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ARTICLE

Associations of *HLA* genetic variants with carbamazepine-induced cutaneous adverse drug reactions: An updated meta-analysis

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Abstract

Aggregated risk of carbamazepine (CBZ)-induced cutaneous adverse drug reactions (cADRs) with different *HLA* variants are unclear and limited in terms of the power of studies. This study aimed to assess the aggregated risk of CBZ-induced cADRs associated with carrying the following *HLA* variants: *HLA-B*15:02*, *HLA-B*15:11*, *HLA-B*15:21*, *HLA-B*38:02*, *HLA-B*40:01*, *HLA-B*46:01*, *HLA-B*58:01*, *HLA-A*24:02*, and *HLA-A*31:01*. Literature was searched in different databases following PRISMA guidelines. The outcomes were measured as odds ratio (OR) using RevMan software by a random/fixed effects model, where $p < 0.05$ was set as statistical significance. In total, 46 case–control studies met the inclusion criteria and were included in this analysis consisting of 1817 cases and 6614 controls. It was found that case-patients who carried the *HLA-B*15:02* allele were associated with a significantly increased risk of CBZ-induced Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) compared to controls (OR 26.01; 95% CI 15.88–42.60; $p < 0.00001$). The aggregated risk of cADRs was slightly higher in Asian compared to Caucasian patients (Asians: OR 14.84; 95% CI 8.95–24.61; $p < 0.00001$; Caucasians: OR 11.65; 95% CI 1.68–80.70; $p = 0.01$). Further, *HLA-B*15:11*, *HLA-B*15:21*, or *HLA-A*31:01* allele was also associated with significantly increased risk of CBZ-induced cADRs (*HLA-B*15:11:* OR 6.08; 95% CI 2.28–16.23; $p = 0.0003$; *HLA-B*15:21:* OR 5.37; 95% CI 2.02–14.28; $p = 0.0008$; *HLA-A*31:01:* OR 5.92; 95% CI 4.35–8.05; $p < 0.00001$). Other *HLA* variants were not found to have any significant associations with CBZ-induced cADRs. Strong associations between the *HLA-B*15:02*, *HLA-B*15:11*, *HLA-B*15:21*, or *HLA-A*31:01* allele with CBZ-induced cADRs have been established in this analysis. Pharmacogenetic testing of particular *HLA* alleles before initiation of CBZ therapy may be beneficial to patients and may help to eradicate cADRs substantially.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Studies assessing the aggregated risk of carbamazepine (CBZ)-induced cutaneous adverse drug reactions (cADRs) associated with carrying *HLA* genetic variants are conflicting and limited in terms of the power of studies. Besides *HLA-B*1502*, *HLA-B*15:11*, or *HLA-A*31:01*, other potential genetic variants of *HLA* (e.g., *HLA-B*15:21*) were not included in these analyses. Further, the associations of *HLA-A*24:02*, *HLA-B*40:01*, *HLA-B*46:01*, and *HLA-B*58:01* alleles with CBZ-induced cADRs are controversial.

WHAT QUESTION DID THIS STUDY ADDRESS?

What is the relationship of some specific *HLA* genetic variants (e.g., *HLA-B*15:02*, *HLA-B*15:11*, *HLA-B*15:21*, *HLA-B*38:02*, *HLA-B*40:01*, *HLA-B*46:01*, *HLA-B*58:01*, *HLA-A*24:02*, or *HLA-A*31:01*) with cADRs?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

In this meta-analysis, strong associations between *HLA-B*15:02*, *HLA-B*15:11*, *HLA-B*15:21*, or *HLA-A*31:01* allele with CBZ-induced cADRs have been established in which the most substantial, robust evidence has been found between *HLA-B*15:02* allele and CBZ-induced Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). Other *HLA* variants (e.g., *HLA-A*24:02*, *HLA-B*40:01*, *HLA-B*46:01*, and *HLA-B*58:01*) were not associated with significantly increased risk of cADRs.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Pharmacogenetic testing of particular *HLA* variants before initiation of carbamazepine therapy may be beneficial to patients and may help to eradicate cADRs substantially. The findings of this analysis may facilitate the rapid translation of some selective *HLA* variants from bench to bedside.

INTRODUCTION

Cutaneous adverse drug reactions (cADRs) such as Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), maculopapular exanthema (MPE), and drug reaction with eosinophilia and systemic symptoms (DRESS) are life-threatening hypersensitivity reactions affecting predominantly the mucous membranes and skin.[1–3] The incidence of cADRs is generally found to be low, but the mortality rates associated with cADRs are high enough (SJS ~1–5%, TEN ~25–35%, DRESS ~10%) to be clinically concerning as reported elsewhere.[4] Medication use (~80% of cases) is one of the most identified and widely accepted reasons for developing life-threatening cADRs. Although different medications such as allopurinol, phenytoin, abacavir, dapsone, flucloxacillin, and cotrimoxazole have been strongly associated with cADRs, carbamazepine (CBZ) is the most studied and causes SJS/TEN in a considerable proportion of patients.[1,5,6] Some studies also found an association between CBZ use and the development of MPE/DRESS.[7–10]

Multiple investigators have reported the relationship between human leukocyte antigen (HLA) encoded by the *HLA* genes and CBZ-induced SJS/TEN. Specifically, the *HLA-B*15:02* allele has been associated with CBZ-induced SJS/TEN predominantly in Asian ethnicities, as reported in multiple studies.[11–13] Because of the strong association found in numerous observational studies, the US Food and Drug Administration (FDA) recommended screening for the *HLA-B*15:02* allele before starting CBZ therapy, particularly in Asian patients.[12] It is unlikely that some studies did not find very strong associations between CBZ-induced SJS/TEN and *HLA-B*15:02* allele, which may be controversial in the clinical decision process for healthcare professionals.[14,15]

Although few meta-analyses have been identified, studies assessing the aggregated risk of CBZ-induced cADRs associated with carrying *HLA* genetic variants are limited in terms of the power of studies and the different genetic variants of *HLA*.[5,11–13,16,17] Besides *HLA-B*15:02*, *HLA-B*15:11*, or *HLA-A*31:01*, other potential genetic variants of *HLA* (e.g., *HLA-B*15:21*) were not included in these analyses. A recent comprehensive review of *HLA* associated with cADRs suggested that not only the *HLA-B*15:02* allele but also *HLA-B75* serotypes (e.g., *HLA-B*15:11*, *HLA-B*15:21*) should be considered in assessing CBZ-induced cADRs.[1] Previous meta-analysis

indicated *HLA-A*24:02*, *HLA-B*40:01*, *HLA-B*46:01*, and *HLA-B*58:01* as strong protective biomarkers[5,11] although some recent studies found these alleles to increase the risk of cADRs.[18,19] There is also a need to update the literature as since 2018 there has been no meta-analysis assessing such associations with a wide range of *HLA* genetic variants. Therefore, this study aimed to review all relevant studies systematically and to assess the aggregated risk of CBZ-induced cADRs associated with the following *HLA* genetic variants: *HLA-B*15:02*, *HLA-B*15:11*, *HLA-B*15:21*, *HLA-B*38:02*, *HLA-B*40:01*, *HLA-B*46:01*, *HLA-B*58:01*, *HLA-A*24:02*, and *HLA-A*31:01*.

METHODS

Literature search strategy

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines as described elsewhere[20] for identifying relevant studies from different data sources. The literature was searched in PubMed, Cochrane Library, and ScienceDirect from the inception date to October 6, 2021. Different keywords reflecting *HLA* genetic variants (e.g., *HLA-B*15:02*, *HLA-B*15:11*, *HLA-B*15:21*, *HLA-B*38:02*, *HLA-B*40:01*, *HLA-B*46:01*, *HLA-B*58:01*, *HLA-A*24:02*, *HLA-A*31:01*) and CBZ with relevant terms of various forms of cADRs (i.e., SJS/TEN/MPE/DRESS) were applied to identify relevant studies. Furthermore, reference lists of all the included studies and published meta-analyses were checked carefully to identify additional studies qualifying for this analysis.

