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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 irinotecan-induced 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;

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 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/m^2) 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 UGT1A1-conjugating enzyme.[8] Although several clinical studies have established the strong association of *UGT1A1*28* genetic 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.[32,33] Therefore, genetic variations of the *ABCC2* gene, especially the c.3972C>T single nucleotide polymorphism, are also suspected to influence inter-individual 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 elsewhere[41] 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 irinotecan-induced 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 irinotecan-induced 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.

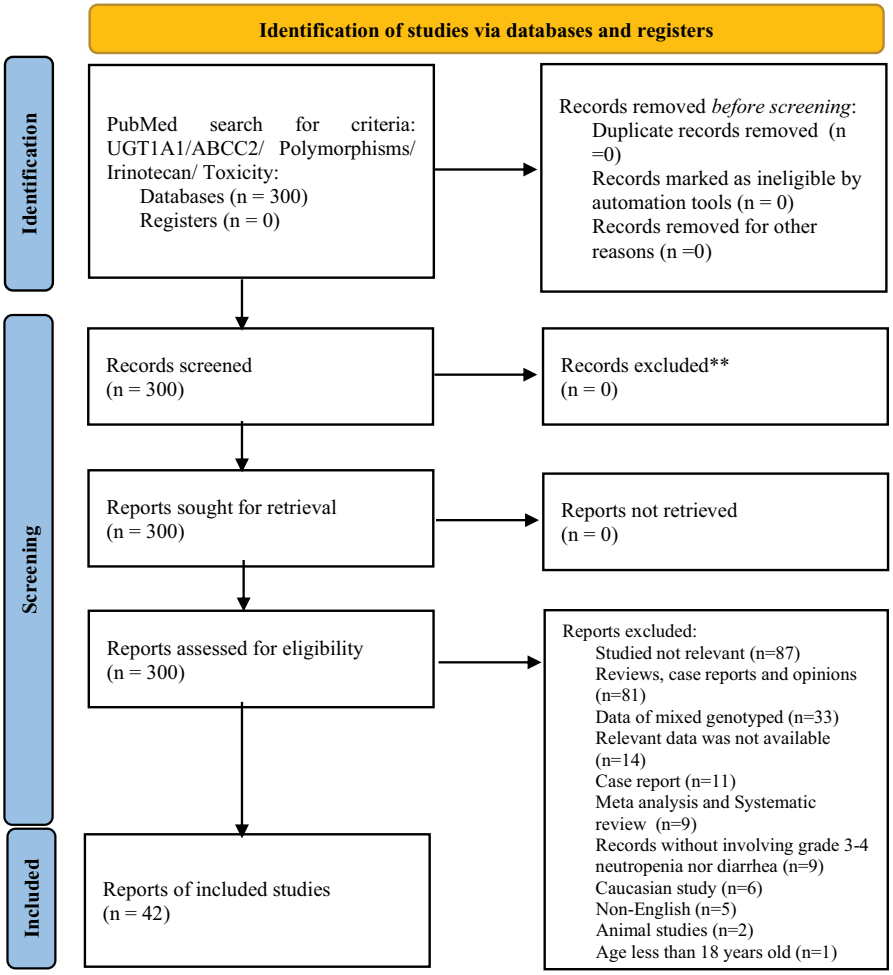

FIGURE 1 Flowchart of eligible studies included in the meta-analysis.

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 homozygous 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

TABLE 1 Baseline characteristics of included studies

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 62 103
Horikawa et al. 2015[30]	Japan	Retrospective	Cervical cancer	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

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 mg/m^2 or 100 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 mg/m^2 or 100 mg/m^2 or 75 mg/m^2	Neutropenia, diarrhea	Invader UGT1A1 Molecular Assay kit
Irinotecan + cisplatin	65 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

