Association of UGT1A1*6 polymorphism with irinotecan-based chemotherapy reaction in colorectal cancer patients: a systematic review and a meta-analysis

Xiaoyun Zhu¹, Ruchao Ma² Xin Ma¹ & Gang Yang¹

¹ Department of Gastroenterology, Gansu provincial hospital, Lanzhou, Gansu 730030, China;
² Department of Cardiology, Lanzhou University Second Hospital, Lanzhou, Gansu 730030, China;
Xiaoyun Zhu & Ruchao Ma contributed equally to this work.

Correspondence to: Gang Yang, Gansu provincial hospital, No. 204, West Donggang Road, Chengguan District Lanzhou, Gansu, 730030, China. E-mail address: xiaohuakeyg@163.com

Abstract

Colorectal cancer (CRC) is a leading cause of cancer-related deaths across the world. Irinotecan (IRI) is commonly used to treat CRC, and IRI-based chemotherapy is linked with adverse reaction and the efficacy of the treatment regimen. The gene UGT1A1 plays a central role in the IRI metabolic pathway. A polymorphism UGT1A1*6 has been widely researched which may be related to response of IRI-based chemotherapy in CRC. All relevant studies were strictly searched from PubMed, Embase, Cochrane Library and Web of science databases to explore the associations between UGT1A1*6 and response of IRI-based chemotherapy with colorectal cancer. Nine articles comprising 1652 patients were included in the final combination. Meta-analysis showed G allele or GG had a lower risk of server late-onset diarrhea compared to A/AA in allele model and homozygote model (G vs. A: OR=0.53, 95% CI: 0.28 to 0.99, P=0.05; GG vs. AA: OR=0.48, 95% CI: 0.23 to 0.99, P=0.05), no significant association was observed in other models. In addition, a significant association between UGT1A1*6 and neutropenia was observed in all models (G vs. A: OR=0.57, 95% CI: 0.46 to 0.71, P=0.00; GG vs. AA: OR=0.28, 95% CI:0.17 to 0.45, P=0.01; GA vs. AA: OR=0.42, 95% CI: 0.26 to 0.70, P=0.00; GG+GA vs. AA: OR=0.32, 95% CI: 0.20 to 0.52, P=0.00; GG vs. AA+GA: OR=0.40, 95% CI: 0.23 to 0.71, P=0.00), whereas, no relationship was found between UGT1A1*6 and clinical response among the different genotypes. UGT1A1*6 may be considered as a biomarker for chemotherapy of IRI-based chemotherapy in colorectal cancer.

Keywords: colorectal cancer; UGT1A1; rs4148323; irinotecan; response; systematic review; meta-analysis.

1. Background

Colorectal cancer (CRC) is the third most common cancer and the most common cause of death all over the world[1]. Although the colon-endoscopy is extensively used to screen the high risk patients, and some new biomarkers were widely used, such as carcino-embryonic antigen (CEA) and carbohydrate antigen 199
the early diagnosis of CRC is difficult, and some patients reach a critical size to produce complications. Hence, the incidence rate of CRC is obviously higher among exposed population, and the therapy of CRC is still on the way. Recently, some new oncogenes were found which play a pivotal role, and many new gene related biomarkers were widely researched[3, 4]. Irinotecan (IRI) is a widely used chemotherapeutic drug in malignant cancer especially in CRC, which can prolong survival time and improve the prognosis in CRC patients[5]. However, the responses of the drug present obvious differences in different individuals[5, 6], so a plenty of researches have attempted to explore the reasons. Genome-wide association studies have demonstrated that many coding or non-coding variants, especially low-frequency or rare coding variants are related to drug response or adverse effects[7], and the researchers found the value for CRC patients to genotyping in Cancer Chemotherapy[8].

A large number of studies found UDP-glucuronosyltransferase (UGT) enzymes involved in the metabolism of IRI, which takes part in glucuronidation and transforms the active metabolite IRI (SN38) into SN38 glucuronide (SN38G)[9]. UGT enzymes are encoded by the UGT gene family[10], which consist with a series of UGT1As. Uridine diphosphate glucoronosyltransferase 1A1 is a member of UGT gene family, which located in 2q37.1 and has 5 exons (NG_033238). Previous studies confirmed that UGT1A1 was a key enzyme in glucuronidation, and suggested that UGT1A1 gene polymorphism was closely related to metabolism of IRI[11]. The SNP UGT1A1*6 (rs4148323) is a missense polymorphism, which resulting in single amino acid change (Gly71Arg) of the UGT1A1 gene (https://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=4148323). Extensive studies have researched the response of IRI in CRC patients exposing different genotypes of UGT1A1*6[12-20], but the conclusion is still controversial. Although a recent meta-analysis performed to analyze the difference in adverse reaction and therapeutic response (TR) between IRI-administered cancer patients with different UGT1A1*6 genotypes[21], and explored the association between cancer and UGT1A1*6, and performed the subgroup analysis, the association between CRC and UGT1A1*6 did not explain deeply. Therefore, we performed a meta-analysis to comprehensively investigate the association between UGT1A1*6 polymorphism and response of IRI-based chemotherapy with CRC.