Inclusion and exclusion criteria of the studies

Studies were included if they fulfilled the following criteria: (i) must be a case–control study in design where all patients have taken CBZ; (ii) reported the relationship between *HLA-B*15:02*, *HLA-B*15:11*, *HLA-B*15:21*, *HLA-B*38:02*, *HLA-B*40:01*, *HLA-B*46:01*, *HLA-B*58:01*, *HLA-A*24:02*, *HLA-A*31:01*, and CBZ-induced cADRs (SJS/TEN/MPE/DRESS); (iii) reported data were sufficient for assessing the relationship of different *HLA* genetic variants among cases and controls; (iv) there were no ethnic restrictions; and (v) articles must be written in English. Studies were excluded based on the following criteria: (i) if the studies were randomized control trials (RCTs) or observational cohort studies; (ii) if they were a review/systematic review/meta-analysis/viewpoint/correspondence/perspective/letter to the editor; and (iii) if they reported insufficient data for assessing the relationship between *HLA* genetic variants and CBZ-induced cADRs.

Data extraction, validity, and quality assessment

At the end of the literature search, all the entries were imported into Rayyan QCRI, a systematic review software tool for the identification of studies.[21] Two authors (M.E. and S.J.) were involved in the selection of studies from Rayyan QCRI in accordance with the inclusion and exclusion criteria. Any disagreement in selected studies by these two authors was resolved by the senior authors (S.C. and B.M.) via discussion with the authors engaged in the study selection process. Finally, full texts of all included studies were downloaded and checked exclusively for the extraction of relevant data. Data extraction was primarily carried out by one author (M.E.) and was double-checked and verified by a second author (S.J.). Any discrepancies were discussed until a consensus between the two authors could be reached. If they were not in consensus, the disagreements were resolved by the lead author (B.M.). The qualities of included studies were assessed following Newcastle-Ottawa Scale (NOS) guidelines.[22]

Assessment of aggregated risk, heterogeneity, sensitivity, and publication bias

The aggregated odds ratio (OR) was measured using the Mantel–Haenssel (M-H) method following a fixed/random effect model based on the magnitude of heterogeneity (I^2 statistics). The heterogeneity was judged depending on the value of I^2 statistics, where $I^2 < 25\%$, $I^2 = 25$–50%, and $I^2 > 50\%$ indicate low, moderate, and high levels of heterogeneity, respectively.[23] If $I^2 > 50$, then the pooled effects were estimated using a random effect model. In contrast, a fixed effect model was applied if $I^2 < 50$ to assess the aggregated risk. All data were analyzed using Review-Manager software (RevMan version 5.3 Windows; The Cochrane Collaboration, Oxford, UK), where the statistical significance (p) was set as <0.05. Sensitivity analysis was performed to check the impacts of any individual study on the pooled risk and the overall effects on the heterogeneity of the studies. Publication bias was assessed by the visual inspection of the funnel plot.[24]

RESULTS

Selection of studies

In total, 1089 articles were identified through a literature search of different databases. After the removal of duplicates, 733 articles were considered for the screening of

titles. After title screening, 381 records were removed, and the remaining 352 were considered for abstract screening. After abstract screening, 166 articles were included for full-text assessment. During full-text assessment, 120 articles were excluded for different reasons, and finally 46 articles met the inclusion criteria for this meta-analysis. The complete selection process following PRISMA guidelines is illustrated in Figure 1.

Characteristics of included studies

The basic characteristics of all included studies are shown in Table 1. Of the 46 studies, 41 were conducted in Asian populations in which 15 studies represented the Chinese population, 5 from Thailand, 5 from India, 3 from Malaysia, 2 from Japan, 1 from Singapore, 2 from Taiwan, and the other 6 studies were from other parts of Asia. Six studies investigated Caucasians, while only one study examined multi-ethnic populations for assessing the risk of cADRs associated with different *HLA* genetic variants (Table 1). A total of 44 studies reported the risk in case patients using tolerant controls, while only 4 studies used the healthy population as controls. Qualities of all included studies as assessed by following NOS ranged from '4' to '9' as shown in Table S1.

Association of *HLA-B*15:02* with CBZ-induced cADRs

In total, 38 studies consisting of 1346 cases, 2504 tolerant controls, and 564 population controls were included for the assessment of the relationship between *HLA-B*15:02* and CBZ-induced cADRs. After pooled estimation, it was found that case-patients who carried the *HLA-B*15:02* allele were associated with a significantly increased risk of cADRs compared to controls (OR 14.63; 95% CI 9.14–23.42; $p < 0.00001$) as shown in Figure 2.

Subgroup analysis further revealed that significantly increased risk of cADRs was driven from SJS/TEN (OR 26.01; 95% CI 15.88–42.60; $p < 0.00001$) but not from MPE (OR 1.56; 95% CI 0.95–2.55; $p = 0.08$) or DRESS (OR 1.97; 95% CI 0.36–10.87; $p = 0.43$) (Figure 3).

Case-patients carrying the *HLA-B*15:02* allele were associated with a significantly increased risk of cADRs

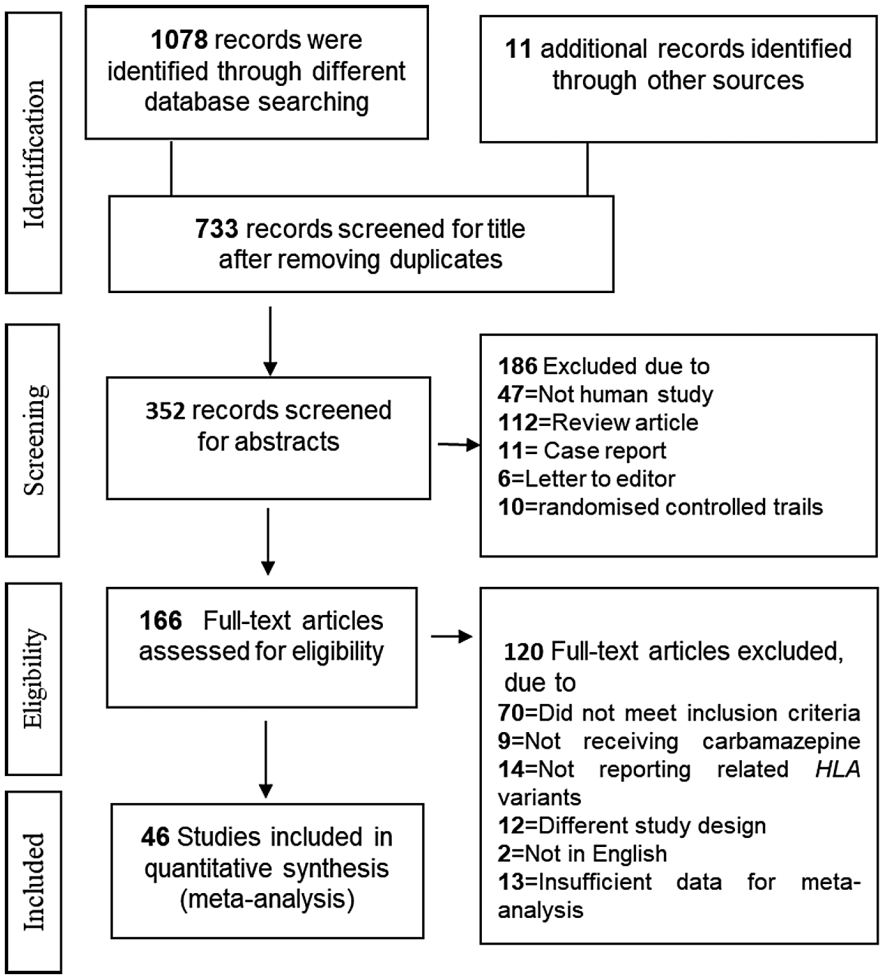

FIGURE 1 PRISMA flowchart for identification of eligible studies. HLA, human leukocyte antigen.

