Meta-Analysis and Systematic Review

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Correlation between adverse events after drug treatment and the *MDR1* C3435T polymorphism in advanced non-small cell lung cancer patients in an Asian population: a meta-analysis

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Abstract

Objective: To determine the association between the multidrug resistance 1 gene (*MDR1*) C3435T polymorphism and adverse drug reactions in advanced non-small cell lung cancer (NSCLC) patients in Asia.

Methods: Literature about the relationship between the *MDR1* C3435T polymorphism and adverse drug reactions in advanced NSCLC patients were collected from three English language databases (PubMed, Cochrane, and Embase) as well as three Chinese databases (Wanfang, China Knowledge Network, and the Chinese Biomedical Literature Database), and summarized by a meta-analysis.

Results: NSCLC patients with the T allele or TT genotype were significantly more likely to experience diarrhea than those with other genotypes under the allele model (odds ratio [OR] = 1.64, 95% confidence interval [CI]: 1.04–2.61), homozygous model (OR = 3.87, 95% CI: 1.49–10.07), and recessive model (OR = 4.48, 95% CI: 1.88–10.68). Similarly, these patients were significantly more likely to experience skin rash under the allele model (OR = 2.41, 95% CI: 1.24–4.66), homozygous model (OR = 4.77, 95% CI: 1.13–20.15), and dominant model (OR = 1.77, 95% CI: 1.03–3.05).

Conclusions: Asian NSCLC patients with the *MDR1* C3435T T allele or TT genotype are significantly more likely to develop diarrhea and rash after drug treatment.

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MDR1, C3435T polymorphism, non-small cell lung cancer, adverse event, meta-analysis, Asian population

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Introduction

Lung cancer accounts for around one-third of all cancer deaths, which is more than the sum of breast, prostate, and colorectal cancer.[1] Non-small cell lung cancer (NSCLC), including squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, and large cell carcinoma, accounts for 80% to 85% of all lung cancer cases.[2] Advanced NSCLC is mainly treated by chemotherapy, and platinum-based chemotherapy is currently the typical treatment. Platinum drugs cause DNA damage by forming intra- or inter-strand crosslinks with DNA, ultimately causing tumor cell death.[3,4] However, there are large individual differences in adverse drug reactions experienced by patients receiving this treatment, with the C3435T polymorphism in the multidrug resistance 1 gene (*MDR1*) being one of the major causes of this.

The *MDR1* P-glycoprotein gene product is expressed on the surface of healthy tissues and tumor cells such as the liver, gastrointestinal tract, and kidney, and performs a range of physiological functions as well as affecting pharmacokinetics.[5] For example, P-glycoprotein in the brush border of intestinal epithelial cells directly interferes with the entry of drugs from the digestive tract to the bloodstream, which affects pharmacokinetics.[6] The functional effects of the *MDR1* polymorphism on its encoded protein are implicated in a variety of diseases, including lung cancer.[7] Many studies have investigated C1236T, G2677T, and C3435T *MDR1* polymorphisms, and several have shown that C3435T alters the expression of certain protein phenotypes. For instance, *MDR1* C3435T was reported to predict adverse drug reactions, although findings are inconsistent.[8–10]

Taking into account the effects of different populations and ethnic differences on genetic polymorphisms, we selected a number of studies to comprehensively evaluate the relationship between the *MDR1* C3435T polymorphism and adverse drug reactions in Asian patients with advanced NSCLC using the basic principles and methods of evidence-based medicine. This meta-analysis evaluation provides a basis for further study of the true association between the *MDR1* C3435T polymorphism and adverse drug reactions.

Methods

Literature inclusion and exclusion criteria

Inclusion criteria were: (1) a cohort study or randomized controlled study; (2) including advanced NSCLC patients treated with drugs, and analyzing the *MDR1* C3435T polymorphism; and (3) including adverse reactions as outcome measures such as diarrhea and liver or kidney toxicity.

Exclusion criteria were: (1) conference abstracts, case reports, or review articles; and (2) repeated reports and studies in which data were unclear. This study was a meta-analysis so the need for ethical approval was waived.