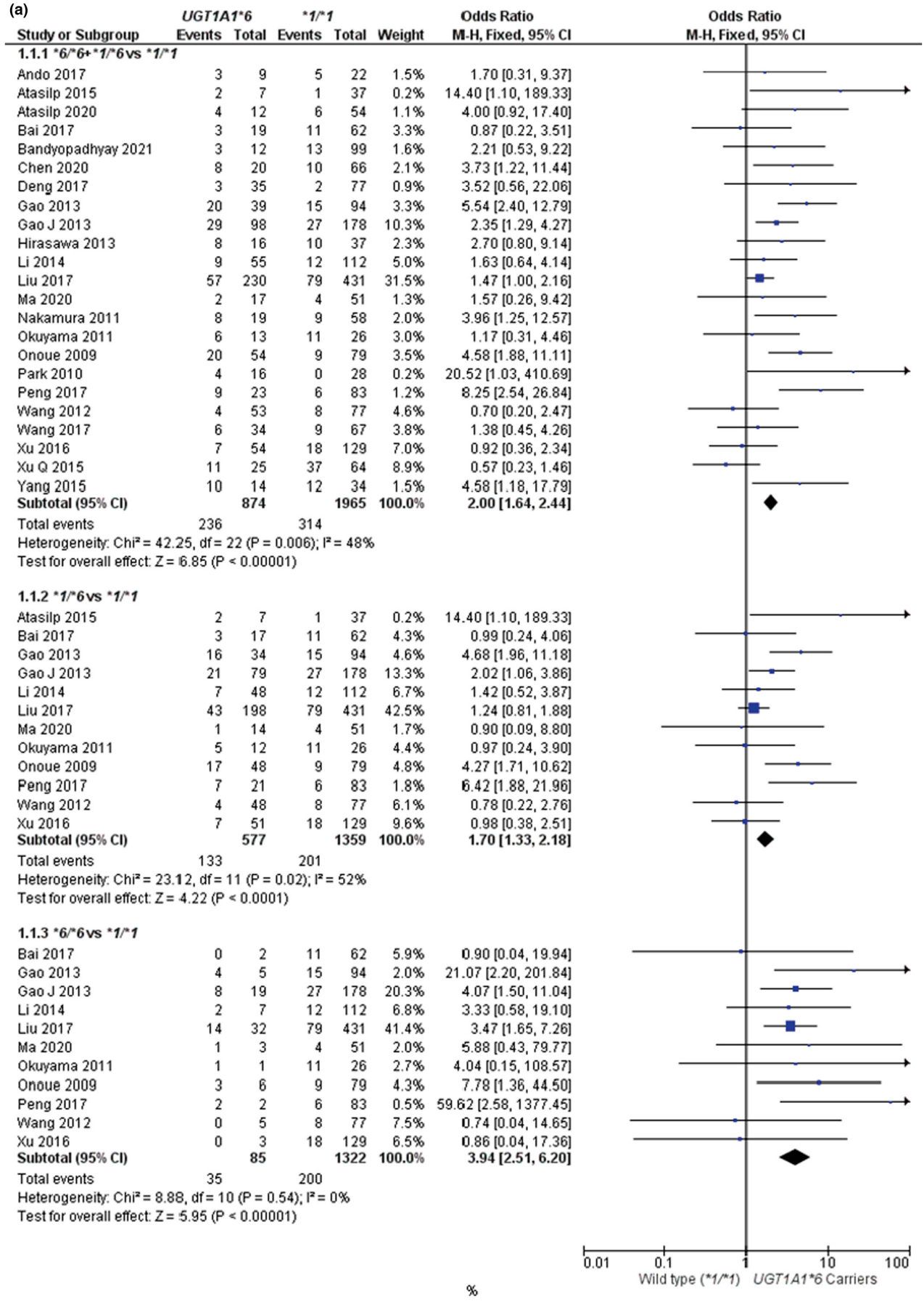

FIGURE 2 (a) Forest plot of the UGT1A1*6 versus UGT1A1*1/*1 for irinotecan-induced neutropenia. (b) Forest plot of the UGT1A1*6 versus UGT1A1*1/*1 for irinotecan-induced diarrhea.