TABLE 1 Baseline characteristics of included studies

Author	Country	Study design	Sample size (case)	Mean age ± SD; % of male	Assessed *HLA* variants	Variant allele in case (*n*/*N*)	Tolerant controls	Healthy controls	Outcomes	Genotyping method
Aggarwal (2014)[62]	North Indian population	Case–control	17	33.9 ± 11.6; 5%	B*15:02	2 /9	0/37		SJS/TEN	PCR-SSP
Amstutz (2013)[81]	Canada	Case–control	42	9.9; 55%	A*31:01 B*15:02	9/42 3/42	3/87 1/87		SCARs	SBT
Capule (2020)[80]	Filipino	Case–control	29	38.1 ± 12.9; 62.5%	A*31:01 A*24:02 B*15:02 B*15:21 B*38:02 B*40:01 B*46:01 B*58:01	1/8 3/8 2/8 4/8 1/8 1/8 1/80	2/32 15/32 2/32 4/32 9/32 2/32 2/32 3/32		SJS/TEN	SSP
Chang (2011)[67]	Multi-ethnic Malaysia (16 Malays, 3 Chinese, 2 Indian)	Case–control	21	–	HLA-B*1502	12/16	–	47/300	SJS/TEN	PCR-SSP
Chong (2014)[72]	Singapore pediatric (Chinese, Malay, India)	Case–control	32	SJS/TEN:13.4 HSS: 8.9	B*1502	6/22	1/10		SCARs	SSP
Cheung (2013)[42]	Hong Kong Han China	Case–control	55	36.1 ± 16.9; 59.3%	B*15:02 B*38:02 B*46:01 B*58:01 B*40:01	24/26 2/27 3/27 2/27 1/27	16/135	275	SJS/TEN	PCR-SSP
Chung (2004)[43]	Han Chinese, Taiwan	Case–control	44	43.0; 58.1	B*1502	44/44	3/101		SJS	MS
Devi (2017)[63]	South Indian population	Case–control	12	11–85; 50%	B*15:02	1/4	0/3		SJS/TEN	PCR SSP
Fricke-Galindo (2014)[82]	Mexican Mestizo	Case–control	21	35 ± 12; 33%	A*31:01:02	2/5	0/18	23/225	MPE	SBT
Genin (2014)[87]	1. Han Chinese Taiwan 2. Caucasian Europe	Case–control	93	–	EUROPE A*31:01 B*15:02 Taiwan A*31:01 B*15:02	10/30 0/30 6/63 41/63	10/257 0/43 3/72 4/72		DRESS, SJS/TEN	SSP

(Continues)

TABLE 1 (Continued)

Author	Country	Study design	Sample size (case)	Mean age ± SD; % of male	Assessed *HLA* variants	Variant allele in case (*n*/*N*)	Tolerant controls	Healthy controls	Outcomes	Genotyping method
Hsiao (2014)[44]	Han Chinese (Taiwan)	Case–control	194	49.2 ± 18; 52%	A* 2402 A*3101 B*1502 B*4001	33/186 16/186 103/186 27/186	43/152 5/152 11/152 57/152		SJS/TEN DRESS MPE	SSO, SBT
He (2013)[45]	Northeastern China	Case–control	35	31.4;57.1%	B*15:02 B*58:01	8/35 4/20	2/125 6/125		SJS/TEN	PCR–SBT
Hung (2006)[73]	Taiwan	Case–control	91	SJS/TEN:43.4; HSS: 51.5; MPE:45.9; 40.7%	A*31:01 A*24:02 B*15:02 B*40:01	9/91 14/91 60/91 16/91	4/144 41/144 6/144 59/144		SJS/TEN HSS MPE	MS
Ihtisham (2019)[64]	North Indian	Case–control	120	25.3; 48.6%	A*31:01	35/81	3/70		MPE	PCR-SSP; PCR-SSO
Khor (2014)[65]	Indian	Case–control	5	39.2; 80%	B*15:02	2/5	2/52		SJS/TEN	SSOP
Khor (2017)[68]	Malaysia; Malay, Chinese, Indian	Case–control	28	36.6;46.4%	B*15:02 A*31:01	20/28 3/28	23/227 12/227		SJS/TEN	SSOP
Kim (2011)[75]	Koreans	Case–control	24	52.1 ± 15.1; 54.2%	A*24:02 A*31:01 B*1502 B*1511	5/24 13/24 1/24 3/24	21/50 7/50 0/50 2/50		SCARs	SSOP
Khosama (2017)[79]	Indonesia	Case–control	14	33.5; 56.7%	B*1502 Javanese Sundanese Padangnese	8/14 3/4 2/4 1/1	14/53		SJS/TEN	SSO
Ko (2011)[74]	Taiwan	Case–control	18	–	B*1502	18/18	2/11		SJS/TEN, SJS	PCR-SBT
Ksouda (2017)[83]	Tunisian	Case–control	14	48.80; 64.2%	A*31:01	4/7	1/25		DRESS	SSO
Kulkantrakorn (2012)[57]	Thailand	Case–control	34	47.0 ± 14.7; 28%	B*1502	32/34	7/40		SJS/TEN	RT-PCR, SSP
Locharernkul (2008)[58]	Thailand	Case–control	31		B*1502	6/11	0/4		SJS MPE	SSP

TABLE 1 (Continued)

Author	Country	Study design	Sample size (case)	Mean age ± SD; % of male	Assessed *HLA* variants	Variant allele in case (*n*/*N*)	Tolerant controls	Healthy controls	Outcomes	Genotyping method
Li (2013)[46]	Han Chinese	Case–control	249	30.8 ± 16.2; 72.5%	A*24:02 A*31:01 B*15:02 B*15:11 B*38:02 B*46:01 B*40:01 B*58:01	16/40 1/40 4/40 2/40 2/40 15/40 7/40 3/40	14/52 1/52 5/52 1/52 9/52 16/52 8/52 13/52		MPE	PCR-SBT
Man (2007)[47]	Han Chinese, Hong Kong	Case–control	24	36; 50%	B*15:02	8/24	16/48		SCARs	SSP
Maekawa (2015)[70]	Japanese	Case–control	210	53; 47.6%	A*31:01	9/21	–	482/2873	SJS/TEN	SSP-PCR
McCormack (2011)[84]	Northern European	Case–control	26	–	A*31:01	38/145		10/257	SCARs	SSP
Mehta (2009)[66]	Indian Hindu	Case–control	8	22.8; 50%	B*1502	6/8	0/10		SJS, SJS/TEN	SSP
Nakkam (2021)[59]	Thailand	Case–control	91	17.3; 40.7%	A*24:02 B*15:02 B*15:11 B*15:21 B*46:01 B*38:02 B*40:01 B*58:01	15/91 76/91 1/91 4/91 19/91 8/91 8/91 7/91	34/144 18/144 0/144 0/144 42/144 6/144 21/144 17/144		SCARs	SSO
Nguyen (2015)[76]	Vietnam	Case–control	38	40.6 ± 18.7; 52.6%	B* 38:02 B* 40:01 B* 46:01 B*58:01 B*15:02	2/38 2/38 5/38 0/38 34/38	2/25 2/25 9/25 4/25 6/25		SCARs	SSOP
Niihara (2011)[71]	Japanese	Case–control	15	50.7; 33.3%	B*15:02 B*15:11 B*40:01 B*46:01 B*58:01	0/15 1/15 2/15 1/15 0/15	0/33 1/33 4/33 3/33 2/33		ADRs SJS/TEN MPE DIHS, EEM	PCR-SSO