Document retrieval

A comprehensive search of three English language databases (PubMed, Cochrane, and Embase) and three Chinese databases (Wanfang, China Knowledge Network, and the Chinese Biomedical Literature Database) was performed to identify related documents by document tracing. The search strategy was designed in accordance with the PICO principle and performed using MESH terms and free terms and their combinations; the PubMed search strategy is listed in Table 1. The search date ended on August 23, 2018, and the most recent update was on April 22, 2019.

Table 1. The PubMed search strategy.

Search	Query
#1	"Carcinoma, Non-Small-Cell Lung" [MESH]
#2	Carcinoma, Non Small Cell Lung OR Carcinomas, Non-Small-Cell Lung OR Lung Carcinoma, Non-Small-Cell OR Lung Carcinomas, Non-Small-Cell OR Non-Small-Cell Lung Carcinomas OR Nonsmall Cell Lung Cancer OR Non-Small-Cell Lung Carcinoma OR Non Small Cell Lung Carcinoma OR Carcinoma, Non-Small Cell Lung OR Non-Small Cell Lung Cancer
#3	"Polymorphism, Single Nucleotide" [MESH]
#4	Nucleotide Polymorphism, Single OR Nucleotide Polymorphisms, Single OR Polymorphisms, Single Nucleotide OR Single Nucleotide Polymorphisms OR Single Nucleotide Polymorphisms SNPs OR Single Nucleotide Polymorphism
#5	ABCB1 OR C3435T OR MDR1 OR MDR-1 OR p-glycoprotein OR P-gp
#6	#1 OR #2
#7	#3 OR #4
#8	#7 AND #5
#9	#6 AND #8

Literature screening, data extraction, and quality evaluation

Published studies were gradually screened using the title, abstract, and full text according to pre-set inclusion and exclusion criteria. Two researchers conducted the screening simultaneously and any disagreements were resolved by discussion with a third researcher.

Data extraction and quality evaluation according to the Newcastle–Ottawa Scale were also independently carried out by two researchers. When their opinions were inconsistent, a third researcher was sought to discuss the solution. The extracted data included the first author, publication year, number of subjects, gene distribution, country, and type of adverse reactions.

Statistical analysis

Data processing was performed using Stata 13.0 software (StataCorp LP, College Station, TX, USA). Heterogeneity between studies was analyzed by the Q test and P values, and was evaluated by I^2. When $P \geq 0.1$ or $I^2 \leq 50\%$, there was no statistical heterogeneity between studies, and combined analysis was conducted using a fixed effect model. When $P < 0.1$ or $I^2 > 50\%$, statistical heterogeneity existed between the studies, and combined analysis was conducted using a random effect model. The odds ratio (OR) and corresponding 95% confidence interval (CI) were used as the combined effect value, and the test level was $\alpha = 0.005$. Potential publication bias was analyzed using Egger's test, and sensitivity analysis was performed if necessary.

Results

Literature search and screening results

According to the search strategy, a total of 475 papers were initially retrieved. One hundred and thirty-five duplicates were

excluded by reading the topic and abstracts, and 319 irrelevant articles were excluded by reading the full text. A further 11 articles were excluded for insufficient data or a lack of content about the *MDR1* C3435T polymorphism and drug toxicity in NSCLC. Finally, 10 suitable papers[8–17] were identified for inclusion in this meta-analysis (Figure 1).

Basic characteristics and quality evaluation of the included studies

A total of 1354 NSCLC patients from China and Japan were included in this meta-analysis. Six types of related adverse effects were identified including overall toxicity, skin rash, diarrhea, hepatotoxicity or nephrotoxicity, gastrointestinal toxicity, and hematologic toxicity. The quality scores of these studies were between 7 and 9 points, indicating that they were of a high quality (Table 2, Figure 2).