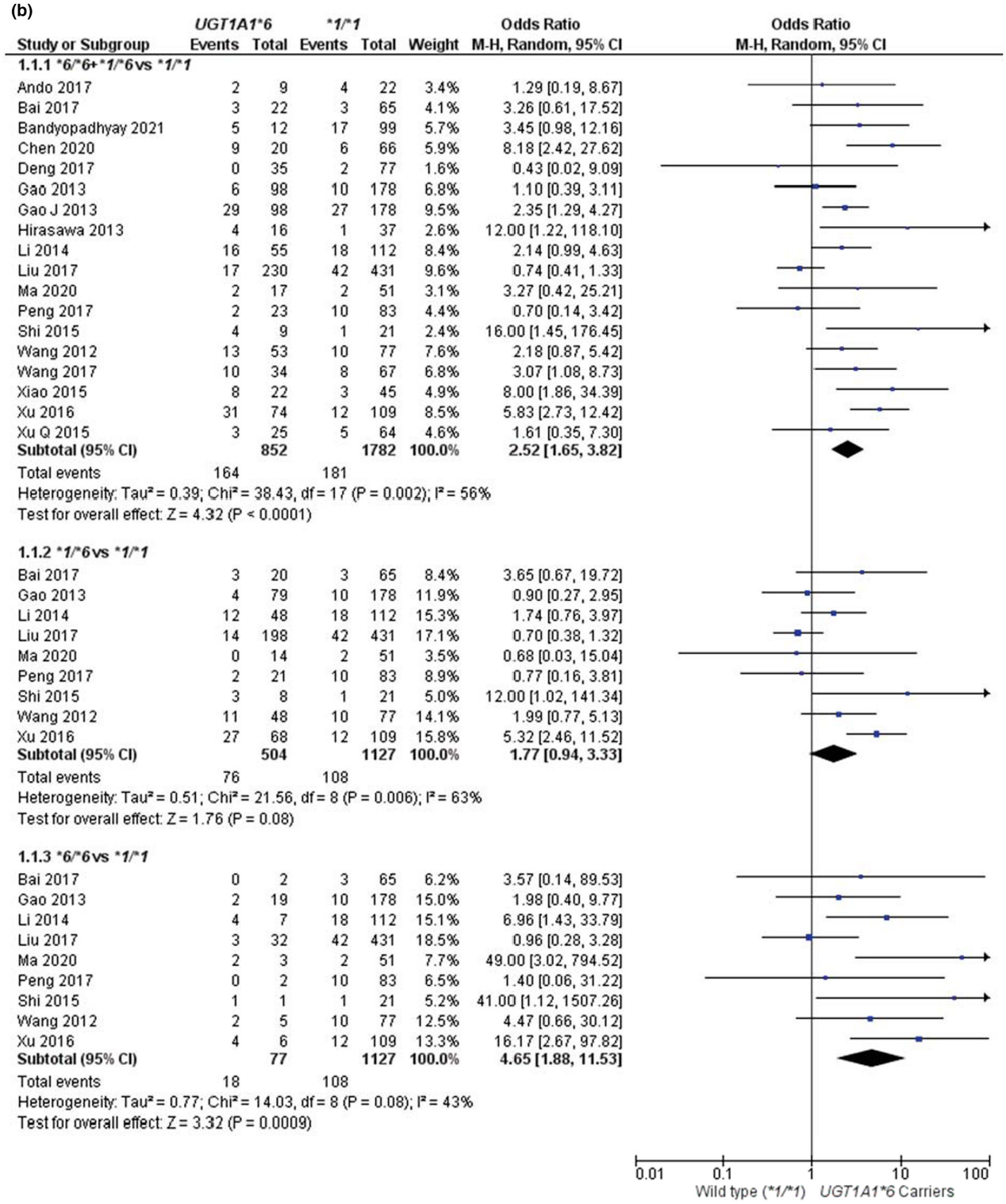

FIGURE 2 (Continued)

