CI 0.58–19.74;

p = 0.18; low dose: OR 2.50; 95% CI 0.97–6.42; p = 0.06; Figure 5b).

Association of *ABCC2 c.3972C>T* with irinotecan-induced severe toxicity

A very small number of studies were found in the literature that had assessed the association of *ABCC2 c.3972C>T* genetic polymorphism with irinotecan toxicity. Only three and two studies had assessed the effects of the *ABCC2 c.3972C>T* genetic variant with irinotecan-induced neutropenia and diarrhea, respectively. After pooled estimation, it was found that patients carrying heterozygous and homozygous *ABCC2 c.3972C>T* variants were not significantly associated with irinotecan-induced neutropenia (OR 1.67; 95% CI 0.98–2.84; p = 0.06) as shown in Figure 6a.

It was further revealed that patients harboring heterozygous and homozygous *ABCC2 c.3972C>T* variants were significantly associated with a reduction in irinotecaninduced diarrhea (OR 0.31; 95% CI 0.11–0.81; p = 0.02; Figure 6b).

Sensitivity and publication bias

After sensitivity analysis, it was found that no individual study affected the pooled risk of either neutropenia or diarrhea profoundly when the aggregated risk was measured against *UGT1A1*6*, *UGT1A1*28*, or *ABCC2* c.3972C>T genetic variants (data not shown). There was no publication bias as determined by the visual inspection of the funnel plot (Figure S3).

DISCUSSION

Toxicity of irinotecan varies greatly and can be even lifethreatening in some cancer patients. The findings of the present analysis indicate that irinotecan-induced severe toxicities (e.g., neutropenia and diarrhea) are significantly associated with Asian cancer patients that carry *UGT1A1*6* and *UGT1A1*28* genetic variants.

Due to the strong association of *UGT1A1*28* with severe toxicity of irinotecan as replicated in multiple studies predominantly in Caucasian cancer patients, the US Food and Drug Administration has already approved *UGT1A1*28* genetic testing before starting irinotecan therapy and recommended reducing the starting dose by at least one level of irinotecan dosage form for cancer patients carrying the *UGT1A1*28/*28* genotype.^{16,77} The Dutch Pharmacogenetics Working Group



