

Unraveling the genetic link: an umbrella review on HLA-B*15:02 and antiepileptic drug-induced Stevens–Johnson syndrome/toxic epidermal necrolysis

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Purpose This umbrella review was conducted to summarize the association between HLA*1502 allele with antiepileptic induced Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

Methods Pubmed, Scopus and EMBASE were searched for eligible reviews in May 2023. Two authors independently screened titles and abstracts and assessed full-text reviews for eligibility. The quality of meta-analyses and case–control studies was appraised with Assessing the Methodological Quality of Systematic Reviews 2 and Newcastle–Ottawa Scale, respectively. Narrative summaries of each antiepileptic drug were analyzed. Preestablished protocol was registered on the International Prospective Register of Systematic Reviews Registry (ID: CRD42023403957).

Results Included studies are systematic reviews, meta-analyses and case–control studies evaluating the association of HLA-B*1502 allele with the following antiepileptics. Seven meta-analyses for carbamazepine, three meta-analyses for lamotrigine (LTG), three case–control studies for oxcarbazepine, nine case–control studies for phenytoin and four case–control studies for phenobarbitone were included. The findings of this umbrella review suggest that there is a strong association between HLA-B-1502 with SJS/TEN for carbamazepine and oxcarbazepine and a milder association for lamotrigine and phenytoin.

Conclusion In summary, although HLA-B*1502 is less likely to be associated with phenytoin or lamotrigine-induced SJS/TEN compared to carbamazepine-induced SJS/TEN, it is a significant risk factor that if carefully screened, could potentially reduce the development of SJS/TEN. In view of potential morbidity and mortality, HLA-B*1502 testing may be beneficial in patients who are initiating lamotrigine/phenytoin therapy. However, further studies are required to examine the association of other alleles with the development of SJS/TEN and to explore the possibility of genome-wide association studies before initiation of treatment. *Pharmacogenetics and Genomics* 34: 154–165 Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.

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Keywords: carbamazepine, HLA, lamotrigine, phenytoin, Stevens–Johnson syndrome, toxic epidermal necrolysis

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Introduction

Carbamazepine is recommended as a first-line treatment for epilepsy [1] and trigeminal neuralgia [2]. However, its use is associated with several life-threatening cutaneous adverse reactions, including Steven–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) [3]. While initially considered idiosyncratic, a significant finding in 2004 revealed a strong association between the HLA-B*15:02 allele and the development of SJS/TEN in carbamazepine users [4]. Subsequent studies have consistently confirmed this association, particularly, in populations with a high incidence of HLA-B*15:02, such as Asians [5,6].

Given these findings, it is widely recommended that patients with ancestral ties to high-risk populations should undergo HLA-B*15:02 testing before initiating carbamazepine treatment. In the 2017 Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline, both carbamazepine and oxcarbazepine should be avoided in patients who are HLA-B*15:02 positive due to the greater risk of SJS/TEN [7,8]. In the 2020 CPIC Guidelines, phenytoin should be avoided, unless the benefits outweigh the risk, in patients with the allele. Apart from these two guidelines, currently, no other established guidelines recommend specific drugs for patients who test positive for HLA-B*15:02.

In the presence of HLA-B*15:02 positive allele, physicians need to consider alternative antiepileptics. However, it remains unclear whether the association extends to other structurally similar antiepileptics such

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as phenytoin and lamotrigine [9]. Notably, in view of positive but limited studies suggesting an association between phenytoin and SJS/TENs, CPIC supports the US Food and Drug Administration recommendations to avoid these agents as substitutes for carbamazepine in individuals who test positive for HLA-B*15:02 [10]. Hence, to make a recommendation about the use of implicated antiepileptics in patients who are known to have the HLA-B*15:02 allele, we conducted a systematic and umbrella review. This review aimed to determine the strength of the association between the HLA*1502 allele and SJS/TEN in patients who are administered implicated antiepileptics.

Methods

This systematic review was performed and reported in compliance with Preferred Reporting Items for Systematic Reviews and Meta Analysis guidelines [11] and was registered with the International Prospective Register of Systematic Reviews (CRD42023403957).