Meta-analysis

The correlation between the *MDR1* C3435T polymorphism and the six adverse reactions after drug treatment for NSCLC was analyzed using five genetic models (allele model: T vs. C; homozygous model: TT vs. CC; heterozygous model: CT vs. CC; recessive model: TT vs. CT + CC; and dominant model: TT + CT vs. CC). Correlation analysis was performed using a fixed-effect model ($P \geq 0.1$, $I^2 \leq 50\%$) except for the association between overall toxicity or gastrointestinal toxicity and the *MDR1* C3435T polymorphism in the heterozygous model and the dominant model ($P < 0.1$,

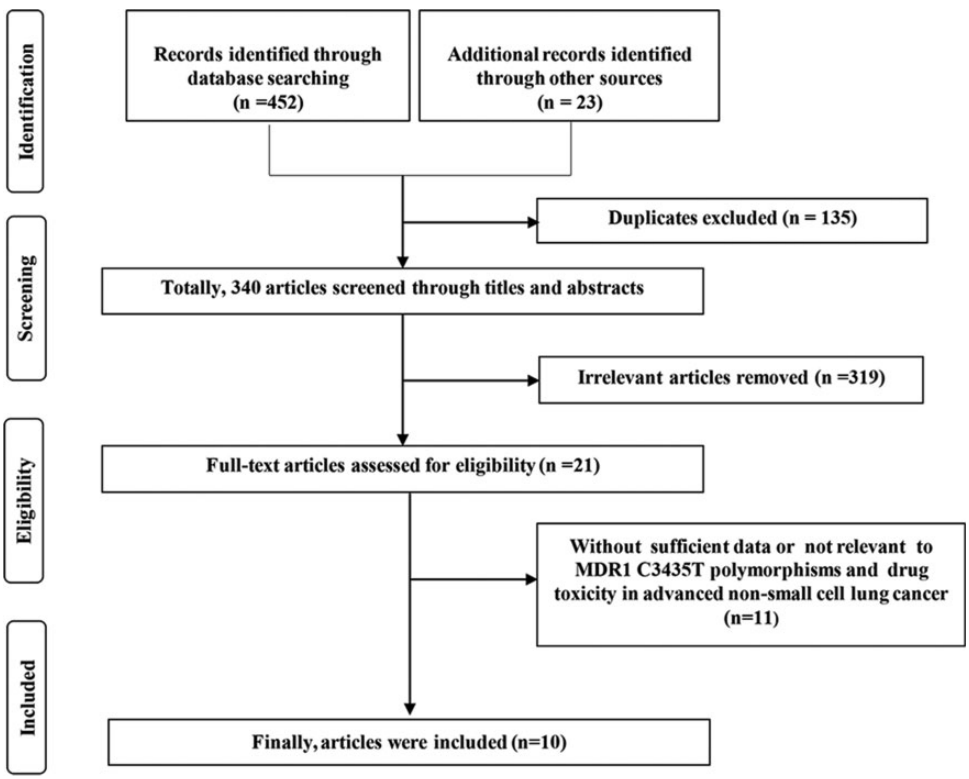

Figure 1. Flow diagram of study selection process.

Table 2. Summary of the included studies and distribution of ABCB1 C3435T genotypes.

Author	Year	Country	Number	Drug	Drug amount or dosage regimens	Adverse events	Presence of ADR			Absence of ADR			NOS
							TT	CT	CC	TT	CT	CC	
Endo-Tsukude[16]	2018	Japan	50	Erlotinib	Oral erlotinib at a standard dose of 150 mg in a prospective clinical study	Overall toxicity	8	27	12	0	1	2	9
		Japan	50	Erlotinib		Skin rash	8	27	11	0	1	3	9
		Japan	50	Erlotinib		Diarrhea	3	5	2	5	23	12	9
Ma[14]	2017	China	48	Gefitinib	All patients treated with only gefitinib at 250 mg day $^{-1}$	Skin rash	7	19	8	0	8	6	8
		China	48	Gefitinib		Diarrhea	5	10	7	2	17	7	8
		China	51	Gefitinib		Hepatotoxicity	0	7	4	6	22	12	8
Qiao[13]	2016	China	231	Platinum	All patients received first-line chemotherapy based on cisplatin (DDP) or carboplatin (CBP)	Leukopenia	6	21	15	28	85	76	8
Ruan[15]	2016	China	226	erlotinib, gefitinib and icotinib hydrochloride	Tyrosine kinase inhibitor	Overall toxicity	8	25	28	26	92	47	8
Qian[12]	2016	China	396	Platinum*	Platinum-based chemotherapy	Overall toxicity	18	63	52	39	126	98	7
		China	396	Platinum*		Hepatotoxicity	6	24	24	51	165	126	7
		China	396	Platinum*		Gastrointestinal toxicity	5	12	17	52	177	133	7
		China	396	Platinum*		Hematologic toxicity	13	42	39	44	147	111	8
Kobayashi[11]	2015	Japan	31	Gefitinib	Gefitinib (250 mg; Iressa; AstraZeneca, Osaka, Japan) was orally administered once daily at 08:00 h	Diarrhea	6	6	3	1	8	7	8
		Japan	31	Gefitinib		Skin rash	5	10	5	2	4	5	8
		Japan	31	Gefitinib		Hepatotoxicity	5	7	5	2	7	5	9
Fukudo[10]	2013	Japan	86	Erlotinib	Erlotinib was orally administered at a standard dose of 150 mg/day until progressive disease or intolerable toxicity	Skin rash	CT+TT:32	NA	15	CT+TT:21	NA	18	9
		Japan	86	Erlotinib		Diarrhea	CT+TT:12	NA	8	CT+TT:41	NA	25	8