2. Methods

2.1 Search strategy

Eligible studies were obtained from PubMed, Embase, Cochrane Library (Cochrane Center Register of Controlled Trails) and Web of science databases with the date up to February 10, 2020. The MeSH terms and full text terms were used as follows: “irinotecan”, “UGT1A1”, “polymorphism”, “UGT1A1*6”,

(CA199) [2], the early diagnosis of CRC is difficult, and some patients reach a critical size to produce complications. Hence, the incidence rate of CRC is obviously higher among exposed population, and the therapy of CRC is still on the way. Recently, some new oncogenes were found which play a pivotal role, and many new gene related biomarkers were widely researched[3, 4]. Irinotecan (IRI) is a widely used chemotherapeutic drug in malignant cancer especially in CRC, which can prolong survival time and
“rs4148323”, “Colorectal Neoplasms”, “chemotherapy”. Furthermore, we perused relevant references to select additional relevant studies.

2.2 Inclusion criteria 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 polymorphism and response of IRI-based chemotherapy with CRC; (3) CRC diagnose based on pathological examination or confirmed by proctoscope; (4) data were sufficient for tumor response (TR) (including complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), which was used the WHO criteria (RECIST, Response Evaluation Criteria in Solid Tumors)[22]; (5) the articles concerning allele frequency which could be sufficient to calculate genotypic odds ratio (OR) with the corresponding 95% confidence intervals (95% CI) in TR; (6) the toxicity measurements were evaluated on the basis of National Cancer Institute Common Toxicity Criteria for Adverse Events, Grade 3-4 neutropenia and Grade 3-4 diarrhea were considered as severe toxicity[23].

Following studies were excluded: (1) reviews, meta-analyses, case reports, letters, comments or duplicated data; (2) animal experiments; (3) studies with undefined genotypes; (4) studies with no effective data; (4) No criteria of diagnosis were described.

2.3 Data extraction

Two reviews (X.Y.Z. and R.C.M.) independently extracted data using standardized criteria. If they could not form a settled consensus, all of the authors must discuss the studies and reach a consensus. Information was carefully extracted as follows in each article: first author’s name, publication year, country, population ethnicity, gender, age, total number of patients, detection genotype methods of UGT1A1*6 polymorphism, the regimen of chemotherapy, IRI dose, response criteria, toxicity criteria, and key elements of risk assessment of bias, etc.

2.4 Quality assessment

The quality of included articles were assessed according to recommendation of Newcastle-Ottawa Scale (NOS)[21]. Eight items were selected for the inclusion of the study, including object selection, comparability among groups, and exposure factors. Researches with NOS scores of 0-3, 4-6, 6-9 were considered as low-quality, medium-quality and high-quality studies respectively.

2.5 Statistical analysis

The OR and 95% CI were used to assess UGT1A1*6 polymorphism and response of IRI-based chemotherapy with CRC in Asian. Cochran’s Q test and I² statistics were employed to evaluate the
heterogeneity assumption. If significant heterogeneity existed (P<0.05, I^2>50%), the random-effects model will be used to pool ORs. Otherwise, fixed-effects model was chosen[24]. We evaluated the UGT1A1*6 polymorphism and response of IRI-based chemotherapy with CRC in Asian using five genetic models: allele comparison (G vs. A), homozygote comparison (GG vs. AA), heterozygote comparison (GA vs. AA), dominant comparison (GG+GA vs. AA) and recessive comparison (GG vs. GA+AA). In addition, subgroup analyses were performed in this article based on different countries.

Begg’s regression test and funnel plot were used to calculate potential publication bias was tested. Sensitivity analysis was also performed to evaluate the stability of the meta-analysis when the significant heterogeneity existed. All of the analyses were performed using the STATA 12.0 software. All statistics were two-tailed and p <0.05 was considered as significant.

