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

Chalirmporn Atasilp[1], Mohitosh Biswas[2], Pimonpan Jinda[1], Nutthan Nuntharadthanaphong[1], Jiratha Rachanakul[1], Yaowaluck Hongkaew[1], Natchaya Vanwong[1], Surasak Saokaew[1], and Chonlaphat Sukasem[3]

[1]Affiliation not available
[2]University of Rajshahi
[3]Faculty of Medicine, Ramathibodi Hospital, Mahidol University

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Abstract

Abstract: Background: 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. It was aimed 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. Methods: Literature was searched in PubMed for eligible studies. Odds ratios (ORs) were measured using RevMan software where P-values<0.05 were statistically significant. Results: Patients 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 carried 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 with heterozygous variants. However, patients carried ABCC2 c.3972C>T genetic variant were not significantly associated with neutropenia (OR 1.67; 95% CI 0.98–2.84; P=0.06) but reduced diarrhea significantly (OR 0.31; 95% CI 0.11–0.81; P=0.02). Conclusions: Both UGT1A1*6 and UGT1A1*28 genetic variants should screen in Asian cancer patients to reduce substantially irinotecan-induced severe toxicities.

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genetic polymorphisms with irinotecan induced toxicity in Asian cancer patients: Meta-analysis

Chalirmporn Atasilp[1], Mohitosh Biswas[2,3,4], Pimonpan Jinda[2,3], Nutthan Nuntharadthanaphong[2,3], Jiratha Rachanakul[2,3], Yaowaluck Hongkaew[5], Natchaya Vanwong[6], Surasak Saokaew[7,8,9], Chonlaphat Sukasem[2,3,10*]

[1]Chulabhorn International College of Medicine, Thammasat University, Pathum Thani, Thailand

[2]Division of Pharmacogenomics and Personalized Medicine, Department of Pathology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

[3]Laboratory for Pharmacogenomics, Somdech Phra Debaratana Medical Center (SDMC), Ramathibodi Hospital, Bangkok, Thailand

[4]Department of Pharmacy, University of Rajshahi, Rajshahi, 6205, Bangladesh

[5]Advance Research and Development Laboratory, Bumrungrad International Hospital, Bangkok, Thailand

[6]Department of Clinical Chemistry, Faculty of Allied Health Sciences, Chulalongkorn University, Bangkok, Thailand.

[7]Division of Pharmacy Practice, Department of Pharmaceutical Care, School of Pharmaceutical Sciences, University of Phayao, Phayao, Thailand.[8]Center of Health Outcomes Research and Therapeutic Safety (Cohorts), School of Pharmaceutical Sciences, University of Phayao, Phayao, Thailand.[9]Unit of Excellence on Clinical Outcomes Research and IntegratioN (UNICORN), School of Pharmaceutical Sciences, University of Phayao, Phayao, Thailand.[10]Pharmacogenomics and Precision Medicine, The Preventive Genomics & Family Check-up Services Center, Bumrungrad International Hospital, Bangkok, Thailand

***** Correspondence: chonlaphat.suk@mahidol.ac.th; Tel.: (+66)-2-200-4330

Abstract: Background: 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. It was aimed 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. Methods: Literature was searched in PubMed for eligible studies. Odds ratios (ORs) were measured using RevMan software where$P$ -values<0.05 were statistically significant. Results: Patients 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 carried 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 with heterozygous variants. However, patients carried *ABCC2c.3972C>T* genetic variant were not significantly associated with neutropenia (OR 1.67; 95% CI 0.98–2.84; P =0.06) but reduced diarrhea singnificantly (OR 0.31; 95% CI 0.11–0.81;P =0.02). Conclusions: Both *UGT1A1*6* and *UGT1A1*28*genetic variants should screen in Asian cancer patients to reduce substantially irinotecan induced severe toxicities.