(continued)

Table 2. Continued

Author	Year	Country	Number	Drug	Drug amount or dosage regimens	Adverse events	Presence of ADR			Absence of ADR			NOS
							TT	CT	CC	TT	CT	CC	
Tamura[17]	2012	Japan	83	Gefitinib	Patients received oral gefitinib at a dose of 250 mg once daily on a compassionate use basis until disease progression or toxicity	Skin rash	CT+TT:16	NA	7	CT+TT:44	NA	16	8
		Japan	83	Gefitinib		Diarrhea	CT+TT:3	NA	1	CT+TT:57	NA	22	8
		Japan	83	Gefitinib		Hepatotoxicity	CT+TT:12	NA	3	CT+TT:48	NA	20	9
Chen[9]	2010	China	95	Cisplatin*	All patients were given platinum-based chemotherapy in one of three types of regimens: NP, GP, and TP	Hematologic toxicity	11	26	13	9	24	12	9
		China	90	Cisplatin*		Gastrointestinal toxicity	11	22	10	14	18	15	9
		China	94	Cisplatin*		Fixed*	1	9	2	18	41	23	9
Han[8]	2007	China	105	Irinotecan	A total of 156 chemo naive patients with advanced NSCLC were prospectively enrolled for irinotecan plus cisplatin chemotherapy	Neutropenia	1	13	12	10	38	31	8
		China	104	Irinotecan		Diarrhea	3	2	5	7	49	38	8

Abbreviations: NA: not applicable; Cisplatin*: cisplatin-based chemotherapy; Platinum*: platinum-based chemotherapy; ADR: adverse drug reaction; Fixed*: hepatotoxicity or nephrotoxicity; NOS: Newcastle–Ottawa scale.

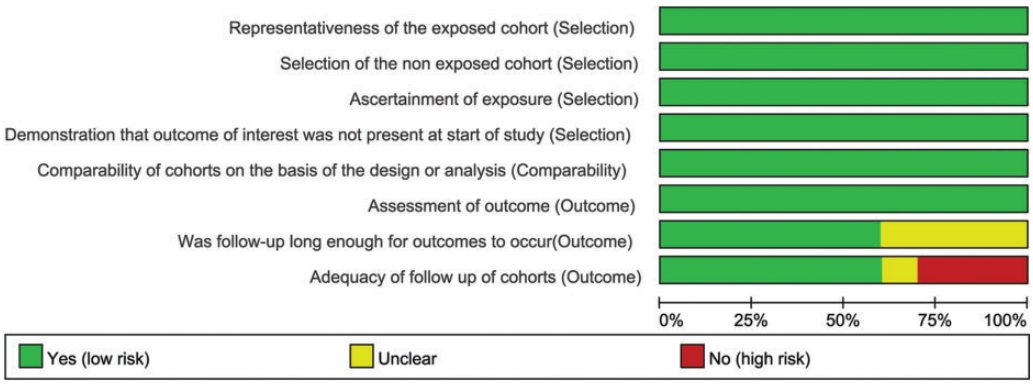

Figure 2. Quality assessment scale of eligible studies.