3. Results
3.1 Study characteristics
As shown in Fig.1, 814 potentially eligible records were initially yielded (PubMed: 229, Embase: 298, Cochrane Library: 71, Web of science: 216). In total, 386 citations were searched after duplicates removed. After different levels of screening based on titles, abstracts and full texts, 156 articles that were reviews or meta-analysis, 10 studies that were case reports, 129 articles that seemed to be not relate to this research, 67 studies that had not be relate to UGT1A1*6, and 15 articles which did not provide sufficient data. Nine articles included 1652 patients finally were selected according to the inclusion criteria[12-20]. The clinical characteristics were summarized in Table 1.

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**Fig 1. Flow diagram of the study selection process**
Table 1 Characteristics and methodological quality of involved studies

| Author  | Year | Country | No. of patients | Age | Gender (M/F) | Genotyping | Regimen                  | IRI dose (mg/m²) | Responsivity criteria | Toxicity criteria | NOS |
|---------|------|---------|-----------------|-----|--------------|------------|--------------------------|-----------------|----------------------|---------------------|-----|
| Liu D   | 2017 | China   | 661             | U   | 406/255      | Sequencing | FLIRI, FOLFOXIRI         | 150 or 180/U    | RECIST               | N4                  | 7   |
|         |      |         | 69              | U   | 46/23        | Sequencing | FOLFOXIRI               | 150/3 weeks     | RECIST               | N3                  | 7   |
| Xu C    | 2016 | China   | 114             | U   | 78/36        | Sequencing | FOLFIRI, THFC + 5FU     | 180/weekly       | RECIST               | N3                  | 7   |
| Li M    | 2014 | China   | 167             | U   | 27-71        | Sequencing | FOLFIRI, IRI + beva, IRI+ CAP | 180/weekly     | RECIST               | N3                  | 7   |
| Gao J   | 2013 | China   | 276             | U   | 21-79        | Sequencing | FOLFIRI, IRI + cetuximab, IRI, XELIRI | 180/weekly     | RECIST               | N3                  | 7   |
| Okuyama Y | 2011 | Japan   | 52              | U   | 35-79        | Sequencing | FLIRI                    | 100-150/weekly   | RECIST               | N3                  | 7   |
| Atasilp C | 2016 | Thailand| 44              | U   | 43-82        | Sequencing | IRI, FOLFIRI + beva, FOLFIRI+ cetuximab | 180/weekly, 100/U | RECIST               | N4                  | 7   |
| Hazama S | 2013 | Japan   | 75              | U   | 50/25        | Sequencing | FOLFIRI                  | 150/weekly       | RECIST               | N3                  | 7   |
| Levesque E | 2013 | Canada  | 167             | U   | 61.5         | Sequencing | FOLFIRI, FOLFIRI + vacizumab | 180/weekly     | RECIST               | N3                  | 7   |
| Bai Y   | 2017 | China   | 27              | U   | U            | Sequencing | IRI, IRI + cisplatin, IRI+ cisplatin + beva, IRI + beva, IRI + beva, FOLFIRI + beva, IRI + beva, IRI + cisplatin | 50/weekly or 130/3 weeks or 80/weekly | RECIST               | N3                  | 7   |

Abbreviations: M, male; F, Female; RFLP, reaction-restriction fragment length polymorphism; PYRS, pyrosequencing; 5FU, 5-fluorouracil; beva, bevacizumab; CAP, capecitabine; CTC, common terminology criteria; FLIRI, IRI + 5FU/LV; FOLFIRI, IRI + infusional 5FU+ LV; IFI, 5FU/LV; IRI, irinotecan; IROX, IRI +OX; LV, leucovorin; RECIST, Response Evaluation Criteria in Solid Tumors; N, National Cancer Institute common toxicity criteria; NOS, Newcastle-Ottawa Scale.

2 UGT1A1*6 polymorphism and IRI-based chemotherapy TR

Many previous researches analyzed the association between UGT1A1*6 polymorphism and IRI-based chemotherapy TR in different genotypes. According to RECIST medical efficacy appraisal standard, the response rate (RR, RR=CR+PR) and disease control rate (DCR, DCR=CR+PR+SD) as endpoint to evaluate IRI-based chemotherapy TR.