1627

Utip of Utip AT-16 + 28 17-1 Odds Ratio Odds Ratio Study of Support Total Events Total Events Total Events MH, Random, 95% CI 1.1 China B 33 3 53 9.0% 15.69 [407, 80.53] Deng 2017 3 95 2 60.8% 1.16 [0.18, 72.2] Gao 2013 27 75 8 81 1.1% 1.44 [0.2, 40.85] Li 2014 14 107 7 103 15.89 [1.6%, 3.52] 1.46, 550] Gao 2013 27 75 8 11.1% 1.44 [0.3, 0.00] 1.43, 3.00] Lu 2014 14 107 7 103 59 166 1.3% 1.23 [0.80, 1.88] Vago 2015 6 24 9.5% 6.00 [1.71, 2.104] 1.80 200 1.80 200, 78, 229 [1.26, 4.37] Heterogeneity Tau" = 0.73, Chi# = 38.72, df = 9 (P < 0.0001); P = 77% 158 [0.66, 12.77] 1.41 [0.33, 10.78, 329 4.0] 1.41 [0.43, 2.45 [1.20, 4.37] Heterogeneity Tau" = 0.02, Chi# = 5.27, df = 3 (P < 0.200, 1.78, 2.39 [0.66, 1.2.77] 1.42 [0.58, 0.32] 1.41 [0.	(a)							
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Deng 2017 3 65 2 50 6.8% 1.16 [0.19, 7.23] Gao 2013 27 75 8 58 11.56 3.52 [1.45, 8.50] Gao 2013 44 143 12 133 12.7% 4.48 [2.24, 8.95] Li 2014 14 107 7 60 11.1% 1.14 [0.43, 3.00] Li 2017 77 71 93 59 168 13.8% 1.23 [0.01, 1.8] Xia 2015 6 29 0 38 3.7% 21.30 [1.15, 395 52] Xia 2016 10 98 15 85 11.7% 0.053 [0.22, 1.25] Yang 2015 16 24 6 24 9.5% 6.00 [1.71, 21.04] Stutotal (65% C) 804 713 100.0% 2.29 [1.20, 4.37] Test for overall effect $Z = 2.53$ ($P = 0.01$) 1.1.2 Japan Ando 2017 6 13 5 22 6.9% 2.91 [0.66, 12.77] Hirasawa 2013 3 3 15 50 1.9% 150.30, 78, 329.40] Horikawa 2015 6 11 8 12 5.5% 0.60 [0.11, 3.24] Kimura 2016 8 20 0 26 2.0% 36.04 [1.92, 675.20] Matsuoka 2020 15 27 7 24 10.3% 3.04 [0.95, 8.71] Minami 2006 32 61 23 66 19.7% 1.58 [0.76, 3.29] Matsuoka 2010 3 18 4 24 5.5% 1.00 [0.19, 51.5] Takanara 2013 8 15 6 29 8.00% 4.38 [1.18, 2.08] Narawa 2010 3 18 4 24 5.5% 1.00 [0.19, 51.5] Takanara 2013 8 15 6 29 8.00% 4.38 [1.13, 16.99] Takanara 2013 8 15 6 0 2.88 12.9% 14.78 [0.71, 306.81] Abasip 2015 3 16 0 288 12.9% 14.78 [0.71, 306.81] Masip 2015 3 16 0 288 12.9% 14.78 [0.71, 306.81] Masip 2015 3 16 0 288 12.9% 14.78 [0.71, 306.81] Takanara 2009 8 13 4 17 6.1% 5.20 [1.07, 25.31] Yamaguchi 2019 9 37 5 37 9.7% 2.006 [0.62, 6.87] Yamaguchi 2019 4 16 1 200 31% 6.33 [0.63, 63.84] Total events 124 91 Heterogeneity: Tau ² = 0.09, Chi ² = 15.27, df = 13 ($P = 0.81$); $P = 0\%$ Test for overall effect $Z = 4.34$ ($P < 0.0000$) L1.31 Thai Abasip 2015 3 16 0 288 12.9% 14.78 [0.71, 306.81] Abasip 2015 3 16 0 0.87, 7% 10.00 [3.14, 31.88] Subtotal (95% Cl) 42 68 100.00% 10.51 [3.56, 31.05] Total events 23 10 Heterogeneity: Tau ² = 0.00, Chi ² = 0.06, df = 1 ($P = 0.81$); $P = 0\%$ Test for overall effect $Z = 4.26$ ($P < 0.0001$) L1.31 Thai Abasip 2015 3 16 0 0.98 12.9% 14.78 [0.71, 306.81] Abasip 2000 Chi ² = 0.06, df = 1 ($P = 0.81$); $P = 0\%$ Test for overall effect $Z = 4.26$ ($P < 0.0001$) L1.31 Thai Abasip 2000 Chi ² = 0.06, df = 1 ($P = 0.81$); $P = 0\%$ Test for overall e	Chen 2020	16	33	3	53	9.0%	15.69 [4.07, 60.53]	
Gao 2013 27 75 8 56 11.5% 3.52 [1.45, 8.50] Gao 2013 44 143 12 133 12.7% 4.48 82[2.48, 85] Li 2014 14 107 7 6 01 11.1% 1.14 [0.43, 3.00] Li 2017 77 193 59 188 13.9% 1.23 [0.90, 1.88] Niao 2015 6 229 0 38 3.7% 21.30 [1.15, 395.62] Xu 2016 10 98 15 85 11.7% 0.53 [0.22, 1.55] Xu 2016 10 98 15 85 11.7% 0.53 [0.22, 1.55] Yang 2015 6 229 120 Heterogeneity: Tau ² = 0.73; Ch ² = 38.72, df = 9 ($^{\circ} < 0.0001$); $l^{=} 7.7\%$ Test for overall effect Z = 2.53 ($^{\circ} = 0.0001$) 1.1.2 Japan Ando 2017 6 13 5 22 6.9% 2.91 [0.66, 12.77] Hirasawa 2013 3 3 15 50 1.9% 16.03 [0.76, 3.294 [0.40, 19.5, 9.71] Matsuoka 2020 15 27 7 24 10.3% 3.04 (1.92, 675.20] Matsuoka 2020 15 21 7 72 41 0.3% 3.04 (1.92, 675.20] Matsuoka 2020 15 21 8 3 21 6.0% 2.31 [0.47, 11.42] Statch 2011 13 122 4 41 9.2% 6.53 [1.10, 26.60] Chuyama 2011 5 18 3 21 6.0% 2.31 [0.47, 11.42] Statch 2011 13 124 41 8 6 27 6.5% 50.71 [1.00, 26.60] Chuyama 2013 3 15 6 0 2.98; M ⁴ 4.38 [1.12, 208] Takahara 2013 8 15 6 0 2.98; M ⁴ 4.38 [1.12, 208] Takahara 2013 8 15 6 29 8.0% 4.38 [1.12, 208] Takahara 2013 8 15 6 0 2.98; M ⁴ 4.38 [1.12, 208] Takahara 2013 3 16 0 2.81 [2.8% 14.78 [0.71, 306.61] Heterogeneity: Tau ² = 0.00; Ch ² = 0.20; l ² = 15% Test for overall effect Z = 4.34 ($^{\circ} < 0.0001$) 1.1.3 Thai Abasilp 2015 3 16 0 28 12.8% 14.78 [0.71, 306.61] Hasilp 2015 3 16 0 28 12.8% 14.78 [0.71, 306.61] Heterogeneity: Tau ² = 0.00; Ch ² = 0.00 (1) 1.1.3 Thai Abasilp 2015 3 16 0 28 12.8% 14.78 [0.71, 306.61] Heterogeneity: Tau ² = 0.00; Ch ² = 0.000 (1) 1.1.3 Thai Abasilp 2015 3 16 0 28 12.8% 10.00 (1.13, 31.88] Subtotal (95% Ct) 2 23 10 4 2 68 100.0% 10.51 [3.56, 31.05] Total events 23 10 Heterogeneity: Tau ² = 0.00; Ch ² = 0.00 (1) 1.01 UCTIAl ⁴ ¹⁶ - 2.82 Carriers (b)	Deng 2017	3	65	2	50	6.8%	1.16 [0.19, 7.23]	
Gao 2013 44 143 12 133 12.7% 4.48 [224, 8.95] L2014 14 107 7 60 11.1% 1.14 [0.43, 3.00] Li 2017 77 193 59 168 13.9% 1.23 [0.01, 1.88] Xiao 2015 6 29 0 38 3.7% 21.30 [1.15, 396.52] Xiu 2016 10 98 15 85 11.7% 0.53 [0.22, 1.25] Yang 2015 16 24 6 24 9.5% 6.00 [1.71, 21.04] Subtotal (95% C) 804 713 100.0% 2.29 [1.20, 4.37] Total events 219 120 Heterogeneity: Tau ² - 0.50; http: 3.8.7, 2 (d - 9 ($e < 0.0001$); P = 77% Test for overall effect Z = 2.53 ($P = 0.01$) 1.2.2 Japan Ando 2017 6 13 5 22 6.9% 2.91 [0.66, 12.77] Hirasawa 2013 3 3 15 50 1.9% 16.03 [0.78, 329.40] Horikawa 2015 6 11 8 12 55% 0.60 [0.11, 3.24] Kimura 2013 8 20 0 26 20% 30.60 (1.92, 675.00] Masuoka 2020 15 27 7 24 10.3% 3.04 [0.92, 675.00] Minami 2006 32 61 23 56 1.9% 5.17 [1.00, 26.60] Okuyama 2011 5 18 3 21 6.0% 2.31 [0.47, 11.42] Sunktava 2013 3 18 4 224 5.6% 1.00 [0.14, 51.69] Takahara 2013 8 15 6 29 8.0% 4.38 [1.13, 16.99] Yamaguchi 2014 4 8 6 37 5.5% 51.71 [1.00, 26.60] Okuyama 2011 5 18 3 21 6.0% 2.31 [0.47, 11.42] Sunktava 2013 8 15 6 2.99 (0.9% 4.38 [1.13, 16.99] Yamaguchi 2019 9 37 5 37 8.7% 2.06 [0.62, 6.87] Yamaguchi 2019 4 16 1 2.0 3.1% 6.33 [0.63, 63.64] Takahara 2003 8 13 4 17 6.1% 5.20 [1.07, 25.31] Yamaguchi 2019 4 16 1 2.0 3.1% 6.33 [0.63, 63.64] Takahara 2003 4 16 1 2.0 3.1% 6.33 [0.63, 63.64] Takahara 2013 4 16 0.00% 2.81 [1.85, 4.28] Takahara 2008 (Chi ^a = 1.5.7, df = 1.3 (P = 0.9); P = 15% Test for overall effect Z = 4.26 ($P < 0.0001$) Heterogeneity: Tau ² = 0.00, Chi ^a = 0.68, df = 1 ($P = 0.81$); P = 0% Test for overall effect Z = 4.26 ($P < 0.0001$) L1.3 Thai Abasilp 2015 3 16 0 28 12.8% 14.78 [0.71, 306.81] Abasilp 2015 3 10 40 08.7% 10.00 [1.4, 51.85] Total events 23 10 Heterogeneity: Tau ² = 0.00; Chi ^a = 0.68, df = 1 ($P = 0.81$); P = 0% Test for overall effect Z = 4.26 ($P < 0.0001$) L1.0 10 10 10 10 100 100 100 100 100 100	Gao 2013	27	75	8	58	11.6%	3.52 [1.45, 8.50]	
Li 2014 14 14 107 7 6 60 11.1% 1.14 [0.43, 3.00] Li 2015 6 29 0 38 3.7% 21.30 [0.18] Xia 2015 6 29 0 38 3.7% 21.30 [0.15, 395.62] Xu 2016 10 98 15 85 11.7% 0.53 [0.22, 1.25] Yang 2015 16 24 6 24 9.5% 6.00 [1.7], 21.04] Subtotal (95% CI) 804 7.13 100.0% 2.29 [1.20, 4.37] Total events 219 120 Heterogeneiky: Tau ² = 0.73; Chi ² = 38.72, df = 9 ($P < 0.0001$); $P = 77\%$ Test for overall effect $Z = 2.53$ ($P = 0.01$) 1.12 Japan Ando 2017 6 13 5 22 6.3% 2.91 [0.66, 12.77] Hirasawa 2013 3 3 15 50 1.9% 16.03 [0.78, 329] Motiva 2018 8 20 0 26 2.0% 38.04 [1.92, 675.20] Matsucka 2020 15 27 7 24 10.3% 3.04 [9.57, 52.0] Matsucka 2020 15 27 7 24 10.3% 3.04 [9.57, 52.0] Matsucka 2020 15 28 12 3 56 19.7% 1.58 [0.76, 3.29] Motiva 2018 8 20 0 26 2.0% 4.38 [1.13, 16.99] Takano 2009 8 13 4 17 6.1% 5.20 [10.7, 25.31] Takano 2009 8 13 4 17 6.1% 5.20 [10.7, 25.31] Takano 2009 8 13 4 17 6.1% 6.33 [0.63, 63.84] Subtotal (95% CI) 292 446 100.0% 2.81 [1.85, 4.28] Total events 124 91 Heterogeneiky: Tau ² = 0.00; Chi ² = 0.06, df = 1 ($P = 0.81$); $P = 0\%$ Test for overall effect $Z = 4.34$ ($P < 0.00001$) 1.13 Thai Alasilg 2015 3 16 0 28 12.3% 14.78 [0.71, 306.81] Alasilg 2015 3 16 0 28 12.3% 14.78 [0.71, 306.81] Alasilg 2015 3 10 40 87.2% 10.00 [3.14, 31.88] Subtotal (95% CI) 292 416 100.0% 2.81 [3.56, 31.05] Total events 23 10 Heterogeneiky: Tau ² = 0.00; Chi ² = 0.06, df = 1 ($P = 0.81$); $P = 0\%$ Test for overall effect $Z = 4.26$ ($P < 0.0001$) (b)	Gao J 2013	44	143	12	133	12.7%	4.48 [2.24, 8.95]	