(Continues)

TABLE 1 (Continued)

Author	Country	Study design	Sample size (case)	Mean age ± SD; % of male	Assessed *HLA* variants	Variant allele in case (*n*/*N*)	Tolerant controls	Healthy controls	Outcomes	Genotyping method
Ramírez (2017)[85]	Caucasian (Romani Spanish	Case–control	27	50; 38.5%	B*1502 A*31:01 B*40:01 B*58:01	1/2 2/4 1/4 1/4	0/23 1/23 0/23 0/23		SJS/TEN DRESS	SSOP
Shafeng (2021)[48]	Northwest China	Case–control	165	–; 80%	B*1502	4/5	19/48		MPE	DFMH
Shi (2012)[49]	Southern China Han China	Case–control	18	27.8 ± 14.9; 61.1%	B*15:02 A*24:02 A*31:01 B*40:01 B*4601 B*15:11 B*38:02	15/18 10/16 1/16 8/18 6/18 2/18 1/18	– 8/32 0/32 – – – –	39/264 86/264 15/264 76/264 63/264 1/264 37/264	SJS/TEN	PCR-SSP, SBT
Shi (2017)[50]	Southern Han Chinese	Case–control	91	–	B*15:02 C*08:01 DRB1*12:02 A*24:02 B*15:11 B*15:02	39/56 42/55 29/54 17/56 4/56 19/132	28/179 38/177 45/176 28/178 0/179 28/179		SJS/TEN MPE	SBT
Shi (2021)[51]	China	Case–control	267	24.8 ± 17.8; 53.9%	B*38:02	18/145	10/179		MPE	SBT
Shirzadi (2015)[86]	Norway	Case–control	86	27; 34%	A*31:01 A*24:02	4/48 14/48	2/79 13/79		MPE, HSS	SSO
Sukasem (2018)[60]	Thailand	Case–control	38	44; 63.2%	B*15:02 B*15:21 B*40:01 B*46:01 B*58:01	17/38 2/38 5/38 8/38 8/38	11/271 4/271 41/271 64/271 22/271	71/470 2/470 58/470 122/470 57/470	SCARs	PCR-SSOP
Sun (2014)[52]	China	Case–control	17	6.9 ± 3.6; 64.7%	B*1502	3/11	2/18		SJS	SSP
Tassaneeyakul (2010)[61]	Thailand	Case–control	42	42.4 ± 17; 35.7%	B*15:02 B*15:21 B*38:02 B*40:01 B*46:01 B*58:01	37/ 42 2/42 2 /42 3/42 9/42 3/42	5/42 0/42 2/42 6/42 11/42 8/42		SJS/TEN	PCR-SBT, PCR SSP
Tan-Koi (2017)[77]	Chinese, Malays and Indians in Singapore	Case–control	91	–	B*15:02	13/13	3/26		SCARs	SBT

TABLE 1 (Continued)

Author	Country	Study design	Sample size (case)	Mean age ± SD; % of male	Assessed *HLA* variants	Variant allele in case (*n*/*N*)	Tolerant controls	Healthy controls	Outcomes	Genotyping method
Then (2011)[69]	Malaysian, Malaysia	Case–control	27	18.07; 33.3%	B*15:02	617	0/8	–	SCARs	SSP
Wang (2014)[53]	Han Chinese	Case–control	27	33; 41%	B*15:02 B*58:01	12/16 0/16	3/39 9/39		SJS/TEN	PCR-SBT
Wang (2011)[54]	Southern China mainland	Case–control	48	32 ± 16.8; 58.3%	B*15:02	19/48	11/80		SJS/TEN MPE	PCR-SSP
Wu (2010)[55]	Central China	Case–control	86	31.5 ± 16.5; 69.4%	B*15:02	11/36	4/50		SJS/TEN, MPE	PCR-SBT
Yuliwulandari (2017)[78]	Indonesia: Javanese and Sundanese	Case–control	12	34.3; 47%	B*15:02 B*15:21 B*38:02 B*40:01 B*58:01	8/12 2/12 0 0 0	4/17 1/17 0 1/17 0	54/236 33/236 25/236 17/236 27/236	SJS/TEN	SSOP
Zhang (2011)[56]	Mainland Han Chinese	Case–control	38	37.9 ± 18.3;0.43%	B*15:02	16/17	2/21	17/185	SJS/TEN	PCR-SSP, PCR-SBT

Abbreviations: ADR, adverse drug reaction; DFMH, digital fluorescence molecular hybridization; DIHS, drug-induced hypersensitivity syndrome; DRESS, drug reaction with eosinophilia and systemic symptoms; EEM, erythema exsudativum multiforme; HLA, human leukocyte antigen; HSS, hypersensitivity syndrome; MPE, maculopapular exanthema; MS, mass spectrometry; PCR-SBT, polymerase chain reaction sequencing-based typing; PCR-SSO, polymerase chain reaction-sequence specific oligonucleotide; PCR-SSOP, polymerase chain reaction-sequence specific oligonucleotide probe; PCR-SSP, polymerase chain reaction-sequence specific primers; RT-PCR, reverse transcription-polymerase chain reaction; SCARs, severe cutaneous adverse drug reactions; SD, standard deviation; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