Search strategy and selection criteria

An electronic search was conducted on the following databases: *Pubmed*, *Scopus* and *Embase*. The search included studies published from inception until 15 May 2023. The key search terms were 'adverse drug reaction', 'Stevens-Johnson syndrome', 'SJS', 'TEN', 'toxic epidermal necrolysis', 'HLA', 'antiseizure', 'anticonvulsant', 'antiepileptic', 'AED', 'phenytoin', 'valpro*', 'carbamazepine', 'oxcarbazepine', 'lamotrigine' and 'phenobar*'. These search keys were combined using Boolean operators. No language or article-type filters were applied during the search process. (See Appendix A, Supplemental digital content 1, <http://links.lww.com/FPC/B479>) To supplement the electronic search, reference lists of the selected studies were examined, and relevant publications were added to the final search results.

Any systematic review, meta-analysis or case-control studies that examined the relationship between SJS/TEN and HLA-B*15:02 in patients who received an aromatic antiepileptic medication were included in the study. Excluded from this study were publications that examined any other adverse effects apart from SJS/TEN and narrative reviews.

Two reviewers (K.M.T. and J.J.L.Y.) independently assessed the titles and abstracts of all search entries to exclude irrelevant studies. The full texts of the remaining studies were then carefully examined against the inclusion and exclusion criteria. Any disagreements regarding study eligibility were resolved through arbitration by a third reviewer (C.W.Y.L.).

Quality assessment

The Assessing the Methodological Quality of Systematic Reviews (AMSTAR-2) tool [12] was utilized to assess the methodological quality of the

meta-analyses included in this umbrella review. AMSTAR-2 is a revised 16-item instrument designed to identify high-quality systematic reviews based on various criteria, including the protocol, comprehensiveness of the literature search, justification for study exclusions, assessment, and consideration of risks of bias, appropriateness of meta-analytic methods and presence of publication bias. Each criterion was rated as a 'Yes', 'Partial Yes', 'No', or 'Not conducted'.

If a meta-analysis was repeated due to the availability of newer publications or the absence of a meta-analysis, the Newcastle-Ottawa Scale (NOS) was used to assess the methodological quality of observational studies that were included in the meta-analysis. NOS is an assessment method developed to assess the quality of nonrandomized studies using a 'star system' which is judged on three broad perspectives: the selection of the study groups; the comparability of the groups and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively. The NOS has been shown to have similar reliability to the Risk of Bias in Non-Randomized Studies of Interventions [13].

Data extraction

Data were extracted independently by two authors (K.M.T. and J.L.Y.) and entered into a standardized format on an Excel file (Microsoft Excel for Mac, Version 16.69.1). For each study included in the review, the following data, if available, was extracted: author, year of publication, type of publication, geographical location of study, sample size and results (number of patients tested HLA*B15:02 in case and control groups).

Statistical methods

Statistical analyses were performed using the 'Metafor' and 'Metaumbrella' packages in Rstudio 2022.07.1. Forest plots were constructed for all included meta-analyses. From this plot, the most recent articles and the articles with the highest number of participants were identified. The references of these publications were then examined to see if the most recent observational studies were included. If more recent observational studies were found, a meta-analysis would be performed.