$I^2 > 50\%$) using a random effects model (Table 3).

Correlation analysis between the *MDR1* C3435T polymorphism and diarrhea was conducted in four studies, and patients with the T or TT genotype were found to be significantly more likely to experience diarrhea after drug treatment ($P < 0.05$) under the allele model (OR = 1.64, 95% CI: 1.04–2.61, $P = 0.035$), homozygous model (OR = 3.87, 95% CI: 1.49–10.07, $P = 0.006$), and recessive model (OR = 4.48, 95% CI: 1.88–10.68, $P = 0.001$) than patients with other genotypes (Figure 3). Subgroup analysis based on the drug used showed that patients with the TT genotype were significantly more likely to experience diarrhea after treatment with gefitinib than other drugs under the homozygous model (OR = 4.91, 95% CI: 1.11–21.63, $P = 0.036$) and recessive model (OR = 5.41, 95% CI: 1.38–21.14, $P = 0.015$). In patients treated with irinotecan, the probability of developing diarrhea was 4.66 times higher in those with the TT genotype than those with CT and CC genotypes (95% CI: 1.01–21.61, $P = 0.049$) (Table 4).

Correlation analysis between the *MDR1* C3435T polymorphism and skin rash was conducted in five studies, and similarly patients with the T or TT genotype were found to be significantly more likely to experience skin rash after drug treatment ($P < 0.05$) under the allele model (OR = 2.41, 95% CI: 1.24–4.66, $P = 0.009$), homozygous model (OR = 4.77, 95% CI: 1.13–20.15, $P = 0.034$), and dominant model (OR = 1.77, 95% CI: 1.03–3.05, $P = 0.038$) (Figure 4). Subgroup analysis based on the drug used showed that the probability of skin rash in patients with TT and CT genotypes was 2.27 times higher than in those with the CC genotype when erlotinib was used (95% CI: 1.01–5.08, $P = 0.047$). When using gefitinib, the probability of skin rash in patients carrying the T genotype was 2.07 times higher than in those carrying the C genotype (95% CI: 1.02–4.20, $P = 0.043$) (Table 4).

A total of three, two, four, and five studies were included in the correlation analysis between the *MDR1* C3435T polymorphism and overall toxicity, gastrointestinal toxicity, hematologic toxicity, and hepatotoxicity and nephrotoxicity, respectively; the incidence of these four adverse reactions was not significantly associated with the polymorphism (Table 3).

Publication bias

Publication bias was analyzed using Egger's test and shown not to exist in these correlation analyses (Table 3).

Table 3. Associations between ABCB1 C3435T genotypes and drug toxicity in advanced non-small cell lung cancer patients.