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

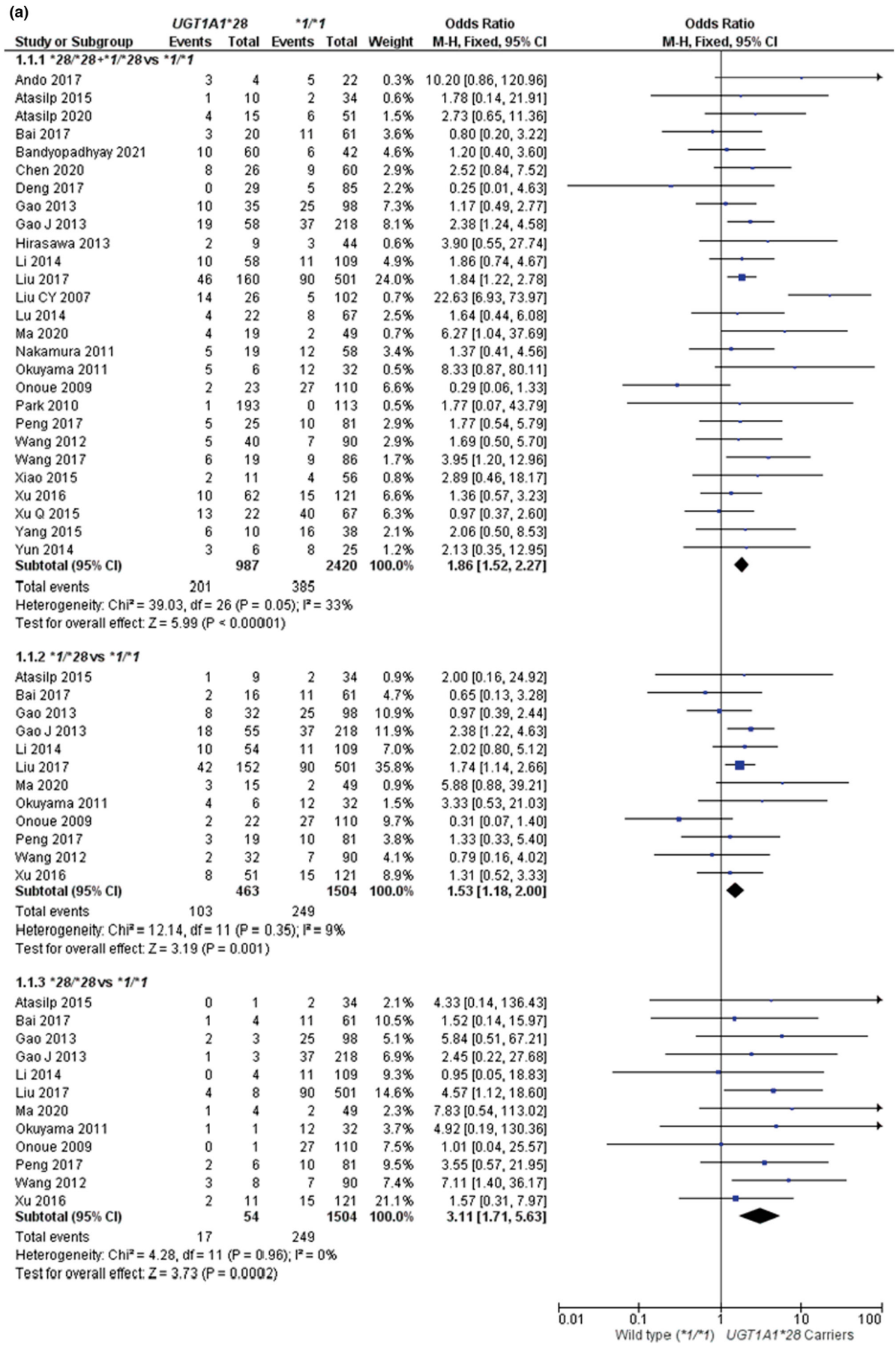

FIGURE 3 (a) Forest plot of the UGT1A1*28 versus UGT1A1*1/*1 for irinotecan-induced neutropenia. (b) Forest plot of the UGT1A1*28 versus UGT1A1*1/*1 for irinotecan-induced diarrhea.