Liu 2017 77 193 59 168 13.9% 1.23 (0.00, 1.83) Xia 2016 6 29 0 38 3.7% 21.30 (11.5, 395.62) Xiu 2016 10 98 15 85 11.7% 0.53 (0.22, 1.25) Xiu 2016 16 24 6 24 9.5% 6.00 (1.7, 2.104) Subtotal (95% C) 804 713 100.0% 2.29 [1.20, 4.37] Total events 219 120 Heterogeneity: Tau ² = 0.73 (DH ² = 9, CP < 0.0001); P= 77% Test for overall effect $Z = 2.53$ ($P = 0.01$) 1.1.2 Japan Ando 2017 6 13 5 22 6.9% 2.91 [0.66, 12.77] Hirasawa 2013 3 15 50 19% 16.03 (0.78, 329.40) Horikawa 2015 6 11 8 12 5.5% 0.60 (0.11, 3.24] Kimura 2015 6 11 8 12 5.5% 0.60 (0.11, 3.24] Matsuoka 2020 15 2.7 7 24 10.3% 3.04 (0.95, 9.71] Minami 2006 32 61 22 0.5% 36.04 (1.92, 675.20] Matsuoka 2020 15 2.7 7 24 10.3% 3.04 (0.95, 9.71] Minami 2006 32 61 32 56 10.9% 1.58 (0.76, 3.29] Motiva 2014 4 8 6 37 5.8% 5.17 [1.00, 26.60] Okuyama 2011 5 18 3 21 6.0% 2.31 [0.47, 11.42] Sunakawa 2013 8 15 6 2.9 8.0% 4.38 (1.13, 16.99] Takahara 2013 8 15 6 2.9 8.0% 4.30 (1.9, 5.15] Takahara 2013 8 15 6 2.9 8.0% 4.30 (1.9, 5.15] Takahara 2013 8 14 12 0.31% 6.33 (0.63, 63.64] Subtotal (95% C) 292 416 100.0% 2.81 [1.8, 4.28] Total events 124 91 Heterogeneity: Tau ² = 0.00; Chi ² = 1.57, df = 1.3 ($P = 0.29$); P = 15% Test for overall effect $Z = 4.34$ ($P < 0.00001$) 1.1.3 Thai Assilp 2015 3 16 0 28 12.8% 14.78 [0.71, 306.81] Assilp 2015 3 16 0 28 12.8% 14.78 [0.71, 306.81] Assilp 2015 3 16 0 28 12.8% 14.78 [0.71, 306.81] Assilp 2015 3 16 0 28 12.8% 14.78 [0.71, 306.81] Assilp 2015 3 16 0 28 12.8% 14.78 [0.71, 306.81] Assilp 2015 3 16 0 0.98; 12.8% 14.78 [0.71, 306.81] Assilp 2015 3 16 0 28 12.8% 14.78 [0.71, 306.81] Assilp 2015 3 16 0 0.98; 12.8% 14.78 [0.71, 306.81] Assilp 2015 3 16 0 0.98; 12.8% 14.78 [0.71, 306.81] Assilp 2015 3 16 0 0.98; 12.8% 14.78 [0.71, 306.81] Assilp 2020 20 26 66 10.000; 10.51 [3.56, 31.05] Total events 23 10 Heterogeneity: Tau ² = 0.00; Chi ² = 0.00; 1; P = 0.% Test for overall effect $Z = 4.26$ ($P < 0.0001$) (b)	Li 2014	14	107	7	60	11.1%	1.14 [0.43, 3.00]	
Xia 2015 6 29 0 38 3.7% 21.30 (1.15, 395.62) Xia 2016 10 98 15 85 11.7% 0.53 (0.22, 1.25) Yang 2015 16 24 6 24 9.5% 6.00 [1.71, 21.04] Subtrotal (95% C) 804 713 100.0% 2.29 [1.20, 4.37] Total events 219 120 Heterogeneilty: Tau" = 0.73, Chi" = 38,72, df = 9 (P < 0.0001); P = 77% Test for overall effect $Z = 2.53$ (P = 0.01) 1.1.2 Japan Ando 2017 6 13 5 22 6 9% 2.91 [0.66, 12.77] Hirasawa 2013 3 3 15 50 1.9% 16.03 [0.76, 329.40] Horikawa 2015 6 11 8 12 55% 0.60 [0.11, 3.24] Kimura 2018 8 20 0 26 2.0% 36.04 [1.92, 675.20] Matsucka 2020 15 27 7 24 10.3% 3.04 [0.45, 9.71] Minami 2006 32 61 23 56 19.7% 1.58 [0.76, 3.29] Moriya 2014 4 8 6 37 5.5% 5.17 [1.00, 2660] Okuyama 2011 5 18 3 21 6.0% 2.31 [0.47, 11.42] Subtrotal (95% C) 2 29 4 16 100.0% 2.81 [1.85, 4.28] Takana 2009 8 13 4 17 6.1% 5.20 [1.07, 253.1] Yamaguchi 2019 9 3.37 5 37 9.7% 2.06 [0.82, 6.87] Yamamoto 2009 4 16 1 20 3.1% 6.33 [0.83, 63.64] Subtrotal (95% C) 2 29 2 416 100.00% 2.81 [1.85, 4.28] Total events 124 91 Heterogeneity: Tau" = 0.00; Chi" = 0.06, df = 1 (P = 0.29); P = 15% Test for overall effect $Z = 4.26$ (P < 0.0001) 1.31 Takan Alasilp 2015 3 16 0 28 12.8% 14.78 [0.71, 306.81] Alasilp 2015 3 16 0 28 12.8% 14.78 [0.71, 306.81] Alasilp 2015 3 16 0 0.28 12.8% 14.78 [0.71, 306.81] Alasilp 2015 3 16 0 0.28 12.8% 14.78 [0.71, 306.81] Alasilp 2015 3 16 0 0.28 12.8% 14.78 [0.71, 306.81] Alasilp 2015 3 16 0 0.28 12.8% 14.78 [0.71, 306.81] Alasilp 2015 3 16 0 0.28 12.8% 14.78 [0.71, 306.81] Alasilp 2015 3 16 0 0.28 12.8% 14.78 [0.71, 306.81] Alasilp 2015 3 16 0 0.28 12.8% 14.78 [0.71, 306.81] Alasilp 2015 3 16 0 0.28 12.8% 14.78 [0.71, 306.81] Alasilp 2015 3 16 0 0.28 12.8% 14.78 [0.71, 306.81] Alasilp 2015 3 16 0 0.28 12.8% 14.78 [0.71, 306.81] Alasilp 2015 1 0 40 87.2% 10.00 [3.14, 31.88] Subtrotal (95% C) 42 2 68 100.0% 10.51 [3.56, 31.05] 0.01 0.1 0.1 10 00000000000000000000000	Liu 2017	77	193	59	168	13.9%	1.23 [0.80, 1.88]	
Xu 2016 10 98 15 85 11.7% 0.53 [0.22, 1.25] Yang 2015 16 24 6 24 9.5% 6.00 [17, 12, 104] Subtotal (95% C) 804 713 100.0% 2.29 [1.20, 4.37] Total events 219 120 Heterogeneiky: Tau" = 0.73, Ch" = 38.72, df = 9 (P = 0.0001); P = 77% Test for overall effect. Z = 2.53 (P = 0.01) 1.1.2 Japan Ando 2017 6 13 5 22 6.9% 2.91 [0.66, 12.77] Hirasawa 2013 3 3 15 50 1.9% 16.03 [0.78, 329.40] Horikawa 2015 6 111 8 12 5.5% 0.60 [0.11, 3.24] Kimura 2018 8 20 0 26 2.0% 3.60.41 [.92, 675.20] Matsuoka 2020 15 27 7 24 10.3% 3.04 [0.95, 9.71] Minami 2006 32 61 2.3 56 19.7% 1.58 [0.76, 3.29] Moriya 2011 5 18 3 21 6.0% 2.31 [0.47, 11.42] Sunkawa 2013 8 15 6 29 8.0% 4.38 [11.3] [6.99] Takahara 2013 8 15 6 29 8.0% 4.38 [11.3] [6.99] Takahara 2013 8 15 6 29 8.0% 4.38 [11.3] [6.99] Takahara 2013 8 15 6 29 8.0% 4.38 [11.3] [6.99] Takahara 2013 8 15 6 29 8.0% 4.38 [11.3] [6.99] Takahara 2013 8 15 6 29 8.0% 4.38 [11.3] [6.99] Takahara 2013 8 15 6 29 8.0% 4.38 [11.3] [6.99] Takahara 2013 8 15 6 29 8.0% 4.38 [11.3] [6.99] Takahara 2013 8 15 6 29 8.0% 4.38 [11.3] [6.99] Takahara 2013 8 15 6 29 8.0% 4.38 [11.3] [6.99] Takahara 2013 8 15 6 29 8.0% 4.38 [11.3] [6.99] Takahara 2013 8 15 6 29 8.0% 4.38 [11.3] [6.99] Takahara 2013 8 15 6 29 8.0% 4.38 [11.3] [6.99] Takahara 2013 8 15 6 29 8.0% 4.38 [11.3] [6.99] Takahara 2015 3 16 0 28 12.8% 14.78 [0.71, 306.81] Aasilp 2020 20 20 26 10 40 87.2% 10.00 [3.14, 31.88] Subtotal (95% CI) 20 26 10 40 87.2% 10.00 [3.14, 31.88] Subtotal (95% CL) 42 68 100.0% 10.51 [3.55, 51.05] Total events 23 10 Heterogeneily: Tau" = 0.00; ChiP = 0.06, df = 1 (P = 0.31); P = 0% Test for overall effect. Z = 4.26 (P < 0.0001) (b)	Xiao 2015	6	29	0	38	3.7%	21.30 [1.15, 395.62]	
Yang 2015 16 24 6 24 9.5% 6.00 [1.71, 21.04] Subtotal (95% CI) 804 713 100.0% 2.29 [1.20, 4.37] Total events 219 120 Heterogeneity. Tau ² = 0.73, Chi ^p = 38.72, df = 9 ($P < 0.0001$); P = 77% Test for overall effect Z = 2.53 (P = 0.01) 1.12 Japan Ando 2017 6 13 5 22 6.9% 2.91 [0.66, 12.77] Hirasawa 2013 3 3 15 50 1.9% 16.03 [0.78, 329 40] Horikawa 2015 6 11 8 12 55% 0.60 [0.11, 3.24] Kimura 2018 8 20 0 26 2.0% 36.04 [1.92, 675.20] Matsuoka 2020 15 27 7 24 10.3% 3.04 [0.95, 9.71] Minami 2006 32 61 23 56 19.7% 1.58 [0.76, 3.29] Motrya 2014 4 8 6 37 5.8% 5.17 [1.00, 26.60] Okuyama 2011 5 18 3 21 6.0% 2.31 [0.47, 11.42] Sunakawa 2010 3 18 4 24 5.8% 1.00 [0.19, 515] Takahara 2013 8 15 6 2.9 8.0% 4.38 [1.13, 16.99] Takahara 2013 8 15 6 2.9 8.0% 4.38 [1.13, 16.99] Takahara 2013 8 15 6 2.9 8.0% 4.38 [1.13, 16.99] Takahara 2013 18 14 17 6.1% 5.20 [1.07, 25.31] Yamaguchi 2019 9 37 5 37 9.7% 2.06 [0.82, 68.7] Yamaguchi 2019 9 37 5 53 7.07% 2.06 [0.82, 68.7] Yamaguchi 2019 4 16 1 20 3.1% 6.33 [0.63, 63.64] Subtotal (95% CI) 292 416 100.0% 2.81 [1.85, 4.28] Total events 124 91 Heterogeneity. Tau ² = 0.09; Chi ² = 15.27, df = 13 (P = 0.81); P = 0.% Test for overall effect Z = 4.84 (P < 0.00001) 1.1.3 Thai Abasilp 2015 3 16 0 28 12.8% 14.78 [0.71, 306.81] Abasilp 2015 3 16 0 28 12.8% 14.78 [0.71, 306.81] Abasilp 2015 3 16 0 0.28 12.8% 14.78 [0.71, 306.81] Abasilp 2015 3 16 0 0.28 12.8% 14.78 [0.71, 306.81] Abasilp 2015 3 16 0 0.28 12.8% 14.78 [0.71, 306.81] Abasilp 2015 3 16 0 0.28 12.8% 14.78 [0.71, 306.81] Abasilp 2015 3 16 0 0.28 12.8% 14.78 [0.71, 306.81] Abasilp 2015 3 16 0 0.28 12.8% 14.78 [0.71, 306.81] Abasilp 2015 3 16 0 0.28 12.8% 14.78 [0.71, 306.81] Abasilp 2015 3 16 0 0.28 12.8% 14.78 [0.71, 306.81] Abasilp 2015 3 16 0 0.28 12.8% 14.78 [0.71, 306.81] Abasilp 2015 3 16 0 0.28 12.8% 14.78 [0.71, 306.81] Abasilp 2015 3 16 0 0.28 12.8% 14.78 [0.71, 306.81] Abasilp 2015 3 16 0 0.28 12.8% 14.78 [0.71, 306.81] Abasilp 2015 3 16 0 0.26 fd = 1 (P = 0.81); P = 0.8% Test for ov	Xu 2016	10	98	15	85	11.7%	0.53 [0.22, 1.25]	