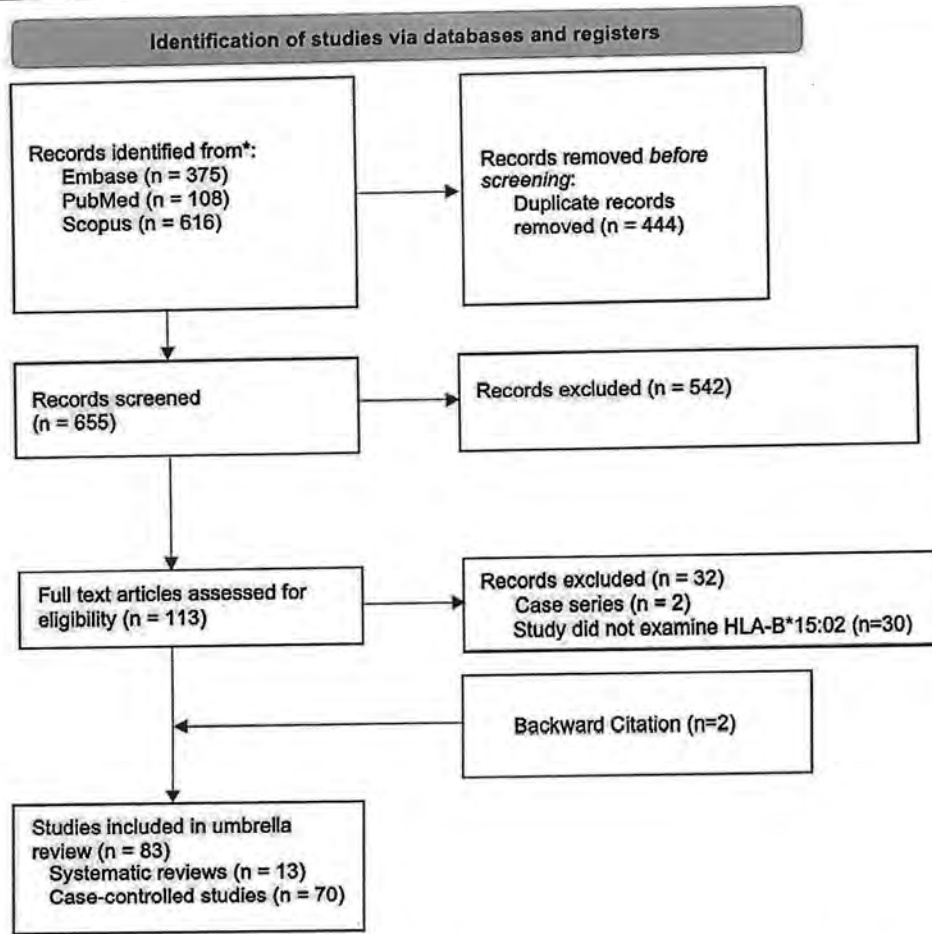
For meta-analyses, random-effects modeling was used for all pooled data. Dichotomous data were pooled using the Mantel-Haenszel odds ratio (OR) with 95% confidence intervals (CIs). The I^2 test was used to estimate the degree of statistical heterogeneity. When more than six studies were included, a funnel plot was plotted to evaluate for publication bias as depicted in Fig. 1 under 'Supporting Information'.

Results

Search results

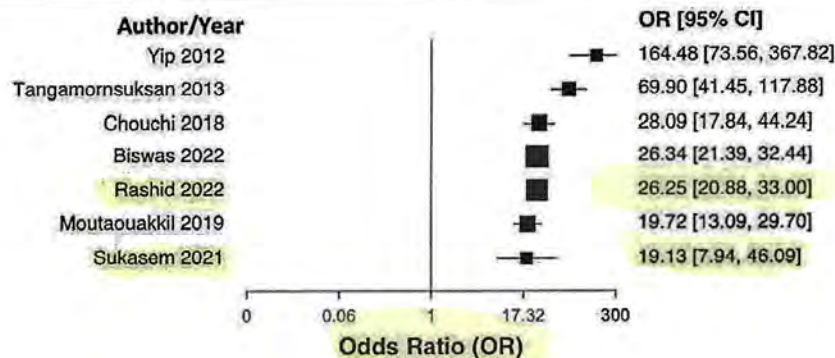
A total of 1099 publications were identified during the initial search. However, 444 duplicates were removed

Fig.1



Funnel plot for meta-analysis of phenytoin. Eggers test for meta-analysis of phenytoin showed an intercept of 1.22 with a *P*-value of 0.948, indicating that there is no evidence of publication bias.

Fig. 2



Study identification PRISMA Flow Diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta Analysis.

(Fig. 2). After screening through the title and abstracts of 655 publications, 113 publications (18 meta-analyses, 93 case-controlled studies and 2 case series) were identified to be meeting the inclusion and exclusion criteria for full-text review. After a full-text review, 32 articles were excluded. Further hand-searching of journals led to the addition of 2 case-controlled studies, and a total of 83 studies (13 meta-analyses and 70 case-controlled studies) were included in the umbrella review.