Keywords: Irinotecan*, UGT1A1, ABCC2,*genetic polymorphisms, toxicity

1. Introduction

Irinotecan, an anticancer prodrug is widely used for the treatment of solid cancer including colorectal, lung, and gastric cancer. 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 interruption of 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 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 observed in ˜25% of cancer patients taking irinotecan, these toxicities may have been related to interindividual *UGT1A1*genetic variability [7]. Being highly polymorphic of *UGT1A1* , the most well-known polymorphism is *UGT1A1*28* with seven TA repeats (A(TA)7TAA) in promoter region leading to ˜70% reduced expression and ˜48% reduced function of UGT1A1 conjugating enzyme [8]. Although several clinical studies have established the strong associa-

tions of *UGT1A1*28* genetic polymorphisms with irinotecan induced severe toxicity such as diarrhea and neutropenia especially in Caucasian cancer patients, however, the results for this association are still inconclusive and controversial especially in Asian cancer patients [9-18].

In addition to *UGT1A1*28* genetic polymorphism, other very important mutation of this gene is *UGT1A1*6* causing ˜30-60% reduced activity of UGT1A1 enzyme and is leading to irinotecan-induced toxicity, especially diarrhea and neutropenia in 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 inheriting both of these polymorphisms (*UGT1A1*6*and *UGT1A1*28),* the toxicities of irinotecan may be exacerbated profoundly due to combined genetic effects as evidenced in some studies [14, 26-28] although the results are again inconclusive and inconsistent as found in other studies [18, 29-31]. In these controversial clinical situations, it is also important to noted 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* especially c.3972C>T single nucleotide polymorphism is also suspected to influence inter-individual variability of irinotecan which may lead to toxicity as well [7, 32-35].

Although there are some meta-analyses that have assessed aggregated risk of neutropenia and diarrhea in cancer patients treating with irinotecan and inherited either *UGT1A1*6* or *UGT1A1*28* but the results were highly conflicting and inconsistent even combined effects (*UGT1A1*6+*28*) were not assessed in majority of these analyses especially in Asian patients [16, 18, 20, 36-40]. Also, there was no meta-analysis appeared in the literature assessing the association of*ABCC2* c.3972C>T genetic polymorphism with irinotecan-induced toxicity. Therefore, this study was aimed to establish a robust evidence by assessing the aggregated risk of neutropenia or diarrhea in Asian cancer patients inherited either*UGT1A1*6, UGT1A1*28* , combination of these variants (*UGT1A1*6+UGT1A1*28*) or *ABCC2* c.3972C>T genetic polymorphisms.

2. Methods

Search strategy

Literature search was carried out in PubMed from the inception to the date up to May 22, 2021 following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines as described elsewhere [41]. Five keywords i.e. “UGT1A1”, “ABCC2” “Polymorphisms”, “Irinotecan” and “Toxicity” was used to search eligible studies in PubMed. Furthermore, relevant references of retrieved articles were also searched and reviewed for inclusion of eligble studies.

Inclusion and exclusion criteria

All eligible Studies were selected with the following inclusion criteria: (1) clinical trials and

observational studies, (2) studies explored the association between*UGT1A1*6* and/or *UGT1A1*28* or *ABCC2* and irinotecan-induced toxicities, (3) studies included patients suffering from neutropenia hematological toxicity and diarrhea (grade III–IV), (4) studies comparing both homozygous and heterozygous versus wild type and (5) studies were published in English.

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

Data extraction and quality assessment of included studies

After selection of eligible studies, data extraction process was carried out by two authors (CA and NV) 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 outcomes data e.g. number of events with irinotecan driven neutropenia/diarrhea corresponds to each genotype group were extracted after reading the full texts in depth. Any disagreements were discussed until consensus between the 2 reviewers could be reached.

The quality of included studies was assessed based on the Newcastle Ottawa Scale (NOS) guidelines. In this scale, quality assessment score ranges from '0' to '9' against '9' criteria set in NOS in which each criterion was given a star (*) corresponds to score '1'. Studies were considered high quality if the NOS score was [?]6 and studies were moderate and low quality if the scores were '4–5' and '0–3', respectively [42, 43].