Subtotal (9% C) 804 713 1000% 2.29 [1.20, 4.37] Total events 219 120 Heterogeneity: Tau ² = 0.73; Chi ² = 38.72, df = 9 (P < 0.0001); P = 77% Test for overall effect Z = 2.53 (P = 0.01) 1.1.2 Japan Ando 2017 6 13 5 22 6.9% 2.91 [0.66, 12.77] Hirasawa 2013 3 3 15 50 1.9% 16.03 [0.78, 329.40] Horikawa 2015 6 11 8 12 55% 0.60 [0.11, 3.24] Kimura 2018 8 20 0 26 2.0% 38.04 [1.92, 675.20] Matsuoka 2020 15 27 7 24 10.3% 3.04 [0.95, 9.71] Minami 2006 32 61 1.23 56 119.7% 1.58 [0.76, 3.29] Moriya 2014 4 8 6 37 5.8% 5.17 [1.00, 26.60] Okuyama 2011 5 18 3 21 6.0% 2.31 [0.47, 11.42] Satah 2011 13 32 4 41 9.2% 6.33 [1.81, 2.208] Sunskawa 2010 3 18 4 24 5.8% 1.00 [0.19, 51.5] Takahara 2013 8 15 6 29 8.0% 4.38 [1.13, 16.99] Takahara 2013 8 15 6 29 8.0% 4.38 [1.13, 16.99] Takahara 2013 8 15 6 29 8.0% 4.38 [1.13, 16.99] Takahara 2013 8 15 6 29 8.0% 4.38 [1.13, 16.99] Takahara 2013 8 15 6 29 8.0% 4.38 [1.13, 16.99] Takahara 2013 8 16 6 12 02.31, % 6.33 [0.63, 36.44] Subtotal (95% C) 292 416 100.0% 2.81 [1.85, 4.28] Total events 124 91 Heterogeneity: Tau ² = 0.09; Chi ² = 15.27, df = 13 (P = 0.29); P = 15% Test for overall effect Z = 4.84 (P < 0.00001) 1.1.3 Thai Abasilp 2015 3 16 0 28 12.8% 14.78 [0.71, 306.81] Abasilp 2015 3 16 0 28 12.8% 14.78 [0.71, 306.81] Abasilp 2015 3 16 0 128 12.8% 14.78 [0.71, 306.81] Abasilp 2020 20 20 26 10 40 87.2% 10.00 [3.14, 31.88] Subtotal (95% C) 42 68 100.0% 10.51 [3.56, 31.05] Total events 2 3 10 Heterogeneity: Tau ² = 0.00; Chi ² = 0.06, df = 1 (P = 0.81); P = 0% Test for overall effect Z = 4.26 (P < 0.0001) (b)	Yang 2015	16	24	6	24	9.5%	6.00 [1.71, 21.04]	
Total events 219 120 Heterogeneity: Tau ² 0.73 (Ch ² = 38.72, df = 9 ($P < 0.0001$); P= 77% Test for overall effect Z = 2.53 (P = 0.01) 1.1.2 Japan Ando 2017 6 13 5 22 6.9% 2.91 [0.66, 12.77] Hirasawa 2013 3 3 15 50 1.9% 16.03 [0.78, 329.40] Horikawa 2015 6 11 8 12 5.5% 0.60 [0.11, 3.24] Kimura 2018 8 20 0 26 2.0% 38.04 [1.92, 675.20] Matsuka 2020 15 27 7 24 10.3% 3.04 [0.95, 9.71] Minami 2006 32 61 23 56 19.7% 158 [0.76, 3.29] Moriya 2014 4 8 6 37 5.5% 5.17 [1.00, 26.60] Okuyama 2011 5 18 3 21 6.0% 2.31 [0.47, 11.42] Satoh 2011 13 32 4 41 9.2% 6.33 [1.81, 22.08] Takahara 2013 8 15 6 29 8.0% 4.38 [1.13, 16.99] Takahara 2013 8 15 6 29 8.0% 4.38 [1.13, 16.99] Takahara 2013 8 15 6 29 8.0% 4.38 [1.13, 16.99] Takahara 2013 8 15 6 29 8.0% 4.38 [1.13, 16.99] Takahara 2013 8 15 6 29 8.0% 4.38 [1.13, 16.99] Takahara 2013 8 15 6 29 8.0% 4.38 [1.13, 16.99] Takahara 2013 8 15 6 29 8.0% 4.38 [1.13, 16.99] Takahara 2013 8 15 6 29 8.0% 4.38 [1.13, 16.99] Takahara 2013 8 15 6 29 8.0% 4.38 [1.13, 16.99] Takahara 2013 8 15 6 29 8.0% 4.38 [1.13, 16.99] Takahara 2013 8 13 4 17 6.1% 5.20 [1.07, 25.31] Yamamoto 2009 4 16 1 20 3.1% 6.33 [0.63, 63.64] Subtotal (95% Ct) 292 416 100.0% 2.81 [1.35, 4.28] Total events 124 91 Heterogeneity: Tau ² = 0.09; Ch ² = 15.27, df = 13 (P = 0.29); P = 15% Test for overall effect Z = 4.26 (P < 0.0001) 1.1.3 Thai Abasilg 2015 3 16 0 28 12.8% 14.78 [0.71, 306.81] Abasilg 2015 20 20 26 10 40 87.2% 10.00 [3.14, 31.88] Subtotal (95% Ct) 42 68 100.0% 10.51 [3.56, 31.05] Total events 23 10 Heterogeneity: Tau ² = 0.00; Ch ² = 0.06, df = 1 (P = 0.81); P = 0% Test for overall effect Z = 4.26 (P < 0.0001) (b)	Subtotal (95% CI)		804		713	100.0%	2.29 [1.20, 4.37]	-
Heterogeneity: Tau ² = 0.73; Ch ² = 38.72, df = 9 ($P < 0.0001$); P = 77% Testfor overall effect Z = 2.53 (P = 0.01) 1.1.2 Japan Ando 2017 6 13 5 22 6.9% 2.91 [0.66, 12.77] Hirasawa 2013 3 3 15 50 1.9% 16.03 [0.78, 329.40] Horikawa 2015 6 11 8 12 5.5% 0.60 [0.11, 3.24] Kimura 2018 8 20 0 2 26 2.0% 38.04 [1.92, 675.20] Matsuoka 2020 15 27 7 24 10.3% 3.04 [0.95, 9.71] Minami 2006 32 61 23 56 19.7% 1.58 [0.76, 3.29] Moriya 2014 4 8 6 37 5.8% 5.17 [1.00, 26.60] Okuyama 2011 5 18 3 21 6.0% 2.31 [0.47, 11.42] Sunakawa 2010 3 18 4 24 5.3% 1.00 [0.19, 5.15] Takano 2009 8 13 4 17 6.1% 5.20 [1.07, 25.31] Yamaguchi 2019 9 37 5 37 9.7% 2.06 [0.62, 6.87] Yamamoto 2009 4 16 1 20 3.1% 6.33 [0.63, 63.64] Subtotal (95% Ct) 292 4416 100.0% 2.81 [1.85, 4.28] Total events 124 91 Heterogeneity: Tau ² = 0.00; Ch ² = 15.27, df = 13 (P = 0.29); P = 15% Test for overall effect Z = 4.84 (P < 0.0001) 1.1.3 Thai Atasilp 2015 3 16 0 28 12.8% 14.78 [0.71, 306.81] Atasilp 2015 3 16 0 28 12.8% 14.78 [0.71, 306.81] Atasilp 2015 3 16 0 28 12.8% 14.78 [0.71, 306.81] Atasilp 2015 3 16 0 28 12.8% 14.78 [0.71, 306.81] Atasilp 2015 3 16 0 10.4% 10.51 [3.56, 31.05] Total events 23 10 Heterogeneity: Tau ² = 0.00; Ch ² = 0.06, df = 1 (P = 0.81); P = 0% Test for overall effect Z = 4.26 (P < 0.0001) (b)	Total events	219		120				
Test for overall effect: $Z = 2.53$ (P = 0.01) 1.1.2 Japan Ando 2017 6 13 5 22 6.9% 2.91 [0.66, 12.77] Hirasawa 2013 3 3 15 50 1.9% 16.03 [0.78, 329,40] Horikawa 2015 6 111 8 12 5.5% 0.60 [0.11, 3.24] Kimura 2018 8 200 0 26 2.0% 36.04 [1.92,675.20] Matsucka 2020 15 27 7 24 10.3% 0.94 [0.95, 9.71] Minami 2006 32 61 23 56 19.7% 1.58 [0.76, 3.29] Moriya 2011 5 18 3 21 6.0% 2.31 [0.47, 11.42] Satoh 2011 13 32 4 41 9.2% 6.33 [1.81, 22.08] Okuyama 2011 5 18 3 21 6.0% 2.31 [0.47, 11.42] Satoh 2011 13 32 4 41 9.2% 6.33 [1.81, 22.08] Takano 2009 8 13 4 17 6.1% 5.20 [1.07, 25.31] Yamamoto 2009 4 16 1 20 3.1% 6.33 [0.63, 63.64] Takano 2009 4 16 1 20 3.1% 6.33 [0.63, 63.64] Takano 2009 4 16 10.0% 2.81 [1.35, 4.28] Total events 124 91 Heterogeneity: Tau ² = 0.09, Chi ² = 15.27, df = 13 (P = 0.29); l ² = 15% Test for overall effect: Z = 4.26 (P < 0.0001) 1.1.3 Thai Atasilp 2015 3 16 0 28 12.8% 14.78 [0.71, 306.81] Atasilp 2015 3 16 0 28 12.8% 10.01 [3.14, 31.88] Total events 23 10 Heterogeneity: Tau ² = 0.00, Chi ² = 0.06, df = 1 (P = 0.81); l ² = 0% Test for overall effect: Z = 4.26 (P < 0.0001) (b)	Heterogeneity: Tau ² =	0.73; Chi ² =	= 38.72,	df = 9 (P	< 0.00	01); I²= 7	7%	
1.12 Japan Ando 2017 6 13 5 22 6.9% 2.91 [0.66, 12.77] Hirasawa 2013 3 3 15 50 1.9% 16.03 [0.78, 329, 40] Horikawa 2015 6 11 8 12 5.5% 0.60 [0.11, 3.24] Kimura 2018 8 20 0 26 2.0% 36.04 [1.92, 675.20] Matsuoka 2020 15 27 7 24 10.3% 3.04 [0.95, 9.71] Minami 2006 32 61 23 56 19.7% 1.58 [0.76, 3.29] Moriya 2014 4 8 6 37 5.8% 5.17 [1.00, 26.60] Okuyama 2011 5 18 3 21 6.0% 2.31 [0.47, 11.42] Satab 2013 3 18 4 24 5.3% 1.00 [0.19, 5.15] Takahara 2013 8 15 6 29 8.0% 4.38 [1.31, 12.208] Sunkawa 2010 3 18 4 24 5.3% 1.00 [0.19, 5.15] Takahara 2013 8 15 6 29 8.0% 4.38 [1.31, 6.36, 36.364] Subtotal (95% CI) 292 416 100.0% 2.81 [1.85, 4.28] Total events 124 91 Heterogeneity: Tau ² = 0.09; Chi ² = 15.27, df = 13 (P = 0.29); P = 15% Test for overall effect $Z = 4.34$ (P < 0.00001) 1.13 Thai Atasilp 2015 3 16 0 28 12.8% 14.78 [0.71, 306.81] Atasilp 2015 3 16 0 28 12.8% 10.00 [3.14, 31.88] Atasilp 2015 3 10 Heterogeneity: Tau ² = 0.00; Chi ² = 0.06], df = 1 (P = 0.81); P = 0% Test for overall effect $Z = 4.26$ (P < 0.0001) (b)	Test for overall effect:	Z = 2.53 (P	= 0.01)					
The sequent is sequent in the sequence of the	112 Janan							
The formation of the f	Ando 2017	e	10	5	22	6.00	2 04 10 66 42 77	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Anuo 2017	0	13	15	22	0.9%	2.91 [0.00, 12.77]	
Holinawa 2015 6 11 6 12 3.5% 0.00 [0.11, 32, 675.20] Matsuoka 2020 15 27 7 24 10.3% 3.04 [0.95, 9.71] Minami 2006 32 61 23 56 19.7% 1.58 [0.76, 3.29] Moriya 2014 4 8 6 37 5.5% 5.17 [1.00, 26.60] Okuyama 2011 5 18 3 21 6.0% 2.31 [0.47, 11.42] Satoh 2011 1 13 32 4 41 9.2% 6.33 [1.81, 22.08] Sunakawa 2010 3 18 4 24 5.8% 1.00 [0.19, 5.15] Takahara 2013 8 15 6 29 8.0% 4.38 [1.13, 16.99] Takahara 2013 8 15 6 29 8.0% 4.38 [1.13, 16.99] Takahara 2013 8 15 6 29 8.0% 4.38 [1.13, 16.99] Takahara 2019 9 8 13 4 17 6.1% 5.20 [1.07, 25.31] Yamaguchi 2019 9 37 5 37 9.7% 2.06 [0.62, 6.87] Yamaguchi 2019 9 4 16 1 20 3.1% 6.33 [0.63, 63.64] Subtotal (95% CI) 292 416 100.0% 2.81 [1.85, 4.28] Total events 124 91 Heterogeneily: Tau ² = 0.09; Chi ² = 15.27, df = 13 (P = 0.29); P = 15% Test for overall effect $Z = 4.84$ (P < 0.00001) 1.1.3 Thai Atasilp 2015 3 16 0 28 12.8% 14.78 [0.71, 306.81] Atasilp 2015 3 16 0 28 12.8% 14.78 [0.71, 306.81] Atasilp 2015 3 16 0 28 12.8% 14.78 [0.71, 306.81] Atasilp 2015 3 16 0 28 12.8% 14.78 [0.71, 306.81] Atasilp 2020 20 20 26 10 40 87.2% 10.00 [3.14, 31.88] Subtotal (95% CI) 42 68 100.0% 10.51 [3.56, 31.05] Total events 23 10 Heterogeneily: Tau ² = 0.00; Chi ² = 0.06, df = 1 (P = 0.81); P = 0% Test for overall effect $Z = 4.26$ (P < 0.0001) (b)	Hirasawa 2013 Harikawa 2015	3	3	15	50	1.9%	10.03 [0.78, 329.40]	