Four trails analyzed the RR, and two studies [13, 18] described two subgroups RR respectively. Thus, we decided to evaluate six trails. Five studies listed out the numbers of patients in different genotypes, but one study only listed out the number of wild genotype (GG) and variant genotype (GA+AA). Therefore five
models were used in five studies, and recessive model was used in all trails. As the results show: (1) allele model: (G vs. A: OR=0.80, 95% CI: 0.55 to 1.41, P=0.60); (2) homozygote model: (GG vs. AA: OR=0.53, 95% CI:0.17 to 1.62, P=0.27); (3) heterozygote model: (GA vs. AA: OR=0.67, 95% CI: 0.21 to 2.14, P=0.50); (4) dominant model: (GG+GA vs. AA: OR=0.57, 95% CI: 0.19 to 1.72, P=0.32); (5) recessive model: (GG vs. GA+AA: OR=0.95, 95% CI: 0.69 to 1.31, P=0.76). There were no significant heterogeneity among these models, I² values were 38.1% (P=0.17), 2.8% (P=0.39), 0 (P=0.67), 0 (P=0.48), 0 (P=0.78) for allele model, homozygote model, heterozygote model, dominant model and recessive model respectively.

We also performed subgroup analysis by countries, and no associations were observed in different country (Fig 2). Full details showed in Table 2 and Table 3.

In addition, the DCR was used to evaluate the TR. We analyzed in five models and found no relationship with UGT1A1*6 polymorphism and IRI-based chemotherapy DCR (Fig 3): (1) allele model: (G vs. A: OR=0.93, 95% CI: 0.59 to 1.46, P=0.75); (2) homozygote model: (GG vs. AA: OR=1.91, 95% CI:0.50 to 7.28, P=0.35); (3) heterozygote model: (GA vs. AA: OR=2.29, 95% CI: 0.58 to 9.0 8, P=0.24); (4) dominant model: (GG+GA vs. AA: OR=2.00, 95% CI: 0.53 to 7.54, P=0.31); (5) recessive model: (GG vs. GA+AA: OR=0.95, 95% CI: 0.69 to 1.31, P=0.97). Full details showed in Table 2 and Table 3.

3.3 UGT1A1*6 polymorphism and IRI -induced severe late-onset diarrhea

Five studies described the association between UGT1A1*6 polymorphism and severe late-onset diarrhea respectively, and one study researched two different nations including Han and Xinjiang Uygur nationality[13], therefore six researches was analyzed finally. Whereas one study only listed out the number of wild genotype (GG) and variant genotype (GA+AA), we used five models in five studies, and six studies were analyzed in recessive model. As the results show (Fig 4.1): (1) allele model: (G vs. A: OR=0.53, 95% CI: 0.28 to 0.99, P=0.05); (2) homozygote model: (GG vs. AA: OR=0.48, 95% CI:0.23 to 0.99, P=0.05); (3) heterozygote model: (GA vs. AA: OR=0.54, 95% CI: 0.24 to 1.23, P=0.14); (4) dominant model: (GG+GA vs. AA: OR=0.49, 95% CI: 0.24 to 1.01, P=0.06); (5) recessive model: (GG vs. GA+AA: OR=0.50, 95% CI: 0.24 to 1.06, P=0.07). We found the heterogeneity in allele model and recessive model, I² values were 73.9% (P=0.00), 70.5% (P=0.01) for allele model and recessive model respectively, the sensitive analysis was performed (Fig 4.2), we found one study had obvious heterogeneity[12], we removed it and analyzed again. Then the heterogeneity decreased and used fixed-effects model, the results showed that UGT1A1*6 polymorphism was associated with late-onset diarrhea (Fig 4.2): (1) allele model (G vs. A: OR=0.41, 95% CI: 0.28 to 0.619, P=0.00); (2) recessive model (GG vs. GA+AA: OR=0.38, 95% CI: 0.24 to 0.60, P=0.00). Full details showed in Table 2 and Table 3.
3.4 UGT1A1*6 polymorphism and IRI-induced severe neutropenia