Study characteristics

The selected articles were published between 2008 and 2023. A total of 83 studies were included in this umbrella review. Each antiepileptic was analyzed separately. For carbamazepine, there were 42 case-control studies [14–54] and 7 meta-analyses [41,55–60]. For lamotrigine, there were 30 case-control studies [16,18,20,28,36,41,44,48,51,61–74] and three meta-analyses [68,70,72]. As all the case-control studies for carbamazepine and lamotrigine were included in the meta-analyses, we only analyzed the results of the meta-analyses.

For oxcarbazepine, there were three case-control studies [22,31,75] and two meta-analyses [59,76]. For phenytoin, there were nine case-control studies [21,22,29,51,77–81] and three meta-analyses [56,70,82]. For phenobarbital, there were four case-control studies [18,31,51,83] and one meta-analysis [56]. As the recent case-control studies for the oxcarbazepine, phenytoin and phenobarbital were not represented in their recent meta-analyses, we repeated the meta-analyses to include all studies. The quality of meta-analyses was appraised with AMSTAR-2, and the quality of case-control studies was appraised with NOS as shown in Table 1 and Table 2, respectively under ‘supporting information’. Characteristics of the studies included in this article are summarized in Table 3 and Table 4 under ‘supporting information’.

Carbamazepine and HLA-B*15:02

A total of seven relevant meta-analyses were identified [41,55–58,60,84]. Four of these studies were found to be of critically low quality. However, the most recent and largest studies [55,56] were rated as high in quality [12] (Table 1 under ‘supporting information’).

All seven meta-analyses consistently demonstrated a strong association between HLA-B*15:02 and carbamazepine-induced SJS/TEN, with ORs ranging from 19.1 (95% CI, 7.9–46.1) to 164.5 (95% CI, 73.6–367.8). These results are visually depicted in Fig. 3.

Notably, the ORs presented in Fig. 3 vary significantly. This is likely due to the nature of older studies [60,84] having smaller sample sizes, which can lead to over/underestimation of effect sizes. The most recent studies from Biswas [55] and Rashid [56] include a larger

sample size and, therefore, are more likely to represent a more precise measure of the true population risk. The most recent study conducted by Biswas *et al.* [55] encompassed 38 studies involving 1346 cases, 2504 tolerant controls and 564 population controls. Based on this analysis, the OR for developing carbamazepine-induced SJS/TEN in the context of HLA-B*15:02 is 26.3 (95% CI, 21.4–32.4).

Lamotrigine and HLA-B*15:02

A total of three meta-analyses [68,70,72] examined the relationship between HLA-B*15:02 and lamotrigine-induced SJS/TEN. The studies were published between 2015 and 2018 and involved exclusively Asian patients. No studies relevant to this question have been added to the literature since the publication by Deng *et al.* in 2018 [72]. Of these studies, two were assessed to be of low quality [68,70] and one was assessed to be of moderate quality [72] (Table 1 under ‘supporting information’).

All three studies consistently demonstrated a strong association between HLA-B*15:02 and lamotrigine-induced SJS/TEN, with ORs ranging from 2.55 (95% CI, 1.29–5.04) to 4.83 (95% CI, 1.27–18.45) as visually depicted in Figure 4. The study conducted by Deng *et al.* in 2018 [72] reported the largest sample size. In this study which included the data from seven studies comprising of 54 cases of lamotrigine-induced SJS/TEN and 313 controls, a significant association between HLA-B*15:02 and lamotrigine-induced SJS/TEN was observed (OR of 2.55; 95% CI, 1.29–5.04).

Oxcarbazepine and HLA-B*15:02

Two meta-analyses [59,76] were identified for oxcarbazepine as shown in Figure 5. In 2018, Liu *et al.* [76] pooled the data from three studies, involving 154 patients, and found a positive association between HLA-B*15:02 and severe cutaneous adverse reactions (SCAR) induced by oxcarbazepine (OR, 18.13; 95% CI, 6.77–48.56). In the same year, Tangamornsuksan also reported a positive association between HLA-B*15:02 and oxcarbazepine-induced SJS/TEN based on two studies, involving 142 patients (OR, 30.2; 95% CI, 3.45–264).