Nindra 2016 6 20 0 0 20 2.0% 30.04 [1.9, 05.20] Matsuoka 2020 15 27 7 24 10.3% 30.04 [0.95, 9,71] Minami 2006 32 61 23 56 19.7% 1.58 [0.76, 3.29] Moriya 2014 4 8 6 37 5.8% 5.17 [1.00, 26.60] Okuyama 2011 5 18 3 21 6.0% 2.31 [0.47, 11.42] Satoh 2011 13 32 4 41 9.2% 6.33 [1.81, 22.08] Sunkawa 2010 3 18 4 24 5.8% 1.00 [0.19, 5.15] Takahara 2013 8 15 6 29 8.0% 4.38 [1.13, 16.99] Yamaguchi 2019 9 37 5 37 9.7% 2.06 [0.62, 6.87] Yamaguchi 2019 9 377 5 37 9.7% 2.06 [0.62, 6.87] Yamaguchi 2019 9 377 5 37 9.7% 2.06 [0.62, 6.87] Yamaguchi 2019 9 377 5 37 9.7% 2.06 [0.62, 6.87] Yamaguchi 2019 9 377 5 37 9.7% 2.06 [0.62, 6.87] Yamaguchi 2019 9 377 5 37 9.7% 2.06 [0.62, 6.87] Yamaguchi 2019 9 377 5 37 9.7% 2.06 [0.62, 6.87] Yamaguchi 2019 9 377 5 37 9.7% 2.06 [0.62, 6.87] Yamaguchi 2019 9 377 5 37 9.7% 2.06 [0.62, 6.87] Yamaguchi 2019 9 377 5 37 9.7% 1.000 [3.14, 31, 86] Subtotal (95% CI) 292 416 100.0% 2.81 [1.85, 4.28] Total events 124 91 Heterogeneity: Tau ² = 0.09, Chi ² = 15.27, df = 13 (P = 0.29); P = 15% Test for overall effect Z = 4.84 (P < 0.00001) 1.1.3 Thai Atasilp 2020 20 26 10 40 87.2% 10.00 [3.14, 31.88] Subtotal (95% CI) 42 68 100.0% 10.51 [3.56, 31.05] Total events 23 10 Heterogeneity: Tau ² = 0.00, Chi ² = 0.06, df = 1 (P = 0.81); P = 0% Test for overall effect Z = 4.26 (P < 0.0001) (b)	Hurikawa 2015 Kimuka 2019	0	20	0	12	0.0%	0.00 [0.11, 3.24]	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Kimura 2018 Mateuoka 2020	16	20	7	20	2.0%	2 04 (0.05 0.71)	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Minomi 2006	22	61	22	24	10.3%	3.04 [0.95, 9.71]	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Moriva 2014	32	01	23	27	5 000	5 17 11 00 26 601	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Okuyama 2014	4	10	2	21	0,0,0	2 21 [0 47 11 42]	
Sunakawa 2010 3 18 4 24 52% 10.01 [0.19,515] Takahara 2013 8 15 6 29 8.0% 4.38 [1.13, 16.99] Takano 2009 8 13 4 17 6.1% 5.20 [1.07, 25.31] Yamaguchi 2019 9 37 5 37 9.7% 2.06 [1.62, 6.87] Yamamoto 2009 4 16 1 20 3.1% 6.33 [0.63, 63.64] Subtotal (95% CI) 292 416 100.0% 2.81 [1.85, 4.28] Total events 124 91 Heterogeneity: Tau ² = 0.09; Chi ² = 15.27, df = 1.3 (P = 0.29); P = 15% Test for overall effect: $Z = 4.34$ (P < 0.00001) 1.1.3 Thai Atasilp 2015 3 16 0 28 12.3% 14.78 [0.71, 306.81] Atasilp 2020 20 26 10 40 87.2% 10.00 [3.14, 31.88] Subtotal (95% CI) 42 68 100.0% 10.51 [3.56, 31.05] Total events 23 10 Heterogeneity: Tau ² = 0.00; Chi ² = 0.06, df = 1 (P = 0.81); P = 0% Test for overall effect: $Z = 4.26$ (P < 0.0001) (b)	Satab 2011	12	22	4	41	0.0%	2.31 [0.47, 11.42]	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Sunakawa 2010	3	18	4	24	5.2%	1 00 00 19 5 15	
Takano 2009 8 13 4 17 61% 5.20 [1.07,25.31] Yamaguchi 2019 9 37 5 37 9.7% 2.06 [0.62, 6.87] Yamamoto 2009 4 16 1 20 3.1% 6.33 [0.63, 63.64] Subtotal (95% CI) 292 416 100.0% 2.81 [1.85, 4.28] Total events 124 91 Heterogeneity: Tau ² = 0.09; Chi ² = 15.27, df = 13 (P = 0.29); I ² = 15% Test for overall effect: $Z = 4.84$ (P < 0.00001) 1.1.3 Thai Atasilp 2015 3 16 0 28 12.8% 14.78 [0.71, 306.81] Atasilp 2020 20 26 10 40 87.2% 10.00 [3.14, 31.88] Subtotal (95% CI) 42 68 100.0% 10.51 [3.56, 31.05] Total events 23 10 Heterogeneity: Tau ² = 0.00; Chi ² = 0.06, df = 1 (P = 0.81); I ² = 0% Test for overall effect: $Z = 4.26$ (P < 0.0001) (b)	Takahara 2013	8	15	6	29	8.0%	4 38 [1 13 16 99]	
Yamaguchi 2019 9 37 5 37 9.7% 2.06 $[0.62, 687]$ Yamamoto 2009 4 16 1 20 3.1% 6.33 $[0.63, 63.64]$ Subtotal (95% CI) 292 416 100.0% 2.81 $[1.85, 4.28]$ Total events 124 91 Heterogeneity: Tau ² = 0.09; Chi ² = 15.27, df = 13 (P = 0.29); l ² = 15% Test for overall effect: Z = 4.84 (P < 0.00001) 1.1.3 Thai Atasilp 2015 3 16 0 28 12.8% 14.78 $[0.71, 306.81]$ Atasilp 2020 20 26 10 40 87.2% 10.00 $[3.14, 31.88]$ Subtotal (95% CI) 42 68 100.0% 10.51 $[3.56, 31.05]$ Total events 23 10 Heterogeneity: Tau ² = 0.00; Chi ² = 0.06, df = 1 (P = 0.81); l ² = 0% Test for overall effect: Z = 4.26 (P < 0.0001) (b)	Takano 2009	ě.	13	4	17	61%	5 20 [1 07 25 31]	
Yamamoto 2009 4 16 1 20 3.1% 6.33 [0.63, 63.64] Subtotal (95% CI) 292 416 100.0% 2.81 [1.85, 4.28] Total events 124 91 Heterogeneity: Tau ² = 0.09; Ch ² = 15.27, df = 13 (P = 0.29); P = 15% Test for overall effect: $Z = 4.84$ (P < 0.00001) 1.1.3 Thai Atasilp 2015 3 16 0 28 12.8% 14.78 [0.71, 306.81] Atasilp 2020 20 26 10 40 87.2% 10.00 [3.14, 31.88] Subtotal (95% CI) 42 68 100.0% 10.51 [3.56, 31.05] Total events 23 10 Heterogeneity: Tau ² = 0.00; Ch ² = 0.06, df = 1 (P = 0.81); P = 0% Test for overall effect: $Z = 4.26$ (P < 0.0001) (b)	Yamaguchi 2019	ğ	37	5	37	9.7%	2 06 10 62 6 871	
Subtotal (95% CI) 292 416 100.0% 2.81 [1.85, 4.28] Total events 124 91 Heterogeneity: Tau ² = 0.09; Chi ² = 15.27, df = 13 (P = 0.29); l ² = 15% Test for overall effect: Z = 4.84 (P < 0.00001) 1.1.3 Thai Atasilp 2015 3 16 0 28 12.8% 14.78 [0.71, 306.81] Atasilp 2020 20 26 10 40 87.2% 10.00 [3.14, 31.88] Subtotal (95% CI) 42 68 100.0% 10.51 [3.56, 31.05] Total events 23 10 Heterogeneity: Tau ² = 0.00; Chi ² = 0.06, df = 1 (P = 0.81); l ² = 0% Test for overall effect: Z = 4.26 (P < 0.0001) (b)	Yamamoto 2009	4	16	1	20	3.1%	6.33 [0.63, 63, 64]	
Total events 124 91 Heterogeneity: Tau ² = 0.09; Ch ² = 15.27, df = 13 (P = 0.29); ² = 15% Test for overall effect: Z = 4.84 (P < 0.00001) 1.1.3 Thai Atasilp 2015 3 16 0 28 12.8% 14.78 [0.71, 306.81] Atasilp 2020 20 26 10 40 87.2% 10.00 [3.14, 31.88] Subtotal (95% Cl) 42 68 100.0% 10.51 [3.56, 31.05] Total events 23 10 Heterogeneity: Tau ² = 0.00; Ch ² = 0.06, df = 1 (P = 0.81); ² = 0% Test for overall effect: Z = 4.26 (P < 0.0001) (b)	Subtotal (95% CI)		292		416	100.0%	2.81 [1.85, 4.28]	•
Heterogeneity: Tau ² = 0.09; Chi ² = 15.27, df = 13 (P = 0.29); ² = 15% Test for overall effect: $Z = 4.84$ (P < 0.00001) 1.1.3 Thai Atasilp 2015 3 16 0 28 12.8% 14.78 [0.71, 306.81] Atasilp 2020 20 26 10 40 87.2% 10.00 [3.14, 31.88] Subtotal (95% Cl) 42 68 100.0% 10.51 [3.56, 31.05] Total events 23 10 Heterogeneity: Tau ² = 0.00; Chi ² = 0.06, df = 1 (P = 0.81); ² = 0% Test for overall effect: $Z = 4.26$ (P < 0.0001) (b)	Total events	124		91				
Test for overall effect: $Z = 4.84$ (P < 0.00001) 1.1.3 Thai Atasilp 2015 3 16 0 28 12.8% 14.78 [0.71, 306.81] Atasilp 2020 20 26 10 40 87.2% 10.00 [3.14, 31.88] Subtotal (95% CI) 42 68 100.0% 10.51 [3.56, 31.05] Total events 23 10 Heterogeneity: Tau ² = 0.00; Chi ² = 0.06, df = 1 (P = 0.81); i ² = 0% Test for overall effect: $Z = 4.26$ (P < 0.0001) (b)	Heterogeneity: Tau ² =	0.09; Chi ² =	= 15.27.	df = 13 (P = 0.2	9); I ² = 15	%	
1.1.3 Thai Atasilp 2015 3 16 0 28 12.3% 14.78 [0.71, 306.81] Atasilp 2020 20 26 10 40 87.2% 10.00 [3.14, 31.88] Subtotal (95% CI) 42 68 100.0% 10.51 [3.56, 31.05] Total events 23 10 Heterogeneity: Tau ² = 0.00; Chi ² = 0.06, df = 1 (P = 0.81); I ² = 0% Test for overall effect: Z = 4.26 (P < 0.0001)	Test for overall effect:	Z = 4.84 (P	< 0.000	01)				
1.1.3 Thai Atasilp 2015 3 16 0 28 12.8% 14.78 [0.71, 306.81] Atasilp 2020 20 26 10 40 87.2% 10.00 [3.14, 31.88] Subtotal (95% CI) 42 68 100.0% 10.51 [3.56, 31.05] Total events 23 10 Heterogeneity: Tau ² = 0.00; Chi ² = 0.06, df = 1 (P = 0.81); I ² = 0% Test for overall effect: $Z = 4.26$ (P < 0.0001) (b)								
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Atasiip 2020 20 26 10 40 87.2% 10.00 [3.14, 31.88] Subtotal (95% CI) 42 68 100.0% 10.51 [3.56, 31.05] Total events 23 10 Heterogeneity: Tau ² = 0.00; Chi ² = 0.06, df = 1 (P = 0.81); I ² = 0% Test for overall effect: Z = 4.26 (P < 0.0001) 0.1 0.1 10 $100Wild type (*1/*1) UGT1A1*6+*28 Carriers(b)$	Atasilp 2015	3	16	0	28	12.8%	14.78 [0.71, 306.81]	_
Subtotal (95% Cl) 42 68 100.0% 10.51 [3.56, 31.05] Total events 23 10 Heterogeneity: Tau ² = 0.00; Chi ² = 0.06, df = 1 (P = 0.81); I ² = 0% Test for overall effect: $Z = 4.26$ (P < 0.0001) 0.01 0.1 1 10 100 Wild type (*1/*1) UGT1A1*6+*28 Carriers (b)	Atasilp 2020	20	26	10	40	87.2%	10.00 [3.14, 31.88]	
Total events 23 10 Heterogeneity: Tau ² = 0.00; Chi ² = 0.06, df = 1 (P = 0.81); I ² = 0% Test for overall effect: Z = 4.26 (P < 0.0001) 0.01 0.1 1 10 $100Wild type (*1/*1) UGT1A1*6+*28 Carriers(b)$	Subtotal (95% CI)		42		68	100.0%	10.51 [3.56, 31.05]	
Heterogeneity: Tau ² = 0.00; Chi ² = 0.06, df = 1 (P = 0.81); i ² = 0% Test for overall effect: Z = 4.26 (P < 0.0001) 0.01 0.1 1 10 100 Wild type (*1/*1) UGT1A1*6+*28 Carriers (b)	Total events	23		10				
Test for overall effect: Z = 4.26 (P < 0.0001) 0.01 0.1 1 10 100 Wild type (*1/*1) UGT1A1*6+*28 Carriers (b)	Heterogeneity: Tau ² =	0.00; Chi ² =	= 0.06, c	if = 1 (P =	0.81);	I ² = 0%		
(b)	Test for overall effect:	Z = 4.26 (P	< 0.000	1)				
0.01 0.1 1 10 100 Wild type (*1/*1) UGT1A1*6+*28 Carriers (b)								
(b) Wild type (*1/*1) UG71A1*6+*28 Carriers								0.01 0.1 1 10 100
(b)								Wild type (*1/*1) UGT1A1*6+*28 Carriers
	(b)							