Seven studies described the association between UGT1A1*6 polymorphism and severe neutropenia respectively, and one study researched two different nations including Han and Xinjiang Uygur nationality[13], thus eight researches was analyzed finally. Whereas one study only listed out the number of wild genotype (GG) and variant genotype (GA+AA), thus four models including allele model (G vs. A), homozygote model (GG vs. AA), heterozygote model (GA vs. AA), dominant model (GG+GA vs. AA) were used in 7 studies, and the recessive model analyzed 8 studies. No significant heterogeneity was found in all gene models expect for recessive model. In recessive model, the random-effect model was used to analysis, and the result showed that UGT1A1*6 polymorphism was the risk of IRI-induced severe neutropenia (GG vs. AA+GA: OR=0.40, 95% CI: 0.23 to 0.71, P=0.00). Other gene models, the fixed-effect model was used to evaluate. Our results showed that UGT1A1*6 polymorphism was associated with IRI-induced severe neutropenia (Fig 5.1): (1) allele model: (G vs. A: OR=0.57, 95% CI: 0.46 to 0.71, P=0.00); (2) homozygote model: (GG vs. AA: OR=0.28, 95% CI:0.17 to 0.45, P=0.005); (3) heterozygote model: (GA vs. AA: OR=0.42, 95% CI: 0.26 to 0.70, P=0.00); (4) dominant model: (GG+GA vs. AA: OR=0.32, 95% CI: 0.20 to 0.52, P=0.00). We further performed sensitive analysis in recessive model (Fig 5.2), and we found one study had obvious heterogeneity [12], we removed it and analyzed again, the heterogeneity decrease statistically. The fixed-effect model was used to analysis again, no obvious change was found (Fig 5.2) (GG vs. GA+AA: OR=0.35, 95% CI: 0.24 to 0.52, P=0.00) than previous result. Full details showed in Table 2 and Table 3.

Moreover, we then performed the subgroup analyses by different countries. Whereas we only analyze five models in China, the other country cannot be analyzed for few studies. There was a statistically increased severe neutropenia in the comparison of five models in China. In different models present different results, we found the significant association in all genetic models between UGT1A1*6 polymorphism and IRI-induced neutropenia in China: (1) allele model: (G vs. A: OR=0.60, 95% CI: 0.47 to 0.76, P=0.00); (2) homozygote model: (GG vs. AA: OR=0.29, 95% CI:0.17 to 0.50, P=0.00); (3) heterozygote model: (GA vs. AA: OR=0.42, 95% CI: 0.23 to 0.74, P=0.00); (4) dominant model: (GG+GA vs. AA: OR=0.33, 95% CI: 0.19 to 0.55, P=0.00); (5) recessive model(GG vs. AA+GA:OR=0.42, 95% CI: 0.24 to 0.71, P=0.00). In recessive model, we also found the significant heterogeneity, so we further performed sensitive analysis. We found one study had obvious heterogeneity [12], we removed it and analyzed again, the heterogeneity decrease statistically. The fixed-effect model was used to analysis again, the result is the same as before (GG vs. GA+AA: OR=0.28, 95% CI: 0.18 to 0.45, P=0.00). Full details showed in Table 2 and Table 3.
### Table 2: Meta-analysis results for clinical responses and adverse reactions

|                        | G vs. A   | GG vs. AA | GA vs. AA | GG+GA vs. AA | GG vs. AA+GA |
|------------------------|-----------|-----------|-----------|--------------|--------------|
|                        | OR (95%CI) | P         | OR (95%CI) | P            | OR (95%CI)   | P            |
| **RR**                 |           |           |           |              |              |              |
| **Country**            |           |           |           |              |              |              |
| China                  | 0.88 (0.55,1.41) | 0.60 | 0.56 (0.14,2.27) | 0.42 | 0.60 (1.45,2.53) | 0.49 | 0.67 (0.14,2.28) | 0.43 | 1.00 (0.70,1.42) | 0.99 |
| Japan                  | 0.57 (0.23,1.37) | 0.21 | 0.48 (0.07,3.13) | 0.44 | 0.80 (11.57) | 0.83 | 0.56 (0.06,3.60) | 0.55 | 0.75 (0.34,1.65) | 0.47 |
| Overall                | 0.80 (0.53,1.21) | 0.29 | 0.55 (0.07,1.62) | 0.27 | 0.67 (0.21,1.24) | 0.50 | 0.57 (0.19,1.72) | 0.52 | 0.95 (0.59,1.51) | 0.70 |
| **DCR**               |           |           |           |              |              |              |
| Overall                | 0.93 (0.59,1.46) | 0.75 | 1.91 (0.30,7.28) | 0.35 | 2.29 (0.58,9.08) | 0.24 | 2.00 (0.53,7.54) | 0.31 | 0.95 (0.69,1.31) | 0.97 |
| **Diarrhea**          |           |           |           |              |              |              |
| Overall               | 0.53 (0.28,0.99) | 0.05 | 0.49 (0.24,1.23) | 0.14 | 0.49 (0.24,1.01) | 0.06 | 0.50 (0.24,1.08) | 0.07 |              |              |
| Overall △             | 0.28 (0.17,0.34) | 0.00 |              |              |              |              |              | 0.38 (0.24,0.62) | 0.00 |
| **Neutropenia**       |           |           |           |              |              |              |
| Country               |           |           |           |              |              |              |
| China                 | 0.60 (0.40,0.76) | 0.00 | 0.29 (0.07,0.50) | 0.00 | 0.42 (0.23,0.74) | 0.00 | 0.33 (0.18,0.55) | 0.00 | 0.42 (0.24,0.71) | 0.00 |
| China △              | 0.28 (0.18,0.43) | 0.00 |              |              |              |              |              | 0.40 (0.24,0.71) | 0.00 |
| Overall               | 0.57 (0.46,0.71) | 0.00 | 0.28 (0.17,0.43) | 0.00 | 0.42 (0.26,0.70) | 0.00 | 0.32 (0.20,0.52) | 0.00 | 0.40 (0.24,0.71) | 0.00 |
| Overall △             | 0.35 (0.24,0.52) | 0.00 |              |              |              |              |              |              |              |