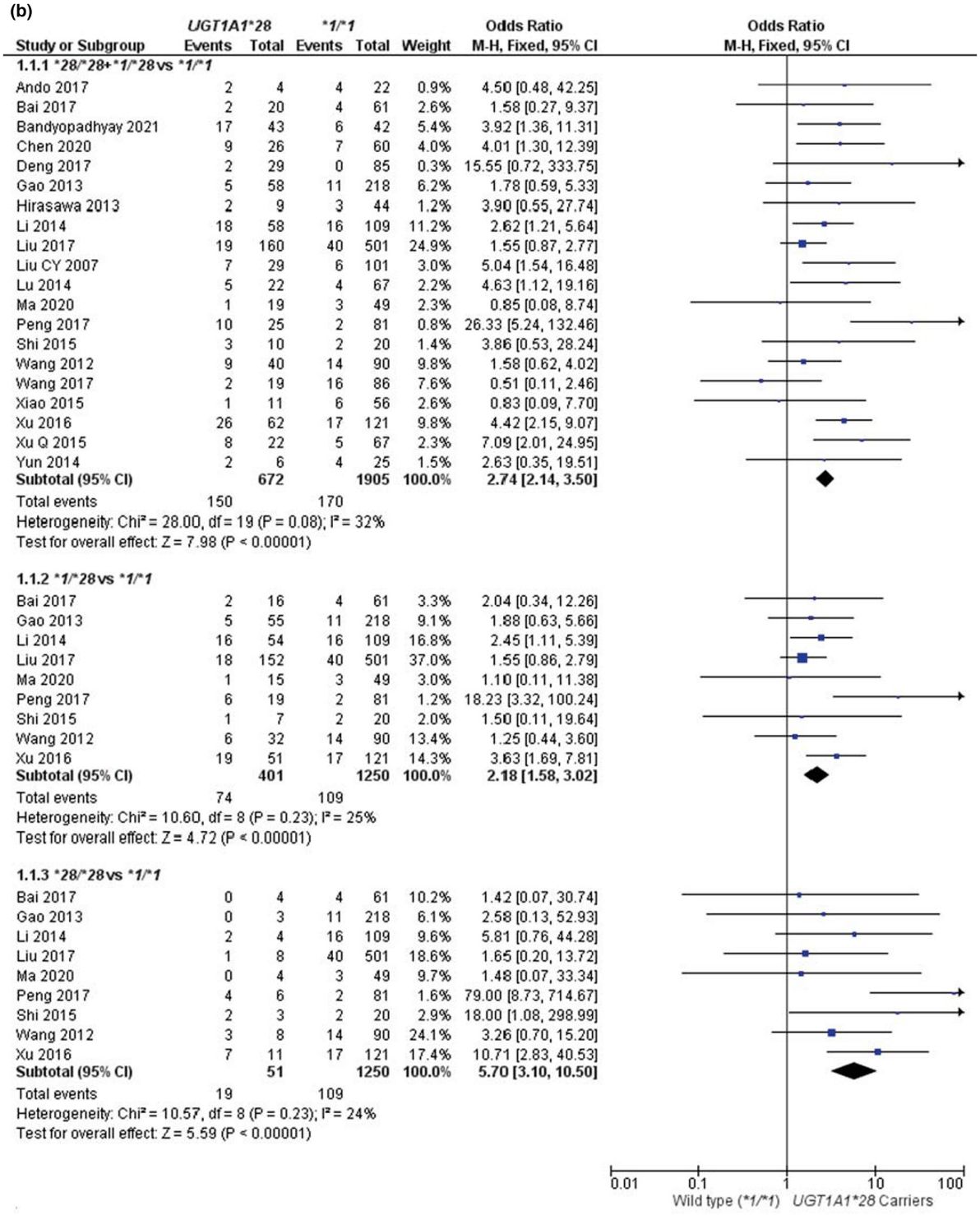

FIGURE 3 (Continued)

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/m^2, 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 irinotecan-induced 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 life-threatening 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