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) by either fixed or random effects model 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 -value<0.1 as described elsewhere [44]. However, 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% indicates low, moderate and high level of heterogeneity, respectively [47]. A random effects model was applied to estimate ORs if I^2>50% and considered that the study had high level of heterogeneity. In contrast, a fixed effects model was used to estimate ORs if I^2<50%. Sensitivity analysis was carried out to assess the impact on any individual studies on measured pooled risk. Publication biasness was detected by visual inspection of the funnel plot where symmetrical distribution of the plot indicated no publication bias [46]. All the calculated$P$ -values were considered statistically significant if the values were<0.05.

3. Results

3.1 General characteristics of included studies

In total, 300 articles were retrieved from PubMed following search strategy which were then screened for selection of interested studies. Following exclusion criteria, 195 articles were removed, and the rest 106 full-texts articles were assessed in depth following eligibility criteria. Finally, 42 articles were included in this meta-analysis for assessing the associations of*UGT1A1*6/*28* or *ABCC2* c.3972C>T with irinotecan induced severe toxicities [12,14,21,22-24,26-31,34,35,47-74]. The complete selection process of articles following PRISMA guidelines is shown in Figure 1.

General characteristics of 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. is shown in Table 1.

3.2 Outcomes of meta-analysis

3.2.1 Association of*UGT1A1*6* with irinotecan induced severe toxicity

The association 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 inherited heterozygous and homozygous variant of the *UGT1A1*6*(*UGT1A1*1/*6* and *UGT1A1*6/*6*) compared to the patients carried 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 carried homozygous variant i.e. *UGT1A1*6/*6* (OR 3.94; 95% CI 2.51–6.20;P <0.00001) compared to the patients carried 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 the patients harbored heterozygous and homozygous variant of the *UGT1A1*6* (*UGT1A1*1/*6* and*UGT1A1*6/*6*) were significantly associated with increased risk of diarrhea compared to the patients inherited wild type genotype i.e.*UGT1A1*1/*1* (OR 2.52; 95% CI 1.65–3.82;P <0.0001), as driven 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 heterozygous variant i.e. *UGT1A1*1/*6* (OR 1.77; 95% CI 0.94–3.33; *P* =0.08) as shown in Figure 2B.

3.2.2 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 carried *UGT1A1*28* genetic polymorphism. It was found that the aggregated risk of neutropenia was significantly higher in patients inherited heterozygous and homozygous variant of the *UGT1A1*28* (*UGT1A1*1/*28* and *UGT1A1*28/*28*) compared to the patients carried wild type genotype i.e. *UGT1A1*1/*1* (OR 1.86; 95% CI 1.52–2.27;*P* < 0.00001), that was mainly driven from the patients who carried homozygous variant i.e. *UGT1A1*28/*28* (OR 3.11; 95% CI 1.71–5.63; *P* =0.0002) than 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 estimated pooled risk for diarrhea from 20 studies, it was found that the patients inherited heterozygous and homozygous variant 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 wild type genotype (*UGT1A1*1/*1),* as shown in Figure 3B. Further analysis indicated that the risk of diarrhea was much striking in patients carried homozygous variant i.e. *UGT1A1*28/*28* (OR 5.70; 95% CI 3.10–10.50; *P* <0.00001) compared to the patients with heterozygous variant i.e. *UGT1A1*1/*28* (OR 2.18; 95% CI 1.58–3.02; *P* <0.00001), Figure 3B.

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

Altogether 27 and 20 studies had 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 the patients carried both of the *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 the patients carried wild type genotype i.e. *UGT1A1*1/*1* (OR 2.89; 95% CI 1.97–4.23; *P* <0.00001), as shown in Figure 4A. Patients with homozygous variants had much stronger effects in 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 4A.

It was also found that the aggregated risk of diarrhea was significantly higher in cancer patients carried both of the *UGT1A1*6* and *UGT1A1*28* variants (heterozygous, *UGT1A1*1/*6+UGT1A1*1/*28;* 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 4B. Further analysis indicated that the risk of diarrhea was much greater in patients carried homozygous variants i.e. *UGT1A1*6/*6+UGT1A1*28/*28* (OR 3.21; 95% CI 2.13–4.85; *P* <0.00001) compared to the 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 4B.