Genetic models	Number	OR (95% CI)	*P*(OR)	Analysis model	I^2 (%)	*P*(H)	*P(Egger)*
Allele (T vs. C)							
Overall toxicity	3	0.85 (0.67, 1.09)	0.211	F(M-H)	48.1	0.146	0.394
Diarrhea	4	1.64 (1.04, 2.61)	0.035	F(M-H)	0	0.479	0.232
Gastrointestinal toxicity	2	0.89 (0.60, 1.31)	0.552	F(M-H)	0	0.356	–
Hematologic toxicity	4	0.93 (0.74, 1.18)	0.552	F(M-H)	0	0.723	0.972
Hepatotoxicity or nephrotoxicity	4	0.85 (0.61, 1.18)	0.332	F(M-H)	0	0.594	0.488
Skin rash	3	2.41 (1.24, 4.66)	0.009	F(M-H)	0	0.582	0.252
Homozygous model (TT vs. CC)							
Overall toxicity	3	0.77 (0.46, 1.29)	0.317	F(M-H)	0	0.426	0.425
Diarrhea	4	3.87 (1.49, 10.07)	0.006	F(M-H)	0	0.719	0.176
Gastrointestinal toxicity	2	0.92 (0.43, 1.96)	0.831	F(M-H)	0	0.567	–
Hematologic toxicity	4	0.86 (0.52, 1.42)	0.552	F(M-H)	0	0.661	0.679
Hepatotoxicity or nephrotoxicity	4	0.69 (0.32, 1.47)	0.340	F(M-H)	0	0.548	0.717
Skin rash	3	4.77 (1.13, 20.15)	0.034	F(M-H)	0	0.704	0.428
Heterozygous model (CT vs. CC)							
Overall toxicity	3	0.79 (0.37, 1.67)	0.530	R(D-L)	61.8	0.073	0.444
Diarrhea	4	0.75(0.35, 1.60)	0.457	F(M-H)	0	0.479	0.485
Gastrointestinal toxicity	2	0.94 (0.28, 3.17)	0.924	R(D-L)	72.5	0.057	–
Hematologic toxicity	4	0.94 (0.66, 1.33)	0.708	F(M-H)	0	0.815	0.541
Hepatotoxicity or nephrotoxicity	4	0.93 (0.56, 1.52)	0.764	F(M-H)	0	0.599	0.333
Skin rash	3	2.56 (1.00, 6.56)	0.051	F(M-H)	0	0.593	0.181
Recessive model (TT vs. CT+CC)							
Overall toxicity	3	0.88 (0.54, 1.43)	0.606	F(M-H)	0	0.922	0.451
Diarrhea	4	4.48 (1.88, 10.68)	0.001	F(M-H)	0	0.854	0.169
Gastrointestinal toxicity	2	0.91 (0.46, 1.79)	0.773	F(M-H)	0	0.732	–
Hematologic toxicity	4	0.90 (0.57, 1.43)	0.651	F(M-H)	0	0.695	0.352
Hepatotoxicity or nephrotoxicity	4	0.70(0.35, 1.40)	0.315	F(M-H)	0	0.403	0.866
Skin rash	3	2.70 (0.72, 10.23)	0.143	F(M-H)	0	0.622	0.565
Dominant model (TT+CT vs. CC)							
Overall toxicity	3	0.80 (0.38, 1.72)	0.571	R(D-L)	65.6	0.055	0.374
Diarrhea	6	1.08 (0.62, 1.88)	0.792	F(M-H)	0	0.727	0.356
Gastrointestinal toxicity	2	0.90(0.35, 2.34)	0.831	R(D-L)	62.7	0.101	–
Hematologic toxicity	4	0.92 (0.66, 1.28)	0.604	F(M-H)	0	0.781	0.674
Hepatotoxicity or nephrotoxicity	5	0.94 (0.60, 1.46)	0.772	F(M-H)	0	0.642	0.110
Skin rash	5	1.77 (1.03, 3.05)	0.038	F(M-H)	7.8	0.362	0.077

Abbreviations: OR: Odds ratio; CI: confidence interval; *P*(H): *P* for heterogeneity; Number: number of included studies; R: random effect model; D-L: DerSimonian–Laird method; F: fixed effect model; M-H: Mantel–Haenszel method.