	UGT1A1*	6+*28	*1/*	1		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.1.1 China							
Bai 2017	4	37	2	44	8.9%	2.55 [0.44, 14.76]	
Chen 2020	9	33	3	53	11.3%	6.25 [1.55, 25.20]	· · · · · · · · · · · · · · · · · · ·
Deng 2017	2	65	0	50	4.1%	3.98 [0.19, 84.70]	
Gao J2 2013	10	146	6	133	14.2%	1.56 [0.55, 4.41]	- -
Li 2014	28	107	6	60	15.0%	3.19 [1.24, 8.23]	
Liu 2017	28	298	31	368	18.5%	1.13 [0.66, 1.93]	- -
Shi 2015	4	17	1	12	6.2%	3.38 [0.33, 34.92]	
Xiao 2015	8	29	1	38	7.0%	14.10 [1.65, 120.61]	$ \longrightarrow$
Xu 2016	38	98	5	85	14.6%	10.13 [3.76, 27.29]	
Subtotal (95% CI)		830		843	100.0%	3.34 [1.67, 6.71]	
Total events	131		55				
Heterogeneity: Tau ² =	0.61; Chi ² :	= 21.71,	df = 8 (P	= 0.00	5); I² = 63	%	
Test for overall effect:	Z = 3.40 (P	= 0.000	7)				
1.1.2 Japan							
Ando 2017	4	13	4	22	13.5%	2.00 [0.40, 9.91]	
Hirasawa 2013	2	3	3	50	6.1%	31.33 [2.17, 452.07]	
Horikawa 2015	2	11	1	12	6.6%	2.44 [0.19, 31.53]	
Kimura 2018	6	20	9	26	18.4%	0.81 [0.23, 2.83]	
Matsuoka 2020	3	27	4	24	13.4%	0.63 [0.12, 3.13]	
Minami 2006	6	61	4	56	17.3%	1.42 [0.38, 5.31]	
Satoh 2011	1	32	0	41	4.4%	3.95 [0.16, 100.31]	
Sunakawa 2010	1	18	0	24	4.3%	4.20 [0.16, 109.28]	
Takano 2009	5	13	0	17	5.0%	22.65 [1.12, 458.89]	_
Yamaguchi 2019	2	37	3	37	11.0%	0.65 [0.10, 4.12]	
Subtotal (95% CI)		235		309	100.0%	1.74 [0.85, 3.55]	-
Total events	32		28				
Heterogeneity: Tau² =	0.32; Chi ² :	= 12.00,	df = 9 (P	= 0.21)	; I² = 25%	6	
Test for overall effect:	Z=1.51 (P	= 0.13)					
							Wild type (*1/*1) UGT1A1*6+*28 Carriers