3.2.4 Subgroup analysis for combined effects of *UGT1A1*6* and *UGT1A1*28* with irinotecan induced severe toxicity

For assessing the effects of the combined *UGT1A1*6* and *UGT1A1*28* varinats in different ethnicities of Asia, this study undertaken subgroup analysis for the toxicities reported in at least two studies in the respective country. Subgroup analysis revealed that patients carried both of the *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 5A.

However, patients carried both of the *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 5B.

Since different studues used irinotecan in treating different types of cancer e.g. colorectal, lung, stomach, cervical, ovarian, esophageal, pancreatic, pulmonary neuroendocrine tumor, and sometimes combination of these cancers, current study was undertaken 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 other cancers group included lung, stomach, cervical, ovarian, esophageal, pancreatic, pulmonary neuroendocrine tumor, combination of these cancers. After analysis, it was found that the patients with either colorectal or other cancers carried both of the *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 6A.

Similar trends were also found in 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 6B.

Because different irinotecan dosing schedule was applied in treating different types of cancer, current study was also undertaken subgroup analysis to assess whether these dosing schedules affected the development of the toxicities. In this analysis, dose was categorized as low, medium and high corresponded to <150 mg/m^2, 150 mg/m^{2}and >150 mg/m^2, respectively. It was found that patients carried both of the *UGT1A1*6* and*UGT1A1*28* variants were associated with significantly increased risk of neutropenia in 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 in medium doses (OR 1.34; 95% CI 0.46-3.87;P =0.59), Figure 7A.

However, patients carried both of the *UGT1A1*6* and*UGT1A1*28* variants were associated with significantly increased risk of diarrhea in only high doses (High dose: OR 2.01; 95% CI 1.19-3.38; P =0.009;) but not in 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 7B.

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

Very small number of studies were found in the literature that had assessed the association of *ABCC2 c.3972C>T*genetic polymorphism with the toxicity of irinotecan. Only three and two studies had assessed the effects of *ABCC2c.3972C>T* genetic variant with irinotecan induced neutropenia and diarrhea, respectively. After pooled estimation, it was found that patients carried heterozygous and homozygous of the*ABCC2 c.3972C>T* variant were not significantly associated with irinotecan induced neutropenia (OR 1.67; 95% CI 0.98–2.84; P =0.06), as shown in Figure 8A.

It was further revealed that patients harbored heterozygous and homozygous of the *ABCC2 c.3972C>T* variant were significantly associated with the reduction of irinotecan induced diarrhea (OR 0.31; 95% CI 0.11–0.81; P =0.02), Figure 8B.

3.2.6 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* or*UGT1A1*28* or *ABCC2* c.3972C>T genetic variants (data not shown here). There was no publication bias as determined by the visual inspection of the funnel plot, Figure 9.

4. Discussion

Toxicity of irinotecan varies greatly and can be even life-threatening in some cancer patients. The findings of current analysis indicated that irinotecan-induced severe toxicities e.g. neutropenia and diarrhea were significantly associated with the Asian cancer patients who carried*UGT1A1*6* and *UGT1A1*28* genetic variants.

Due to strong association of *UGT1A1*28* with severe toxicity of irinotecan as replicated in multiple studies predominantly in Caucasian cancer patients, the Food and Drug Administration of the United States (US FDA) has already approved *UGT1A1*28* genetic testing before starting irinotecan therapy and recommended

to reduce the starting dose by at least one level of irinotecan dosage form for cancer patients carrying *UGT1A1*28/*28* genotype [16, 75]. The Dutch Pharmacogenetics Working Group (DPWG) recommended 30% reduction of the standard starting dose of irinotecan for patients harboring *UGT1A1*28/*28* genotype. Also, the French National Network of Pharmacogenetics (RNPGx) recommended 25-30% dose reduction in patients with *UGT1A1*28/*28* especially if having other toxicity risk factors and contraindicated if taking higher doses [75].

The current findings are supporting these recommendations since toxicities were greatly higher in patients especially when taking high doses of irinotecan (>150mg/m^2) and suggest that such recommendations should specify the high-risk population especially Asian patients. This is because, Asian cancer patients carried either heterozygous or homozygous variant of the *UGT1A1*28* were significantly associated with irinotecan induced neutropenia and diarrhea. Meta-analysis conducted by other research groups have also established such strong association 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, 76], however, current analysis has establised robust evidence for these associations after aggregating data from large number of studies and sample sizes as well.