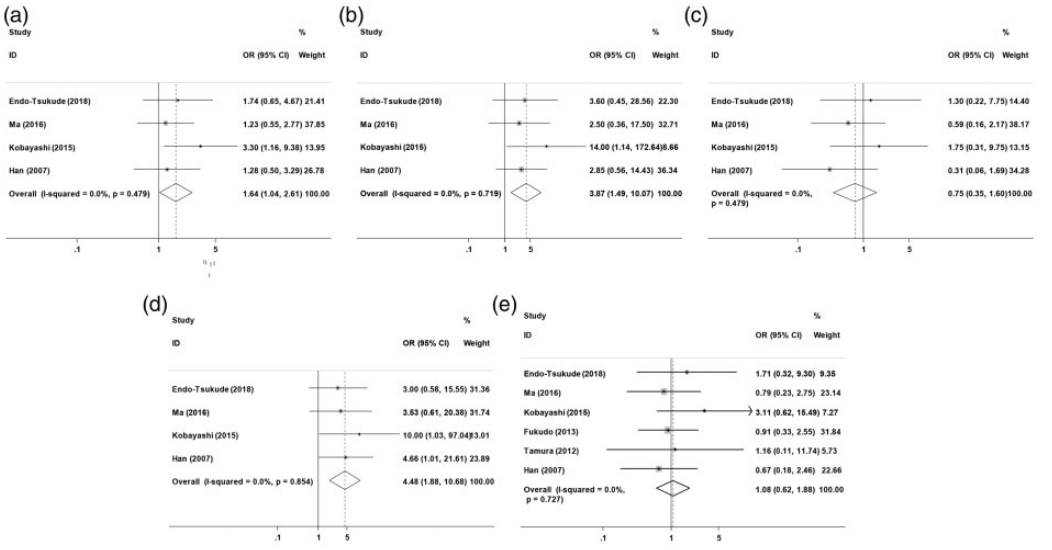

Figure 3. Forest plot of the association between the *MDR1* C3435T polymorphism and major adverse diarrhea events. (a) allele model; (b) homozygous model; (c) heterozygous model; (d) recessive model; (e) dominant model.

Discussion

The *MDR1* gene product P-glycoprotein is an ATP-dependent membrane transporter consisting of two homologous fragments and a linking region. P-glycoprotein is widely distributed in the human body, including the brain, placenta, small intestine, skin, lung, liver, and kidney. It participates in the absorption, distribution, metabolism, and excretion of drugs in the body, thereby protecting human tissues and organs and maintaining their physiological homeostasis.[18] The physiological functions of P-glycoprotein are diverse, and it can produce a relatively specific response to drugs according to differences in individuals and tissues.

C3435T in *MDR1* is located in exon 26 and is a synonymous mutation. This was suggested not to cause significant changes in protein expression, but to attenuate the transporting function of P-glycoprotein by altering its conformation.[19] However, other studies found that P-glycoprotein expression in the renal cortex and duodenum was significantly lower in individuals with the *MDR1* TT genotype than in those with wild-type, suggesting that C3435T may also affect P-glycoprotein expression in certain tissues.[20,21]

Diarrhea occurs when the amount of fluid entering the colon exceeds its absorption capacity and/or the absorption capacity of the colon decreases, leading to an increase in the amount of water excretion in the feces. Our meta-analysis showed that the probability of diarrhea occurring in NSCLC patients carrying the T allele or TT genotype was 2.06-fold and 6.03-fold higher, respectively, than in patients with other genotypes. This suggests a weakening of the transport of these chemotherapeutic drugs caused by a conformational change in P-glycoprotein, leading to intestinal epithelial cell damage and diarrhea.

A common side-effect of the use of erlotinib and gefitinib is the occurrence of skin

Table 4. Subgroup analysis of the effect of different drugs on the C3435T polymorphism related to diarrhea and skin rash.

	Allele (T vs. C)			Homozygous model (TT vs. CC)			Heterozygous model (CT vs. CC)			Recessive model (TT vs. CT+CC)			Dominant model (TT+CT vs. CC)		
Subgroup	N	OR (95% CI)	*P*	N	OR (95% CI)	*P*	N	OR (95% CI)	*P*	N	OR (95% CI)	*P*	N	OR (95% CI)	*P*
Diarrhea															
Drugs															
Erlotinib	1	1.74 (0.65, 4.67)	0.271	1	3.60 (0.45, 28.56)	0.225	1	1.30 (0.22, 7.75)	0.770	1	3.00 (0.58, 15.55)	0.191	2	1.10 (0.46, 2.61)	0.835
Gefitinib	2	1.79 (0.95, 3.36)	0.072	2	4.91 (1.11, 21.63)	0.036	2	0.89 (0.32, 2.46)	0.816	2	5.41 (1.38, 21.14)	0.015	3	1.32 (0.54, 3.19)	0.544
Irinotecan	1	1.28 (0.50, 3.29)	0.606	1	2.85 (0.56, 14.43)	0.206	1	0.31 (0.06, 1.69)	0.176	1	4.66 (1.01, 21.61)	0.049	1	0.67 (0.18, 2.46)	0.543
Skin rash															
Drugs															
Erlotinib	1	6.14 (0.73, 51.95)	0.096	1	5.17 (0.23, 114.05)	0.298	1	7.36 (0.69, 78.7)	0.099	1	1.99 (0.10, 40.50)	0.655	2	2.27 (1.01, 5.08)	0.047
Gefitinib	2	2.07 (1.02, 4.20)	0.043	2	4.64 (0.91, 23.60)	0.064	2	2.03 (0.71, 5.81)	0.186	2	2.92 (0.67, 12.79)	0.155	3	1.46 (0.70, 3.02)	0.313