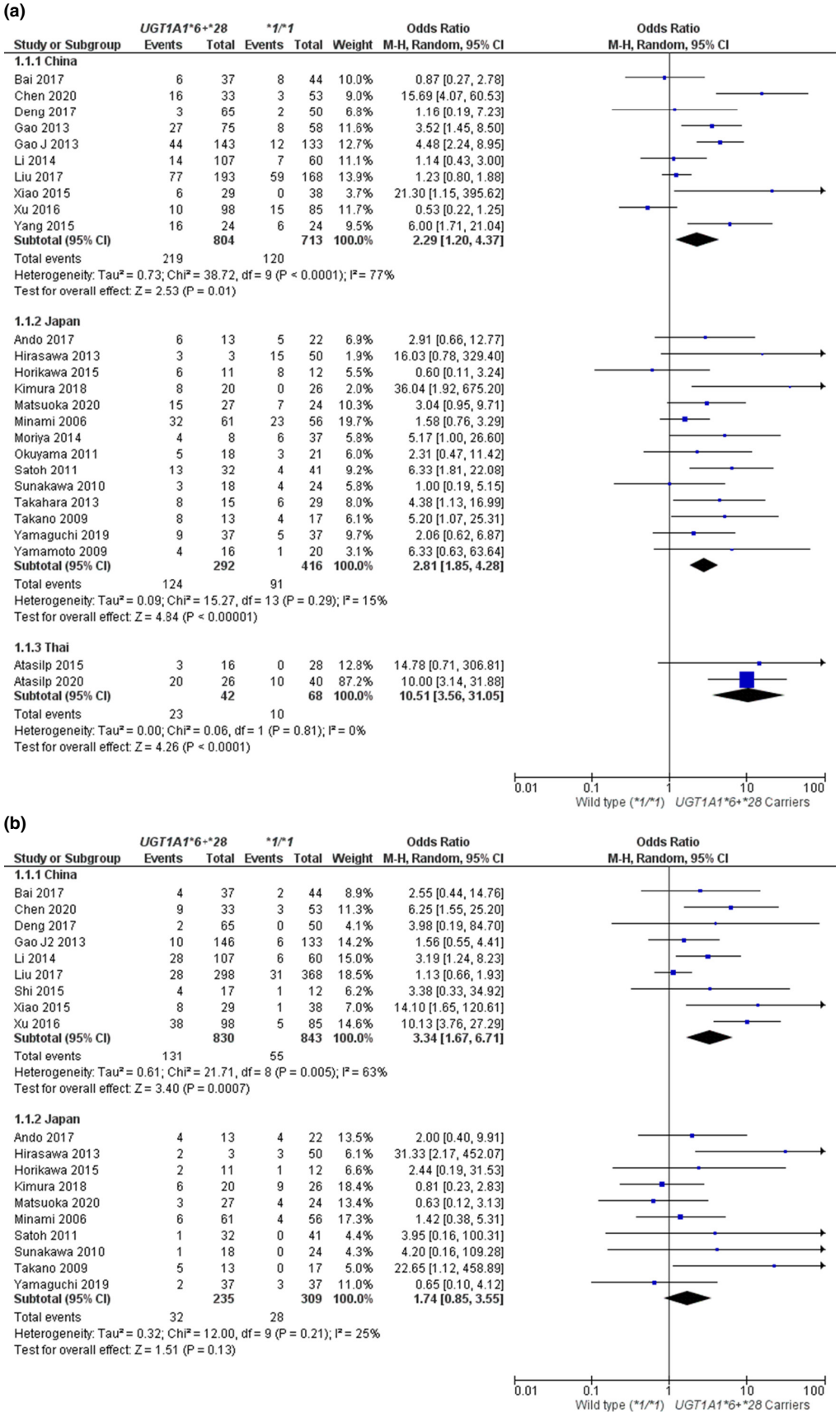

FIGURE 4 (a) Forest plot of the UGT1A1*6 + UGT1A1*28 versus UGT1A1*1/*1 for irinotecan-induced neutropenia in different Asian ethnicities. (b) Forest plot of the UGT1A1*6 + UGT1A1*28 versus UGT1A1*1/*1 for irinotecan induced diarrhea in different Asian ethnicities.