Current study also found that *UGT1A1*6* genetic variant was significantly associated with irinotecan induced severe toxicity 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,* current study concluded that patients inherited both of these variants especially with homozygous variants (*UGT1A1*6/*6*$_+$*UGT1A1*28/28*) had significant striking effects in experiencing irinotecan-induced toxicities i.e. neutropenia and diarrhea. The findings of current analysis suggest that inheriting these genetic variants were probably associated with reduced function of UGT1A1 which maximize the active irinotecan concentration in the blood and developing toxicities. Although genetic testing kit of *UGT1A1*6* and *UGT1A1*28* has been recommended in clinical practice in Japan for cancer patients taking irinotecan [32], however, other parts of Asia are lacking regulatory consensus for recommending such genetic testing. This may be partly because many Asian countries are not well positioned for preceding pharmacogenomics research or may have lack sufficient robust evidence for the associations of *UGT1A1*6* and *UGT1A1*28* genetic variants with irinotecan induced severe toxicities.

The findings of current analysis may therefore be considered as sufficiently robust evidence since the pooled risk was measured from reasonably large number of sample sizes and providing strong evidence that patients were being at significantly greater risk of irinotecan induced toxicities i.e. neutropenia and diarrhea when harbored both *UGT1A1*6* and *UGT1A1*28* genetic variants especially homozygous variants. These findings may facilitate translational of *UGT1A1*6* and *UGT1A1*28* pharmacogenomics into clinical practice in the form of precision irinotecan therapy and may reduce associated severe toxicities profoundly in cancer patients. Drug regulatory body and poly makers of Asian regions should emphasize such strong genetic relations with irinotecan induced severe toxicities and should prepare national guidelines to adhere preemptive screening of *UGT1A1*6* and *UGT1A1*28* genetic variants before prescribing irinotecan.

All ethnic group of Asian patients developed toxicities who carried both *UGT1A1*6* and *UGT1A1*28* genetic variants except diarrhea in Japanese patients. Without knowing specific reason, it is hard to explain such association although lifestyle, food and comedications may affect this association. This yet to be elucidated in future studies explaining why Japanese patients were not significantly associated with diarrhea who carried both of the *UGT1A1*6* and *UGT1A1*28* genetic variants and taking irinotecan.

The effects of *UGT1A1*6* and *UGT1A1*28* genetic variants are applicable in any type of cancer where irinotecan is clinically warranted since both colorectal and different other cancers were significantly associated with toxicities. Diarrhea and neutropenia were observed especially when patients used high doses of irinotecan >150 mg/m^2 with exception of neutropenia in low doses, however, the results are consistent with a previous analysis [10]. Although toxicities at low doses are usually exceptional but 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 association. However, dose dependent analysis of this

study suggesting that irinotecan induced toxicities may be prevented by adjusting doses of irinotecan and needs further stratification.

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

In spite of establishing significant associations of increased risk of irinotecan induced toxicities e.g. neutropenia and diarrhea in Asian cancer patients inherited *UGT1A1*6* and *UGT1A1*28* genetic variants, nevertheless, there are some limitations in this study. Firstly, this study did not consider the confounding factors affecting the toxicity outcomes e.g. chemotherapy regimen, comedications, food, sex, age etc. Secondly, this analysis only extracted the data from studies published in English language, which may limit the access to useful information published in other languages.

5. Conclusions

The *UGT1A1*6* and *UGT1A1*28* genetic polymorphisms especially when patients carried homozygous of these 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 both of the *UGT1A1*6* and **28* genetic variants should screen in Asian cancer patients to reduce irinotecan toxicities substantially. Also, suggested to avoid high doses of irinotecan (>150mg/m^2) to reduce toxicities significantly. It is high time to prepare national guidelines for adhering routine preemptive screening of *UGT1A1*6* and *UGT1A1*28* variants in cancer patients before prescribing irinotecan. This may facilitate rapid translation of *UGT1A1*6* and *UGT1A1*28* pharmacogenomics into the clinical practice in the form of precision irinotecan therapy.