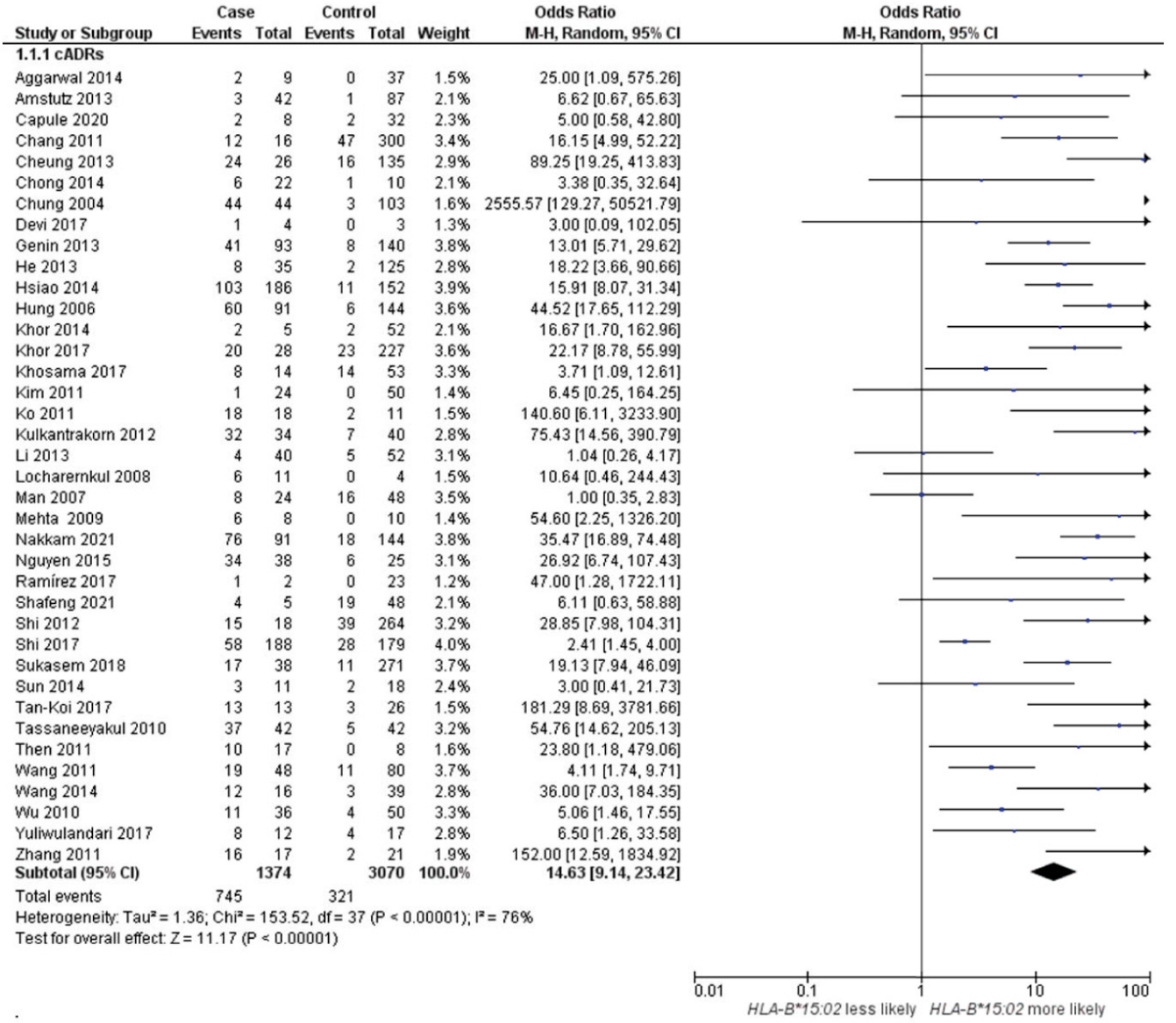

FIGURE 2 Forest plot for the association of *HLA-B*15:02* with carbamazepine-induced cutaneous adverse drug reactions. cADRs, cutaneous adverse drug reactions; HLA, human leukocyte antigen; M-H, Mantel–Haenssel method.

compared to controls in both Asian (OR 14.84; 95% CI 8.95–24.61; $p < 0.00001$) and Caucasian patients (OR 11.65; 95% CI 1.68–80.70; $p = 0.01$), although the risk was slightly higher in patients of Asian ethnicities (Figure 4).

Association of *HLA-B*15:21*, *HLA-B*38:02*, or *HLA-B*40:01* with CBZ-induced cADRs

It was found that only the *HLA-B*15:21* allele was associated with significantly increased risk of cADRs (OR 5.37; 95% CI 2.02–14.28; $p = 0.0008$) but the other alleles were not found to have any significant associations (for *HLA-B*38:02*: OR 0.92; 95% CI 0.46–1.83; $p = 0.81$; for *HLA-B*40:01*: OR 0.66; 95% CI 0.40–1.08; $p = 0.10$) (Figure 5).

Association of *HLA-B*46:01* or *HLA-B*58:01* with CBZ-induced cADRs

It was also found that neither *HLA-B*46:01* (OR 0.84; 95% CI 0.60–1.17; $p = 0.30$) nor *HLA-B*58:01* (OR 0.70; 95% CI 0.29–1.69; $p = 0.43$) allele was associated with significantly increased risk of cADRs as shown in Figure S1.

Association of *HLA-B*15:11*, *HLA-A*24:02*, or *HLA-A*31:01* with CBZ-induced cADRs

It was further found that both the *HLA-B*15:11* and *HLA-A*31:01* alleles were associated with significantly increased risk of cADRs (for *HLA-B*15:11*: OR 6.08; 95%

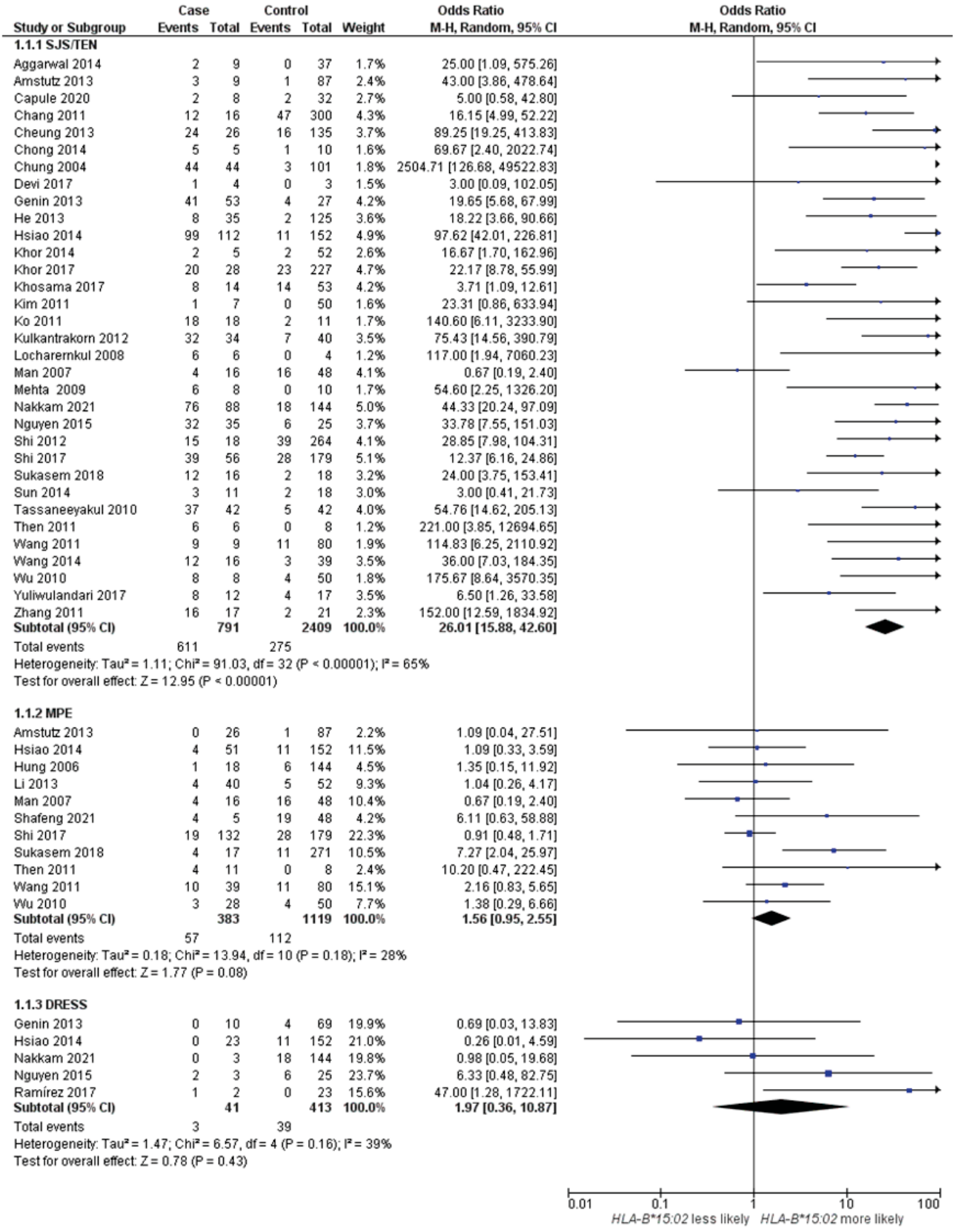

FIGURE 3 Forest plot for the association of *HLA-B*15:02* with carbamazepine-induced different forms of cutaneous adverse drug reactions. cADRs, cutaneous adverse drug reactions; DRESS, drug reaction with eosinophilia and systemic symptoms; HLA, human leukocyte antigen; M-H, Mantel–Haenssel method; MPE, maculopapular exanthema; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