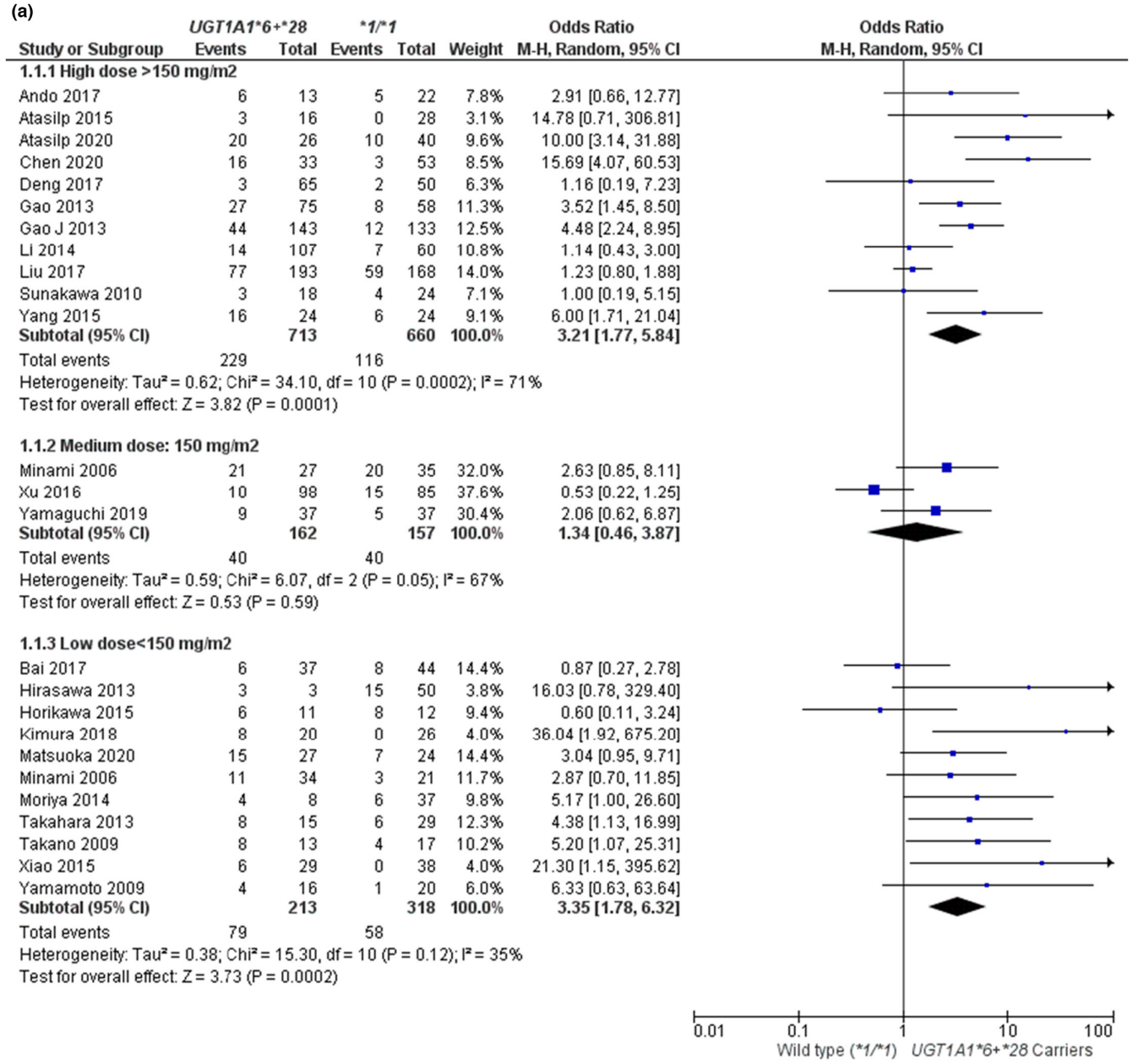

FIGURE 5 (a) Forest plot of the UGT1A1*6 + UGT1A1*28 versus UGT1A1*1/*1 for irinotecan-induced neutropenia in different dosing schedules. (b) Forest plot of the UGT1A1*6 + UGT1A1*28 versus UGT1A1*1/*1 for irinotecan-induced diarrhea in different dosing schedules.

(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*28* were 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 established robust evidence for these associations after aggregating data from a large number of studies and sample sizes.