Supplementary Materials: Supplementary Table 1: Quality assessment of the included studies by Newcastle Ottawa Scale (NOS).

Author Contributions: Conceptualization, CS, CA and MB; Data curation CA, NV, YH and NN; Formal analysis; MB, SS and NV; Methodology, CS, CA, NV and MB; Project administration, PJ and JR; Supervision, CS; Writing—original draft, CA, MB, NV and CS. The final manuscript was revised by all authors, and this version was approved to be published.

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Table 1 . Baseline characteristics of included studies

Author	Country	Study design	Type of Cancer	No. of patients	Regimen	IRI dose (mg/m2)/schedule	Toxicity assessment	Genoty method
Hirasawa A., et al. 2013	Japan	Retrospective	Gynecologic cancer	53	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 UGT1A Molecular Assay kit
Ando K., et al. 2017	Japan	Prospective	Colorectal cancer	35	XELIRI	200/biweekly	Neutropenia, Diarrhea	N/A

Author	Country	Study design	Type of Cancer	No. of patients	Regimen	IRI dose (mg/m2)/schedule	Toxicity assessment	Genotyping method
Atasilp C., et al. 2015	Thailand	Retrospective	Colorectal cancer	44	FOLFIRI or FOLFIRI + cetuximab or FOLFIRI + bevacizumab or Modified FOLFIRI or Single irinotecan or Irinotecan + cetuximab/capecitabine	180/biweekly, 100/day 1	Neutropenia	Pyrosequ
Atasilp C., et al. 2020	Thailand	Retrospective and Prospective	Colorectal cancer	66	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	Pyrosequ Real-time PCR

Author	Country	Study design	Type of Cancer	No. of patients	Regimen	IRI dose (mg/m2)/schedule	Toxicity assessment	Genotyping method
Bai Y., et al. 2017	China	Retrospective	Lung cancer, Colorectal cancer, Esophageal cancer	81	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
Bandyopadhyay A et al. 2021	India	observational cohort	Small cell lung cancer (SCLC) cell lung cancer	213	Irinotecan + cisplatin	100 (day 1 of a 3-week cycle) or 65(days 1 and 8 of a 3-week cycle)	Neutropenia, Diarrhea	polymerase chain reaction (PCR)–restriction fragment length polymorphism (RFLP)
Chen Yang., et al. 2015	China	Retrospective	Pancreatic cancer	48	FOLFIRI	180/biweekly	Neutropenia	Direct sequenc
Choi YH., et al. 2012	Korea	Retrospective	Colorectal cancer	29	CPT-11 + S-1	225/every 3 weeks	Neutropenia, Diarrhea	Direct sequenc
Chun-Yu Liu., et al. 2007	China	Retrospective	Colorectal cancer	128	FOLFIRI	180/biweekly	Neutropenia, Diarrhea	Direct sequenc

Author	Country	Study design	Type of Cancer	No. of patients	Regimen	IRI dose (mg/m2)/schedule	Toxicity assessment	Genotyping method
Deng B., et al. 2017	China	Retrospective	Malignant tumor	115	FOLFIRI	180/biweekly	Neutropenia, Diarrhea	Direct sequenc
Gao J., et al. 2013	China	Retrospective	Gastric cancer, Esophageal cancer	133	Irinotecan + cisplatin or FOLFIRI or single irinotecan or irinotecan + cetuximab	180 mg/m2	Neutropenia	Direct sequenc
Gao J., et al. 2013	China	Retrospective	Colorectal cancer	276	FOLFIRI or single irinotecan or irinotecan + capecitabine	180 mg/m2	Neutropenia, Diarrhea	Direct sequenc
Han JY., et al. 2007	Korea	Prospective	Non-Small Cell Lung Cancer	107	Single irinotecan or irinotecan + cisplatin	65 or 80/every 3 weeks	Neutropenia and Diarrhea	Sequenc
Han JY., et al. 2009	Korea	Prospective	Non-Small Cell Lung Cancer	107	Single irinotecan or irinotecan + cisplatin	65 or 80/every 3 weeks	Neutropenia and Diarrhea	Sequenc
Hironobu Minami., et al. 2006	Japan	Retrospective	Lung, Colon, Stomach and others	55	Single irinotecan	100/weekly	Neutropenia	Pyroseq
				62	Irinotecan + Cisplatin	150/biweekly		
				103	IROX	200/every 3 weeks		