**NOTES:** △ represent greater heterogeneity.

### Table 3: Test for heterogeneity in different analysis

|                        | G vs. A   | GG vs. AA | GA vs. AA | GG+GA vs. AA | GG vs. AA+GA |
|------------------------|-----------|-----------|-----------|--------------|--------------|
|                        | I²         | P         | I²         | P            | I²          | P            |
| **RR**                 |           |           |           |              |              |              |
| **Country**            |           |           |           |              |              |              |
| China                  | 31.3%      | 0.23      | 0.0%       | 0.62         | 0.0%        | 0.81         | 0.0%        | 0.69         | 0.0%        | 0.66         |
| Japan                  | 62.6%      | 0.10      | 67.9%      | 0.08         | 47.5%       | 0.17         | 63.8%       | 0.10         | 0.0%        | 0.46         |
| Overall                | 38.1%      | 0.17      | 2.8%       | 0.39         | 0.0%        | 0.67         | 0.0%        | 0.48         | 0.0%        | 0.78         |
| **DCR**               |           |           |           |              |              |              |
| Overall                | 0.0%       | 0.84      | 0.0%       | 0.73         | 0.0%        | 0.60         | 0.0%        | 0.69         | 0.0%        | 0.97         |
| **Diarrhea**          |           |           |           |              |              |              |
| Overall                | 73.9%      | 0.00      | 24.2%      | 0.26         | 0.0%        | 0.61         | 1.2%        | 0.4          | 70.5%       | 0.01         |
|                        | 17.2%      | 0.31      |              |              |              |              |              |              | 27.2%       | 0.24         |
| **Neutropenia**       |           |           |           |              |              |              |
| Country               |           |           |           |              |              |              |
| China                 | 0.0%       | 0.42      | 0.0%       | 0.93         | 0.0%        | 0.95         | 0.0%        | 0.96         | 57.9%       | 0.05         |
| China △              | 0.0%       | 0.62      |              |              |              |              |              |              | 0.0%        | 0.62         |
| Overall               | 3.1%       | 0.41      | 0.0%       | 0.99         | 0.0%        | 0.99         | 0.0%        | 1.00         | 59.2%       | 0.02         |
| Overall △             | 46.3%      | 0.08      |              |              |              |              |              |              |              |              |

**NOTES:** △ represent greater heterogeneity.
3.6 Publication bias

We performed the funnel plot and Begg’s test to assess the publication bias in all included literatures. Publication bias was not found among the studies by funnel plot. Begg’s regression test suggested that there were no obvious statistical publication bias. Details showed in Table 4 and Fig 6-9.

**Table 4** P values for Begg’s test for clinical responses and adverse reactions

|        | G vs. A | GG vs. AA | GA vs. AA | GG+GA vs. AA | GG vs. AA+GA |
|--------|---------|-----------|-----------|--------------|--------------|
| RR     | 0.81    | 1.00      | 0.81      | 0.81         | 1.00         |
| DCR    | 1.00    | 0.30      | 0.30      | 0.30         | 0.73         |
| Diarrhea | 0.46    | 0.81      | 0.81      | 0.81         | 0.71         |
| Neutropenia | 0.90    | 0.37      | 1.00      | 0.76         | 0.90         |