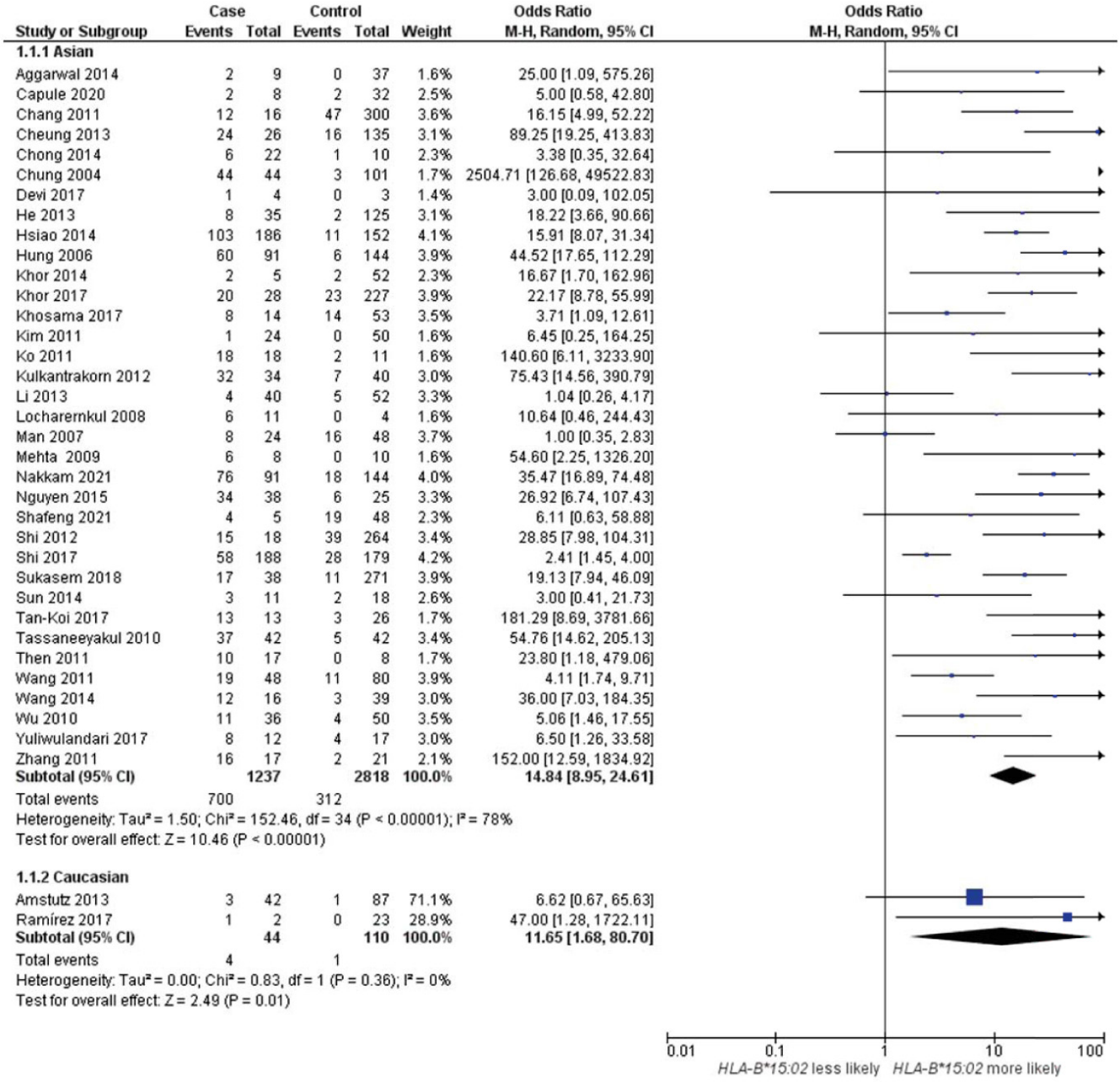

FIGURE 4 Forest plot for the association of *HLA-B*15:02* with carbamazepine-induced cutaneous adverse drug reactions in different ethnicities. cADRs, cutaneous adverse drug reactions; HLA, human leukocyte antigen; M-H, Mantel–Haenssel method.

CI 2.28–16.23; $p = 0.0003$; for *HLA-A*31:01*: OR 5.92; 95% CI 4.35–8.05; $p < 0.00001$) but the *HLA-A*24:02* allele was not found to have any significant association (OR 1.04; 95% CI 0.82–1.31; $p = 0.77$) (Figure 6).

Multivariate analysis between *HLA-B*15:02* and cADRs adjusted for gender and age

In the meta-regression analysis, the gender had a statistically significant impact on the OR of *HLA-B 15:02*, but there was no significant effect of age on the estimated OR of *HLA-B 15:02* (Figure S1). The studies that had a higher percentage of males in their sample had lower OR of *HLA-B 15:02* than other studies ($p = 0.0304$). When the variable age was incorporated into model 2, the performance of fitting was not better than model 1 (likelihood ratio test had p value >0.05). However, there was a trend showing the potential impact of variable age in model 2, whose F statistics resulted in a p value = 0.0605. The impact of gender was once again confirmed in model 2 by the permutation test (F and CE_{gender} had p values equal to 0.0605 and 0.0320, respectively) (Table S1).