Author	Country	Study design	Type of Cancer	No. of patients	Regimen	IRI dose (mg/m2)/schedule	Toxicity assessment	Genotyping method
Horikawa N., et al. 2015	Japan	Retrospective	Cervical cancer	23	CPT-11 + Nedaplatin (NDP) every 3 weeks	60 (day 1 and 8)	Neutropenia, Diarrhea	Direct sequenc
Kimura K., et al. 2018	Japan	Retrospective	Rectal cancer	46	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 daysper week for 5 weeks)	Neutropenia, Diarrhea	Invader assay
Liu D., et al. 2017	China	Retrospective	Colorectal cancer	661	Single irinotecan or irinotecan + target treatment or irinotecan + fluorouracil (5-Fu, Capecitabine, S-1 or tegafur) or FOLFOXIRI	180 mg/m2 or 150 mg/m2	Neutropenia, Diarrhea	Direct sequenc

Author	Country	Study design	Type of Cancer	No. of patients	Regimen	IRI dose (mg/m2)/schedule	Toxicity assessment	Genoty method
Masahide Onoue., et al. 2009	Japan	Prospective	Lung, Gastric, Colorectal and Others	133	Single irinotecan or Irinotecan + Platinum or Irinotecan + other anticancer agents or FOLFIRI	<100 or 101-150 or 151-200 or >200/weekly or biweekly or every 3 or 4 weeks	Neutropenia	Direct sequenc
Matsuoka et al. 2020	Japan	Retrospective	Cervical cancer	51	Irinotecan + NDP	60/(days 1 and 8) or 60/(days 1 and 15)	Neutropenia, Diarrhea	Direct sequenc
Minmin Li., et al. 2014	China	Retrospective	Colorectal cancer	167	FOLFIRI or Irinotecan + Cetuximab/Bevacizumab or Irinotecan + Raltitrexed or Irinotecan + Capecitabine	180/biweekly or 180/every 3 weeks	Neutropenia, Diarrhea	Pyrosec
Moriya, H. et al. 2014	Japan	Retrospective	Gynecological cancer	44	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 sequenc

Author	Country	Study design	Type of Cancer	No. of patients	Regimen	IRI dose (mg/m2)/schedule	Toxicity assessment	Genotyping method
Nakamura Y., et al. 2011	Japan	Randomized phase II trial	Non-small Cell Lung Cancer	77	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 sequenc
Okuyama Y., et al. 2011	Japan	Prospective	Colorectal cancer	39	FOLFIRI	150 mg/m2 or 100 mg/m2	Neutropenia	polymer chain reaction restricti frag-ment length polymo
Park SR., et al. 2010	Korea	Retrospective	Gastric cancer	44	Irinotecan + oxaliplatin	150/every 3 weeks	Neutropenia	Direct sequenc
Peng H., et al. 2017	China	Retrospective	Gastrointestinal cancer, lung cancer	106	FOLFIRI or Single irinotecan or irinotecan + cisplatin or irinotecan + capecitabine	180 mg/m2 or 90 mg/m2	Neutropenia, Diarrhea	Direct sequenc
Satoh T., et al. 2011	Japan	Prospective	Gastrointestinal cancer	73	Single irinotecan	150mg/m2 or 100 mg/m2 or 75 mg/m2	Neutropenia, Diarrhea	Invader UGT1A Molecu-lar Assay kit
Shi Y., et al. 2015	China	Retrospective	Small cell lung cancer	29	Irinotecan + cisplatin	65 mg/m2	Diarrhea	Direct sequenc
Shaojun Chen., et al. 2020	China	Retrospective	Colorectal cancer	86	FOLFIRI	180/biweekly	Neutropenia, Diarrhea	Pyroseq