FIGURE 4 (a) Forest plot of the UGT1A1*6 + UGT1A1*28 versus UGT1A1*1/*1 for irinotecan-induced neutropenia in different Asian ethnicities. (b) Forest plot of the UGT1A1*6 + UGT1A1*28 versus UGT1A1*1/*1 for irinotecan induced diarrhea in different Asian ethnicities.





FIGURE 5 (a) Forest plot of the UGT1A1*6 + UGT1A1*28 versus UGT1A1*1/*1 for irinotecan-induced neutropenia in different dosing schedules. (b) Forest plot of the UGT1A1*6 + UGT1A1*28 versus UGT1A1*1/*1 for irinotecan-induced diarrhea in different dosing schedules.

(DPWG) recommended a 30% reduction in the standard starting dose of irinotecan for patients harboring the *UGT1A1*28/*28* genotype. Also, the French National Network of Pharmacogenetics (RNPGx) recommended a 25%–30% dose reduction in patients with *UGT1A1*28/*28* especially if they had other toxicity risk factors and contraindicated if taking higher doses.⁷⁷

The present findings support these recommendations since toxicities were greatly higher in patients especially when taking high doses of irinotecan (> 150 mg/m^2) and suggest that such recommendations should specify the high-risk population especially Asian patients.

This is because Asian cancer patients carrying either the heterozygous or homozygous variant of UGT1A1*28were significantly associated with irinotecan-induced neutropenia and diarrhea. Meta-analyses conducted by other research groups have also established similar strong associations in Asian cancer patients.^{36,37} Although some studies did not find such associations in Asian cancer patients due to claiming low frequency of UGT1A1*28,^{18,26,39,78} the present analysis has however establised robust evidence for these associations after aggregating data from a large number of studies and sample sizes.