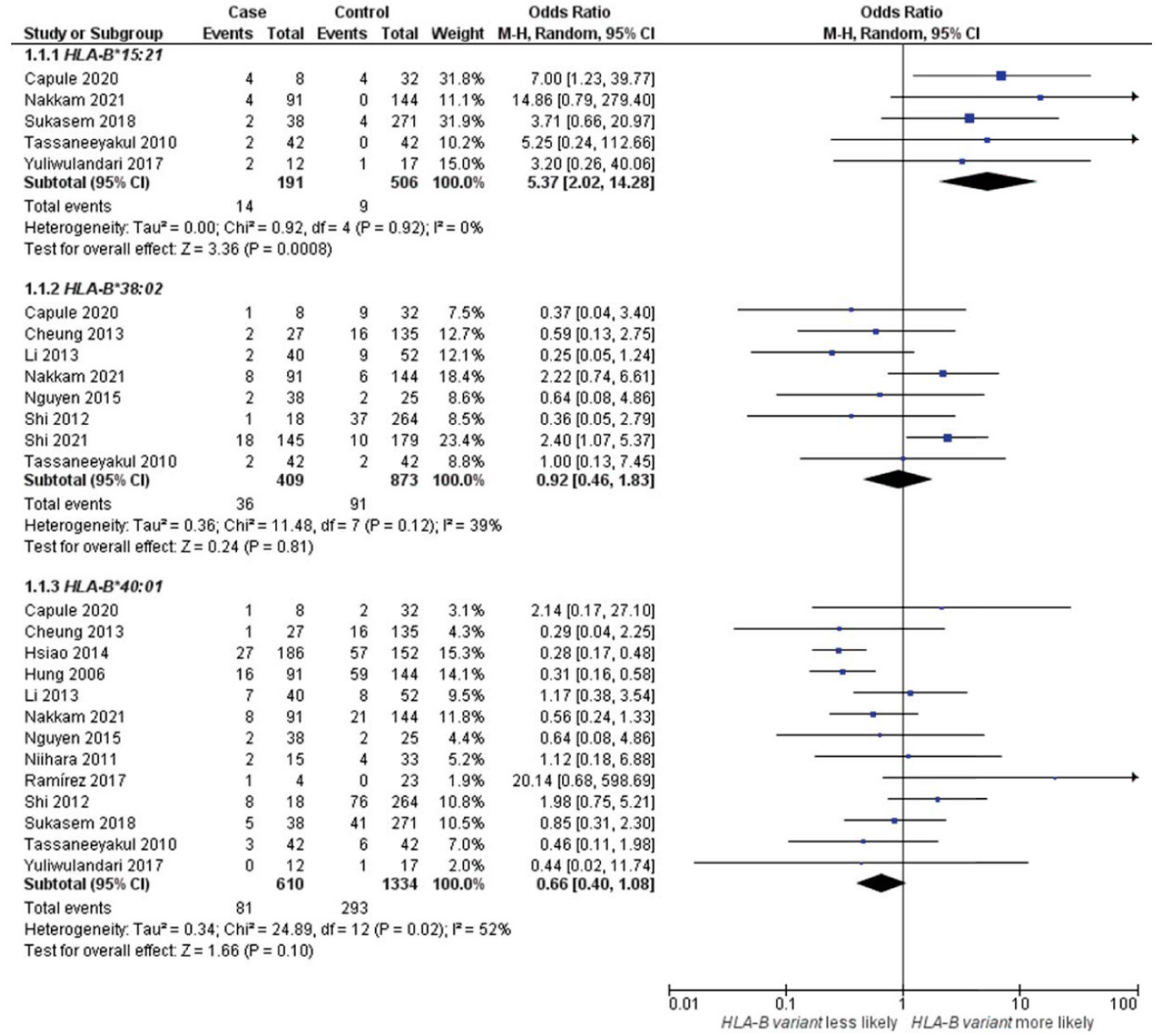

FIGURE 5 Forest plot for the association of *HLA-B*15:21*, *HLA-B*38:02* or *HLA-B*40:01* with carbamazepine-induced cutaneous adverse drug reactions. cADRs, cutaneous adverse drug reactions; HLA, human leukocyte antigen; M-H, Mantel–Haenssel method.

Heterogeneity, sensitivity, and publication bias

Since various *HLA* genetic models were used to assess the aggregated risk of cADRs, different degrees of heterogeneity (very low to high) were found in this analysis. However, it is assumed that in the case of a high level of heterogeneity, many confounding factors such as age, race, dose of CBZ, comorbidity, co-medications, molecular technologies applied to detect *HLA* variants, etc., might contribute to the high degree of heterogeneity. From the sensitivity analysis it was found that no single study affected either the pooled risk or level of heterogeneity. There was no publication bias as determined from the funnel plot (Figure S1).

DISCUSSION

Of nine *HLA* alleles, as investigated in this analysis, the results indicate that four *HLA* variants (*HLA-B*15:02*, *HLA-B*15:11*, *HLA-B*15:21*, and *HLA-A*31:01*) are strongly associated with increased risk of cADRs in patients taking CBZ. The highest strong association (~15-fold) is found for the patients carrying the *HLA-B*15:02* allele with CBZ-induced cADRs. These results were found predominantly from Asian studies (35 studies) compared to Caucasian studies (2 studies), indicating that Asian patients might be at greater risk than Caucasian patients. The results of the current analysis also firmly established that *HLA-B*15:02* is a phenotypic biomarker since it was strongly associated

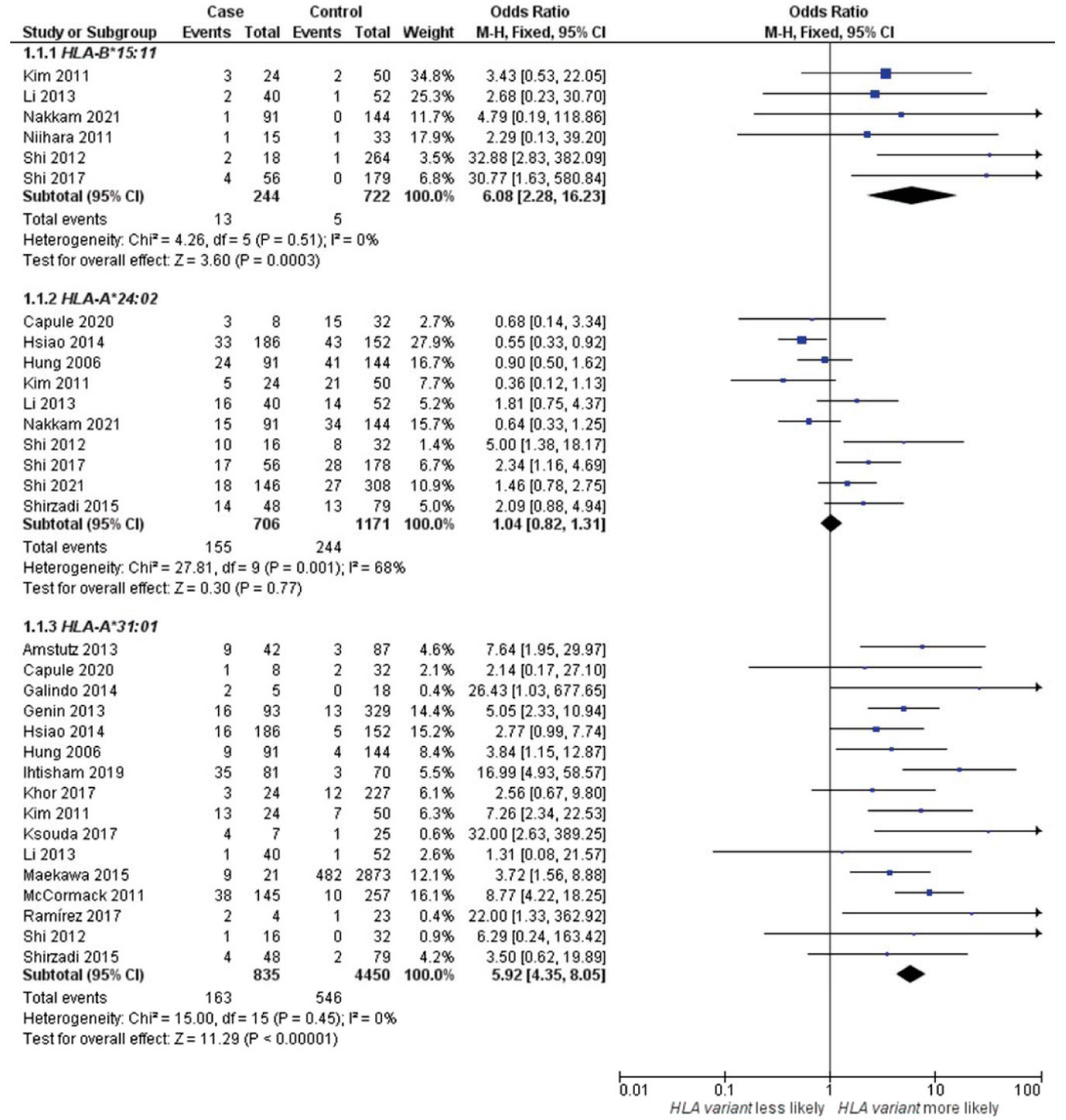

FIGURE 6 Forest plot for the association of *HLA-B*15:11*, *HLA-A*24:02*, or *HLA-A*31:01* with carbamazepine-induced cutaneous adverse drug reactions. cADRs, cutaneous adverse drug reactions; HLA, human leukocyte antigen; M-H, Mantel–Haenssel method.

with increased risk of CBZ-induced SJS or TEN (~26-fold) but not the other adverse events such as MPE or DRESS. These findings are consistent with previous meta-analyses and suggestions also.[1,11–13,17] Our findings may be considered superior to previous analyses in terms of power and robustness since the aggregated risk was measured from a relatively large sample size (total studies = 38, consisting of 1346 cases and 3138 controls).