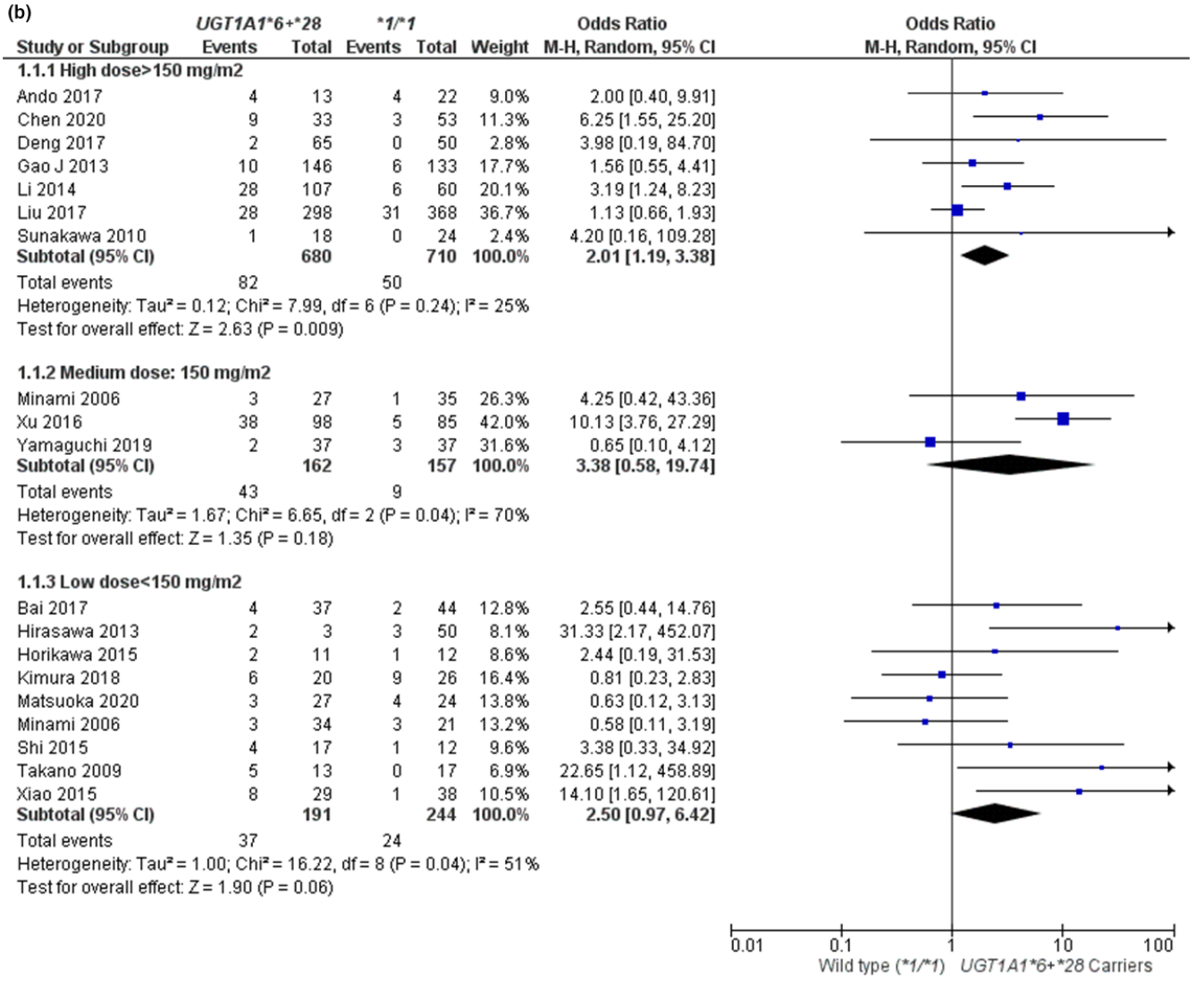

FIGURE 5 (Continued)

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 irinotecan-induced 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

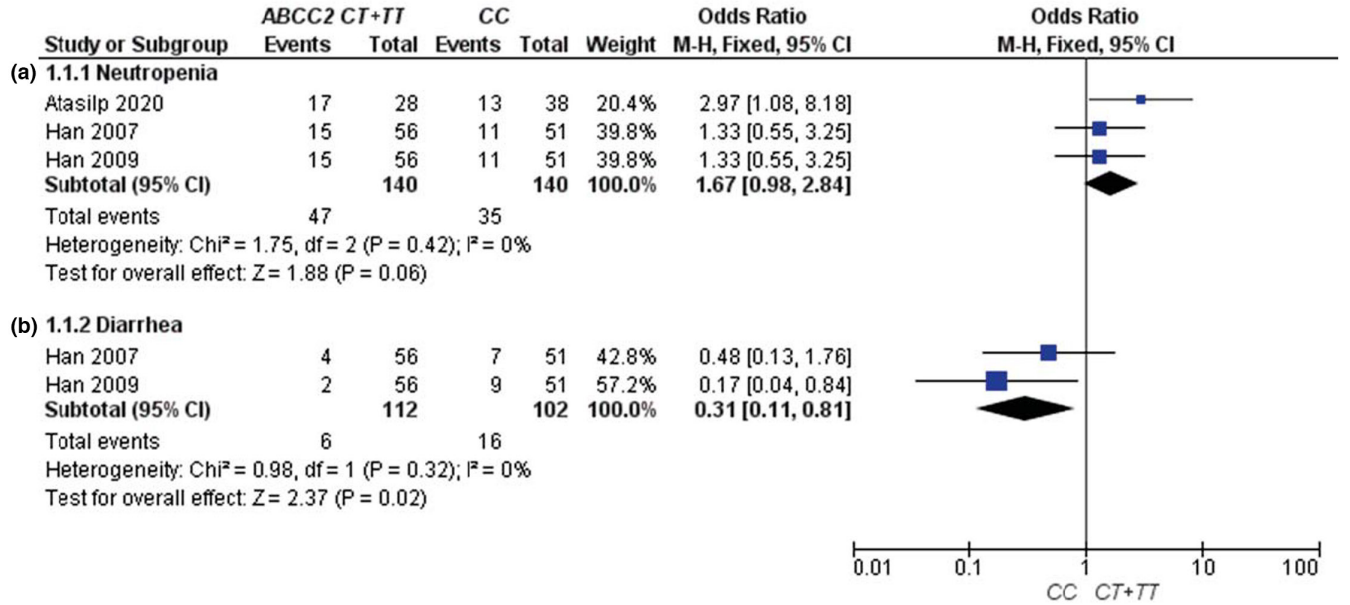

FIGURE 6 Forest plot of the ABCC2 CT + TT versus CC for irinotecan-induced toxicities. (a) Association of ABCC2 CT + TT versus CC with neutropenia. (b) Association of ABCC2 CT + TT versus CC with diarrhea.

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 pre-emptive 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 irinotecan-induced 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.

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 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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