4 Discussion

Recent advances in chemotherapy for CRC, IRI-based chemotherapy treatment as an effective way for CRC patients and was considered to be the first-line treatment option. However, the obvious concern is efficacy and toxic side effects, especially the serious toxicity restricted its application, such as severe neutropenia and diarrhea. A large of studies found that variations of genes linked with efficacy and toxicity of IRI-based chemotherapy for CRC. UGT1A1 linked with activity of glucuronidation, and involves in the metabolism of IRI. Studies have indicated an association between UDP-glucuronosyltransferase-1A1 (UGT1A1) genetic polymorphisms and irinotecan-induced toxicity. UGT1A1 gene concludes many SNPs[25, 26], and SNPs in candidate gene significantly associated with transcription or translation or regulation[27]. UGT1A1*28 is a member of family in SNPs of UGT1A1 gene, previous meta-analysis evaluated the impact of UGT1A1*28 polymorphisms with irinotecan-induced toxicity, and demonstrated UGT1A1*28 polymorphisms may be considered as a marker of irinotecan-induced toxicity in chemotherapy of cancer[28]. In 2005, the U.S. Food and Drug Administration (FDA) recommended that the UGT1A1*28 was noted as a label for patients[29]. The other SNPs in UGT1A1 gene, the UGT1A1*6 (rs4148323) polymorphism is a missense polymorphism, which effects the translation of UGT1A1 protein (Gly71Arg)[30], the substitution of Gly influence the hydrophobicity and secondary structure of protein and the efficiency of SN38 glucuronidation activity may be decreased[30]. A large number of researches show UGT1A1*6 associated with the efficacy and toxicities of IRI-based chemotherapy in CRC, but the conclusions still not to be agreed. Previous studies found UGT1A1*6 polymorphism was higher related to RR in Asian[12, 13, 17]. Xu et al[13], and reported that wild UGT1A1*6 genotype has significant lower late-onset diarrhea, but no difference in neutropenia between wild genotype and mutant genotype in Xinjiang province of China. However, Gao et al. [15]studied that UGT1A1*6 polymorphism was closely
associated with severe neutropenia, but not linked with late-onset diarrhea. Moreover, the study in Thai did not showed that UGT1A1*6 polymorphism significantly increased severe neutropenia[17]. Based on the controversial conclusions, we performed a meta-analysis to comprehensively investigate the association between UGT1A1*6 polymorphism and efficacy and adverse reaction. This study describes an important molecular biomarker in chemotherapy treatments for CRC, especially in Irinotecan-based combination chemotherapy.

Most studies reported that no association between UGT1A1*6 polymorphism and clinical response among the different genotypes. In this meta-analysis, no relationship was found between UGT1A1*6 polymorphism and clinical response, same results were analyzed in subgroup analysis. Our results are similar to previous studies.

In this study, we found that UGT1A1*6 polymorphism is a risk variant for severe drug toxicities in IRI-based Chemotherapy with CRC patients. Our finding demonstrated that patients carrying base mutation increasingly likely to encounter severe neutropenia (grade III-IV) in all models. In subgroup analysis, UGT1A1*6 polymorphism still increases the risk of severe neutropenia. Similarly, UGT1A1*6 polymorphism increase risk of severe diarrhea (grade III-IV) in allele comparison and homozygote comparison, the results of subgroup analysis is same to overall analysis.

Compared with previous meta-analysis, our study was the first report to estimate the relation between UGT1A1*6 polymorphism and clinical response and toxicity in colorectal cancer. This study analyzed the association between UGT1A1*6 polymorphism and IRI-based chemotherapy TR and toxicity, and found the genotyping of UGT1A1*6 polymorphism may be useful for clinical application. Although we attempt to explore their clinical relevance, several limitations still exist in our research. First, many difference among primary studies, including chemotherapy regimens, research method and doses. Especially, different chemotherapy regimens were used in individual treatment, such as FOLFIRI, IRI and cisplatin, which would influence the efficacy and adverse reaction. Second, the variability in IRI doses maybe a source of heterogeneity, but no effective data were used to subgroup analysis by IRI doses. Third, the toxicity clinical responses were related to gender, as a study reported the incidence of serve neutropenia was higher in female than male, but no effective data were collected for analysis by gender. In addition, part of studies only included wild genotype and variant genotype, and other models were not analyzed expect recessive model. Moreover, the interference of other factors, such as environmental and other genetic factors, as ABCB1 C3435T polymorphism. Finally, the sample size was limited. Thereby, more studies with a larger sample sizes and high quality clinical studies need to research, and enhance the reliability and stability of
5 Conclusion

In conclusion, this meta-analysis suggested that the UGT1A1*6 polymorphism linked with IRI-induced adverse reaction with CRC, especially increase the incidence of severe late-onset diarrhea and neutropenia. No relationship was found between UGT1A1*6 polymorphism and clinical response.