In addition, the strong associations of *HLA-B*15:11* and *HLA-A*31:01* with CBZ-induced cADRs as found in the present analysis are also in line with the findings of previous meta-analyses, though our findings were aggregated from a larger sample size.[5,11,13,16] Although no meta-analysis was found in the literature, the findings of our study indicate a strong relationship between the *HLA-B*15:21* allele and CBZ-induced cADRs and may

be considered a novel insight. However, it is important to note here that the prevalence of this allele is very low in major populations (~0.0003% in European Caucasians, ~0.01% in Chinese, ~0.03% in South Asians), and is not reported in African and East Asian populations, which may restrict assessment of such associations in these populations.

Previous meta-analyses found *HLA-A*24:02*, *HLA-B*40:01*, *HLA-B*46:01*, and *HLA-B*58:01* as strong protective biomarkers; however, the present analysis found a trend towards reduction of risk but did not reach statistical significance, suggesting conducting more research is needed to establish such associations. A meta-analysis conducted by Wang et al.[5] found a strong protective association between *HLA-B*40:01*, *HLA-B*46:01*, or *HLA-B*58:01* with CBZ-induced SJS/TEN in Asian populations. Another meta-analysis conducted by Grover et al.[11] only found a significant protective association between *HLA-B*40:01* allele carriers and CBZ-induced cADRs in Asian patients. Both of these analyses were conducted on a relatively small sample size restricted to Asian populations. In contrast, our analyses included a relatively large sample size compared to previous analyses and was not restricted to any ethnicities. Although there was a trend towards a reduction in the risk of cADRs for the patients who carried *HLA-B*40:01*, *HLA-B*46:01*, or *HLA-B*58:01* allele as revealed in the present analysis, future studies are warranted to confirm these findings.

The cADRs (e.g., SJS, TEN, MPE, or DRESS) could be minimized or eradicated considerably if *HLA*-specific genetic information is known before or during the prescription of CBZ. Since our results robustly established strong associations of *HLA-B*15:02*, *HLA-B*15:11*, *HLA-B*15:21*, and *HLA-A*31:01* with CBZ-induced cADRs, clinicians and policymakers should consider our findings to generate national and international guidelines for the implementation of precision medicine of CBZ therapy by proposing a panel of *HLA* genetic testing as supported by this study. Although some countries, including Thailand, have national guidelines for screening *HLA-B*15:02* before CBZ therapy, other risk alleles such as *HLA-B*15:11*, *HLA-B*15:21,* and *HLA-A*31:01* are usually not uniformly covered in the guidelines.[1] The findings of the present analysis reinforce the consideration of a panel of *HLA* genetic variants (i.e., *HLA-B*15:02*, *HLA-B*15:11*, *HLA-B*15:21*, and *HLA-A*31:01*) for the reduction of CBZ-induced cADRs substantially and should revise the national and international guidelines accordingly.

Besides, the impact of gender on the risk of severe cutaneous adverse drug reactions (SCARs) was also reported by other authors[25–27] and is consistent with the findings of the present analysis. Hsu et al.[28] found a statistically significant sensitivity to SCARs in females compared to males in the American population. Kannenberg et al.[29] observed the dominance of females over males in SCARs patients in the South African population. The same result was also found in Japanese patients.[30] The impact of gender can be hypothetically explained by the hormonal or genetic differences between males and females.[26] However, further studies are needed in order to clearly understand the explanatory biological processes.

The present analysis observed a trend towards the impact of variable age on SCARs. Many authors also confirmed the role of age on the development of SCARs.[31–33] Even so, most researchers believe that the effect of age was actually just a consequence of the fact that older patients tend to have more drugs and chronic diseases than younger ones. Therefore, older patients might have a higher possibility of developing SCARs.

CBZ is generally administered as long-term therapy for the clinical conditions for which it is indicated, therefore safety requirements should be of high priority. Since certain *HLA* variants cause severe adverse events, as evidenced in this analysis, mandating considering either preemptive or reactive genetic screening of selective *HLA* alleles (*HLA-B*15:02*, *HLA-B*15:11*, *HLA-B*15:21*, and *HLA-A*31:01*) among populations at high risk, especially those from Asian countries, is recommended to optimize the safety of CBZ. Since the prevalence of *HLA-B*15:02* is comparatively high in Asian populations, particularly in Southeast populations compared to Caucasians as described elsewhere[1] and is also supportive as found in this analysis (~25% vs. ~3%), the pharmacogenomic testing of *HLA-B*15:02* would be cost-effective in these specific populations before prescribing CBZ, which is in line with recommendations of a recent cost-effectiveness analysis.[34] Although the *HLA-A*31:01* allele is considered a universal biomarker, its prevalence is slightly higher in European populations compared to Asian populations, as reported elsewhere.[1] Other strongly associated alleles (e.g., *HLA-B*15:11* and *HLA-B*15:21*) have a comparatively low prevalence in Asian populations (~2% for *HLA-B*15:11* and ~3% for *HLA-B*15:21*) as found in this analysis. These alleles were not reported in European populations, which is also supportive from a recent comprehensive review of *HLA*.[1]

Some studies suggest that the pharmacogenomic testing of *HLA-B*15:02* would be more cost-effective if the prevalence of this allele was more than 5% or at least greater than 2.5%.[1,35,36] This suggestion might be applicable to other *HLA* risk alleles (e.g., *HLA-B*15:11* or *HLA-B*15:21*), although this has not yet been quantified. Despite the cost-effectiveness issue of pharmacogenetic

testing, there is a strong need to consider some other factors, such as ethical, legal, and social issues (ELSI), pharmacogenomics education, and so on, before implementation of such pharmacogenetic screening in real clinical settings.[1,12] Many countries, including Thailand, are advancing precision medicine initiatives, especially in Asian regions. Thailand has become the focal point for innovating new technologies to accelerate the translation of pharmacogenomics into routine clinical practice.[37] The innovation of the PPM card, which is a pharmacogenomics identity card from the Division of Pharmacogenomics and Personalized Medicine (PPM) of Mahidol University in Thailand led by Dr. Chonlaphat Sukasem as described elsewhere[1,38] may expedite the implementation of precision medicine to the bedside and may be considered in other parts of the world for advancing precision medicine initiatives.

There are some limitations of this analysis. Although the present analysis focused on and addressed nine *HLA* variants with CBZ-induced cADRs, other potential *HLA* risk alleles (e.g., *HLA-B*57:01*, *HLA-Cw*08:01*, and *HLA-DRB1*12:02*) were not included in this analysis which may increase the risk of developing cADRs for patients taking CBZ.[1,39] Further, the clinical efficacy and safety of CBZ may also be affected by the genetic polymorphisms of *CYP3A4/5*, *CYP2C8*, *ABCB1*, etc., which were not considered in this analysis.[40,41]

CONCLUSIONS

The results of this study show a strong association between *HLA-B*15:02*, *HLA-B*15:11*, *HLA-B*15:21*, or *HLA-A*31:01* allele with CBZ-induced cADRs. The most substantial, robust evidence has been found between *HLA-B*15:02* allele and CBZ-induced SJS/TEN. Pharmacogenetic testing of particular *HLA* alleles before initiation of CBZ therapy may be beneficial to patients and may help to eradicate cADRs substantially. Such *HLA* genetic status information may assist clinicians in determining the optimal therapy of CBZ.

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

ETHICAL APPROVAL

Ethical approval was not required since the study comprised a meta-analysis of published results.

AUTHOR CONTRIBUTIONS

M.B. wrote the manuscript. C.S. and M.B. designed the research. C.S., M.B., M.E., and J.S. performed the research. M.B., M.E., and J.S. analyzed the data.

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