Abbreviations: OR: Odds ratio; CI: confidence interval;

rash, which is characteristic of selective epidermal growth factor tyrosine kinase inhibitors.[22–24] Irinotecan is a DNA topoisomerase I inhibitor that blocks DNA replication and inhibits RNA synthesis, and is specific for the S phase of the cell cycle. It affects the proliferation, differentiation, migration, and adhesion of keratinocytes, leading to the development of a rash, papules and pustules, and dry skin. We speculate that the epidermal cells of NSCLC patients carrying the T allele or TT genotype are likely to show weakened transport activity of chemotherapeutic drugs, causing skin rash and leading to lesions following epidermal cell growth inhibition.

This meta-analysis showed that there was no significant correlation between C3435T and the other adverse effects caused by drug treatments, but these findings may be altered because of the inclusion of subjects other than Chinese and Japanese. Our study also has some limitations: 1) the medications used in included studies were different, including single drugs and drug combinations, which were not distinguished between, and 2) only the correlation between C3435T and adverse drug reactions was considered, without taking into account the two other common *MDR1*polymorphisms at nucleotides 1236[8,10,11,13–16] and 2677.[8–11,14,16]

In conclusion, this meta-analysis indicates that Asian NSCLC patients carrying the *MDR1* C3435T T allele or TT genotype have a significantly increased risk of experiencing diarrhea and skin rash after drug treatment. This information will provide a reference value to aid drug selection and adverse reaction prevention during future NSCLC treatment. Further studies should consider the effects of polymorphisms, environmental factors, and individual behavioral factors on the efficacy of drugs in the treatment of NSCLC.

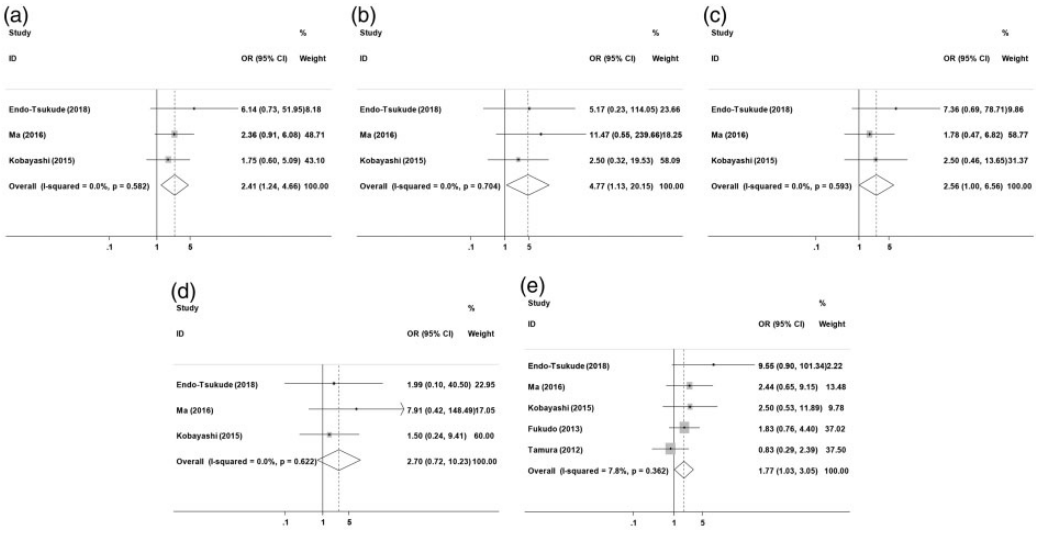

Figure 4. Forest plot of the association between the *MDR1* C3435T polymorphism and major adverse skin rash events. (a) allele model; (b) homozygous model; (c) heterozygous model; (d) recessive model; (e) dominant model.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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