Abbreviations

CRC: Colorectal cancer; IRI: Irinotecan; NOS: Newcastle-Ottawa Scale; UGT: UDP-glucuronosyltransferase; TR: Tumor response; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; RR: Response rate; DCR: Disease control rate; OR: Odds ratio; M, male; F, Female; RFLP, reaction-restriction fragment length polymorphism; PYRS, pyrosequencing; 5FU, 5-fluorouracil; beva, bevacizumab; CAP, capecitabine; CTC, common terminology criteria; FLIRI, IRI + 5FU/LV; FOLFIRI, IRI + infusional 5FU+ LV; IFL, 5FU/LV; IRI, irinotecan; IROX, IRI +OX;LV, leucovorin; RECIST, Response Evaluation Criteria in Solid Tumors; N, , National Cancer Institute common toxicity criteria; NOS, Newcastle-Ottawa Scale

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Availability of data and materials

All data generated or analyzed during the present study are included in this published article.

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Authors’ contributions

Conception and design of the study: X.Y.Z., R.C.M. and G.Y. Acquisition of data: X.Y.Z. and R.C.M. Analysis and interpretation of the data: X.Y.Z, R.C.M. and G.Y. Writing and revision of the manuscript: R.C.M., X.Y.Z and G.Y. All of the authors reviewed the manuscript.

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Fig 2: Forests for UGT1A1*6 polymorphism and IRI-based chemotherapy RR. “A” represents allele model (G vs. A); “B” represents homozygote model (GG vs. AA); “C” represents heterozygote model (GA vs. AA); “D” represents dominant model (GG+GA vs. AA); “E” represents recessive model (GG vs. GA+AA).
Fig 3: Forests for UGT1A1*6 polymorphism and IRI-based chemotherapy RR. “A” represents allele model (G vs. A); “B” represents homozygote model (GG vs. AA); “C” represents heterozygote model (GA vs. AA); “D” represents dominant model (GG+GA vs. AA); “E” represents recessive model (GG vs. GA+AA).
Fig. 4.1: Forests for UGT1A1*6 polymorphism and IRI-induced severe late-onset diarrhea.

"A" represents allele model (G vs. A); "B" represents homozygote model (GG vs. AA); "C" represents heterozygote model (GA vs. AA); "D" represents dominant model (GG+GA vs. AA); "E" represents recessive model (GG vs. GA+AA).
Fig 4.2: Forests for UGT1A1*6 polymorphism and IRI-induced severe late-onset diarrhea.

“A” represents sensitive analysis in allele model; “B” represents the results of removing heterogeneity in allele model; “C” represents sensitive analysis in recessive model; “D” represents the results of removing heterogeneity in recessive model.
Fig 5.1: Forests for UGT1A1*6 polymorphism and IRI-induced severe neutropenia. “A” represents allele model (G vs. A); “B” represents homozygote model (GG vs. AA); “C” represents heterozygote model (GA vs. AA); “D” represents dominant model (GG+GA vs. AA); “E” represents recessive model (GG vs. GA+AA).
Fig 5.2: Forests for UGT1A1*6 polymorphism and IRI-induced severe neutropenia.

"A" represents sensitive analysis in recessive model; "B" represents the results of removing heterogeneity in recessive model;
Fig 6: Forests for Begg’s test for RR. “A” represents allele model (G vs. A); “B” represents homozygote model (GG vs. AA); “C” represents heterozygote model (GA vs. AA); “D” represents dominant model (GG+GA vs. AA); “E” represents recessive model (GG vs. GA+AA).
Fig 7: Forests for Begg’s test for DCR. “A” represents allele model (G vs. A); “B” represents homozygote model (GG vs. AA); “C” represents heterozygote model (GA vs. AA); “D” represents dominant model (GG+GA vs. AA); “E” represents recessive model (GG vs. GA+AA).
Fig 8: Forests for Begg’s test for IRI-induced severe late-onset diarrhea. “A” represents allele model (G vs. A); “B” represents homozygote model (GG vs. AA); “C” represents heterozygote model (GA vs. AA); “D” represents dominant model (GG+GA vs. AA); “E” represents recessive model (GG vs. GA+AA).
Fig 9: Forests for Begg’s test for IRI-induced severe neutropenia. “A” represents allele model (G vs. A); “B” represents homozygote model (GG vs. AA); “C” represents heterozygote model (GA vs. AA); “D” represents dominant model (GG+GA vs. AA); “E” represents recessive model (GG vs. GA+AA).