Author	Country	Study design	Type of Cancer	No. of patients	Regimen	IRI dose (mg/m2)/schedule	Toxicity assessment	Genotyping method
Sunakawa Y., et al. 2010	Japan	Retrospective	Colorectal cancer	42	FOLFIRI	180/biweekly	Neutropenia, Diarrhea	Direct sequenc
Takahara N., et al. 2013	Japan	Prospective	Pancreatic cancer	44	Single irinotecan	100 (days 1, 8 and 15 for every 4 weeks)	Neutropenia	Direct sequenc
Takano M., et al. 2009	Japan	Prospective	Gynecologic cancer	30	Irinotecan + cispatin	60 (day 1, 8,15 for every 4 weeks)	Neutropenia, Diarrhea	Invader UGT1A Molecular Assay
T. Yamaguchi et al. 2019	Japan	Retrospective	Gastric cancer	74	Irinotecan-based regimen	150/biweekly	Neutropenia, Diarrhea	The Invader® UGT1A Molecular Assay kit
Wang Y et al. 2012	China	Retrospective	Colorectal cancer	130	FOLFIRI or IFL	180/biweekly or 125/every 6 weeks	Neutropenia, Diarrhea	Direct sequenc
WANG et al. 2017	China	Retrospective	Lung, Colon, Rectum, Esophagus, Stomach and others	206	Irinotecan + anti-tumor platinum drugs or Irinotecan + 5-Fluorouracil 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 sequenc

Author	Country	Study design	Type of Cancer	No. of patients	Regimen	IRI dose (mg/m2)/schedule	Toxicity assessment	Genotyping method
Xiao XG., et al. 2015	China	Retrospective	Extensive-stage small-cell lung cancer (E-SCLC)	67	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	Pyrosequ
Xu, C. et al. 2016	China	Retrospective	Colorectal cancer	183	FOLFIRI or Irinotecan + Capecitabine	150/biweekly or 150/every 3 weeks	Neutropenia, Diarrhea	Direct sequenc
Xu Ma., et al. 2020	China	Retrospective	Pulmonary neuroendocrine tumours (PNTs)	68	Single irinotecan or irinotecan + cisplatin	60 (days 1, 8 and 15 for every 4 weeks)	Neutropenia, Diarrhea	quantitat fluorescent polymerase chain reaction
Xu Q, Ding YY., et al. 2015	China	Retrospective	Ovarian cancer	89	Irinotecan + cisplatin	60 (days 1 and 8 for every 3 weeks)	Neutropenia, Diarrhea	Pyrosequ
Yamamoto N., et al. 2009	Japan	Prospective	Non–Small Cell Lung Cancer	36	Single CPT-11	100 (days 1 and 8 for every 3 weeks)	Neutropenia	Direct sequenc

Author	Country	Study design	Type of Cancer	No. of patients	Regimen	IRI dose (mg/m2)/schedule	Toxicity assessment	Genotyping method
Yan-Yan Lu., et al. 2014	China	Retrospective	Lung and Gastrointestinal cancer	89	Irinotecan + Cisplatin, Nedaplatin, Carboplatin or Lobaplatin; modified FOLFIRI; Irinotecan + Platinum, Fluorouracil, Pemetrexed or Raltitrexed	100-175/biweekly or 100-175/every 3 weeks	Neutropenia, Diarrhea	Direct sequenc
Yun F., et al. 2014	China	Retrospective	Small cell lung cancer	31	Single irinotecan	80 (days 1 and 8 for every 3 weeks)	Neutropenia, Diarrhea	Direct sequenc

Here, FOLFIRI, Irinotecan+5-Fluorouracil+Leucovorin; IFL, Irinotecan + 5-Fluorouracil; IROX, Irinotecan + Oxaliplatin; FLIRI, Irinotecan + 5-Fluorouracil + Folic acid; XELIRI, Irinotecan + capecitabine + bevacizumab; Lv5FU2-IRI, Irinotecan + 5-Fluorouracil + Folic acid; U, Unknown; Invader UGT1A1 Molecular Assay kit, Third Wave Technologies, Madison, WI, USA; WHO, World Health Organization criteria; NDP, Nedaplatin

Assessment of studies by NOS indicated that the included studies were of high quality where the NOS score ranged from '7' to "9', as shown in Supplementary Table S1.

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