(b)	UGT1A1*	6+*28	*1/*	1		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Random, 95% Cl
1.1.1 High dose>150	mg/m2							
Ando 2017	4	13	4	22	9.0%	2.00 [0.40, 9.91]		
Chen 2020	9	33	3	53	11.3%	6.25 [1.55, 25.20]		
Deng 2017	2	65	0	50	2.8%	3.98 [0.19, 84.70]		
Gao J 2013	10	146	6	133	17.7%	1.56 [0.55, 4.41]		
Li 2014	28	107	6	60	20.1%	3.19 [1.24, 8.23]		
Liu 2017	28	298	31	368	36.7%	1.13 [0.66, 1.93]		_ _
Sunakawa 2010 Subtotal (95% CI)	1	18 680	0	24 710	2.4% 100.0%	4.20 [0.16, 109.28] 2.01 [1.19, 3.38]		
Total events	82	000	50		1001070	2101 [1110, 0100]		•
Heterogeneity: Tau ² :	= 0.12: Chi ² :	= 7.99. 0	if = 6 (P =	0.24):	I² = 25%			
Test for overall effect	: Z = 2.63 (P	= 0.009)					
1.1.2 Medium dose:	150 mg/m2							
Minami 2006	3	27	1	35	26.3%	4.25 [0.42, 43.36]		
Xu 2016	38	98	5	85	42.0%	10.13 [3.76, 27.29]		_
Yamaguchi 2019	2	37	3	37	31.6%	0.65 [0.10, 4.12]		
Subtotal (95% CI)		162		157	100.0 %	3.38 [0.58, 19.74]		
Total events	43		9					
Heterogeneity: Tau ² :	= 1.67; Chi²:	= 6.65, 0	if = 2 (P =	: 0.04);	I ² = 70%			
Test for overall effect	: Z = 1.35 (P	= 0.18)						
1.1.3 Low dose<150	mg/m2							
Bai 2017	4	37	2	44	12.8%	2.55 [0.44, 14.76]		
Hirasawa 2013	2	3	3	50	8.1%	31.33 [2.17, 452.07]		
Horikawa 2015	2	11	1	12	8.6%	2.44 [0.19, 31.53]		
Kimura 2018	6	20	9	26	16.4%	0.81 [0.23, 2.83]		
Matsuoka 2020	3	27	4	24	13.8%	0.63 [0.12, 3.13]		
Minami 2006	3	34	3	21	13.2%	0.58 [0.11, 3.19]		
Shi 2015	4	17	1	12	9.6%	3.38 [0.33, 34.92]		
Takano 2009	5	13	0	17	6.9%	22.65 [1.12, 458.89]		
Xiao 2015	8	29	1	38	10.5%	14.10 [1.65, 120.61]		
Subtotal (95% CI)		191		244	100.0%	2.50 [0.97, 6.42]		
Total events	37		24					
Heterogeneity: Tau ² :	= 1.00; Chi²	= 16.22,	df = 8 (P	= 0.04); I² = 51%	6		
Test for overall effect	: Z = 1.90 (P	= 0.06)						
							0.01	0,1 1 10 100
								Wild type (*1/*1) UGT1A1*6+*28 Carriers

FIGURE 5 (Continued)

The present study also found that the UGT1A1*6 genetic variant was significantly associated with irinotecan-induced severe toxicities such as neutropenia and diarrhea, which is consistent with the findings of previous analyses.^{36,37} However, after assessing the combined effects of UGT1A1*6 and UGT1A1*28, the present study concluded that patients with both these variants, and especially with homozygous variants (UGT1A1*6/*6₊UGT1A1*28/28), experienced a significant effect as regards irinotecan-induced toxicities (i.e., neutropenia and diarrhea). The findings of the present analysis suggest that inheriting these genetic variants is probably associated with reduced function of UGT1A1, which maximizes the active irinotecan concentration in the blood and the risk of developing toxicities. Although genetic testing of UGT1A1*6 and UGT1A1*28 has been recommended in clinical practice in Japan for cancer patients taking irinotecan,³¹ other parts of Asia lack regulatory consensus as regards recommending such genetic testing. This may partly be because many Asian countries are not well positioned regarding previous pharmacogenomics research or may lack sufficiently robust evidence for the association of *UGT1A1*6* and *UGT1A1*28* genetic variants with irinotecan-induced severe toxicities.

The findings of the present analysis may therefore be considered as sufficiently robust evidence since the pooled risk was measured using a reasonably large number of sample sizes and provided strong evidence that patients were at a significantly greater risk of irinotecaninduced toxicities (i.e., neutropenia and diarrhea) when harboring both *UGT1A1*6* and *UGT1A1*28* genetic variants, especially homozygous variants, and therefore these polymorphisms may be considered to be important risk biomarkers. These findings may facilitate the translation of *UGT1A1*6* and *UGT1A1*28* pharmacogenomics into

		ABCC2 CT+TT		CC		Odds Ratio		Odds Ratio
	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
(a)	1.1.1 Neutropenia							
	Atasilp 2020	17	28	13	38	20.4%	2.97 [1.08, 8.18]	
	Han 2007	15	56	11	51	39.8%	1.33 [0.55, 3.25]	
	Han 2009	15	56	11	51	39.8%	1.33 [0.55, 3.25]	
	Subtotal (95% CI)		140		140	100.0%	1.67 [0.98, 2.84]	◆
	Total events	47		35				
Heterogeneity: Chi ² = 1.75, df = 2 (P = 0.42); l ² = 0%								
	Test for overall effect:	Z= 1.88 (P	= 0.06)	6				
(b)	1.1.2 Diarrhea							
	Han 2007	4	56	7	51	42.8%	0.48 [0.13, 1.76]	
	Han 2009	2	56	9	51	57.2%	0.17 [0.04, 0.84]	
	Subtotal (95% CI)		112		102	100.0%	0.31 [0.11, 0.81]	
	Total events	6		16				
Heterogeneity: Chi ² = 0.98, df = 1 (P = 0.32); i ² = 0%								
	Test for overall effect:	Z= 2.37 (P	= 0.02)					
							L	
							0.0	01 0.1 1 10 100
								CC CT+TT

FIGURE 6 Forest plot of the ABCC2 CT + TT versus CC for irinotecan-induced toxicities. (a) Association of ABCC2 CT + TT versus CC with neutropenia. (b) Association of ABCC2 CT + TT versus CC with diarrhea.

clinical practice in the form of precision irinotecan therapy and may reduce associated severe toxicities profoundly in cancer patients. Drug regulatory bodies and policymakers in Asian regions should emphasize such strong genetic relations with irinotecan-induced severe toxicities and should prepare national guidelines recommending preemptive screening for *UGT1A1*6* and *UGT1A1*28* genetic variants prior to prescribing irinotecan. The findings of this study will also assist clinicians in suggesting genotyping for *UGT1A1*6* and *UGT1A1*28* polymorphisms prior to administering irinotecan therapy as part of standard care and may be considered an appropriate recommendation for Asian cancer patients.

All ethnic groups of Asian patients carrying both *UGT1A1*6* and *UGT1A1*28* genetic variants developed toxicities except for diarrhea in Japanese patients. Without knowing the specific reason, it is hard to explain such an association although lifestyle, food, and co-medications may affect this association. It has still to be elucidated by future studies why Japanese patients carrying both *UGT1A1*6* and *UGT1A1*28* genetic variants and taking irinotecan were not significantly associated with diarrhea.

The effects of the *UGT1A1*6* and *UGT1A1*28* genetic variants are applicable to any type of cancer where irinotecan is clinically warranted since both colorectal and other different cancers were significantly associated with toxicities. Diarrhea and neutropenia were observed especially when patients used high doses of irinotecan >150 mg/ m^2 with the exception of neutropenia with low doses; however, these results are consistent with a previous analysis.¹⁰ Although toxicities at low doses are usually exceptional, confounding factors such as surgery, radiation, etc. may also contribute to irinotecan-induced neutropenia. Future clinical studies are warranted to establish the mechanism for such an association. Although it is difficult to conclude whether the non-significant risk of diarrhea and neutropenia with the intermediate dose was mainly due to the dose classification, the dose-dependent analysis conducted in the present study suggests that irinotecaninduced toxicities may be prevented by adjusting the irinotecan dose, and this needs further stratification as it has also been suggested by other studies.^{79,80}

Statistically significant associations were not found between the *ABCC2 c.3972C>T* genetic polymorphism and irinotecan-driven neutropenia in the present analysis. This may partly be because a very small number of studies (only three) and sample sizes were used in establishing this association, which may underpower the clinical outcomes. Although diarrhea was reduced significantly in patients carrying the *ABCC2 c.3972C>T* genetic variant, the findings are once again underpowered and such an association should be investigated in relatively large sample sizes in different ethnic groups.

Despite establishing significant associations of increased risk of irinotecan-induced toxicities (e.g., neutropenia and diarrhea) in Asian cancer patients with inherited *UGT1A1*6* and *UGT1A1*28* genetic variants, the present study nevertheless has some limitations. First, the study did not consider the confounding factors affecting the toxicity outcomes (e.g. chemotherapy regimen, co-medications, food, sex, age, etc.). Second, the analysis only extracted data from studies published in the English language, which may limit access to useful information published in other languages.

1630

In summary, the UGT1A1*6 and UGT1A1*28 genetic polymorphisms, especially when patients carried homozygous variants, were significantly associated with irinotecan-induced severe toxicities such as neutropenia and diarrhea in Asian cancer patients. The findings of this analysis suggest that screening for both the UGT1A1*6 and UGT1A1*28 genetic variants should be carried out in Asian cancer patients to reduce irinotecan toxicities substantially. Also, it is suggested that high doses of irinotecan $(>150 \text{ mg/m}^2)$ should be avoided to reduce toxicities significantly. Based on the robust evidence revealed by the present analysis, it is suggested that national guidelines be prepared recommending routine preemptive screening of UGT1A1*6 and UGT1A1*28 variants particularly in cancer patients before prescribing irinotecan. This may facilitate rapid translation of UGT1A1*6 and UGT1A1*28 pharmacogenomics into clinical practice in the form of precision irinotecan therapy.

AUTHOR CONTRIBUTIONS

C.A., M.B., N.V., and C.S. wrote the manuscript. C.S., C.A., M.B., and M.V. designed the research. C.A., N.V., Y.H., N.N., P.J., and J.R. performed the research. M.B., S.S., and N.V. analyzed the data.

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

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