The study by Tangamornsuksan *et al.* [59] examined SJS/TEN [as opposed to Liu which also examined SCAR which includes not only SJS/TEN but also drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)] but was found to have missed one study, we performed a repeat meta-analysis using the findings of three case-controlled studies involving 346 subjects [22,31,75]. In this analysis, a strong positive association was again found between HLA-B*15:02 and oxcarbazepine-induced SJS/TEN (OR, 29.23; 95% CI, 10.71–79.79). No significant heterogeneity was detected (I^2 test = 0%).

Table 1 AMSTAR-2 of meta-analyses included in the study

	Authors	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Conclusion
CBZ	Biswas <i>et al.</i> 2022 [55]	Y	Y	Y	Y	Y	Y	Y	Partial Y	Y	N	Y	Y	Y	Y	Y	Y	High
	Rashid <i>et al.</i> 2022 [56]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	High
	Sukasem <i>et al.</i> 2021 [41]	Y	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	Y	Critically low
	Moutaouakil <i>et al.</i> 2019 [57]	Y	Partial Y	N	Partial Y	N	N	N	N	N	N	Y	Y	Y	N	N	Y	Critically low
	Chouchi <i>et al.</i> 2018 [58]	Y	Y	Y	Y	Y	Y	Y	Partial Y	N	N	Y	N	N	Y	Y	Y	Critically low
	Tangamornsuksan <i>et al.</i> 2013 [84]	Y	N	N	Partial Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Low
	Yip <i>et al.</i> 2012 [60]	Y	Y	Y	Y	Y	N	Y	Y	N	N	Y	N	N	Y	N	N	Critically low
																		Moderate
LTG	Deng <i>et al.</i> 2018 [72]	Y	Partial Y	N	Partial Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Low
	Zeng <i>et al.</i> 2015 [68]	Y	N	N	Partial Y	N	Y	Partial Y	Partial Y	Y	N	Y	Y	Y	Y	Y	Y	Low
	Li <i>et al.</i> 2015 [70]	Y	N	Y	Y	Y	Y	N	Partial Y	Partial Y	N	Y	N	Y	Y	Y	Y	Low
OXC	Liu <i>et al.</i> 2018 [76]	Y	N	N	Partial Y	Y	Y	Y	Y	N	N	Y	N	N	Y	Y	Y	Critically low
	Tangamornsuksan <i>et al.</i> 2018 [59]	Y	N	Y	Partial Y	Y	Y	Y	Y	Y	N	Y	N	N	Y	N	N	Critically low
PHT	Li <i>et al.</i> 2015 [70]	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	N	N	Y	Y	Y	Critically low
	Phung <i>et al.</i> 2021 [82]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	High
	Rashid <i>et al.</i> 2022 [56]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	High
PB	Rashid <i>et al.</i> 2022 [56]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	High

CBZ, Carbamazepine; LTG, Lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin.

Table 2 NOS of case-control studies for oxcarbazepine, phenytoin and phenobarbital included in the study

	Authors	Selection				Comparability		Exposure			Score	Quality
		Q1	Q2	Q3	Q4	Q1	Q2	Q1	Q2	Q3		
OXC	Hung <i>et al.</i> 2010 [22]	1	1	0	1	1		1	1	1	7	Good
	Sun <i>et al.</i> 2014 [31]	1	1	1	1	1		1	1	1	8	Good
	Chen <i>et al.</i> 2017 [75]	1	1	0	1	1		1	1	1	7	Good
PHT	Lochareonkul <i>et al.</i> 2008 [29]	1	1	0	1	1		1	1	1	7	Good
	Devi <i>et al.</i> 2018 [21]	1	1	1	1	1		0	1	1	7	Good
	Hung <i>et al.</i> 2010 [22]	1	1	1	1	1		0	1	1	7	Good
	Wang <i>et al.</i> 2014 [51,84]	1	1	1	1	1		0	1	1	7	Good
	Manuyakorn <i>et al.</i> 2020 [77]	1	1	1	1	1		0	1	1	7	Good
	Sukasem <i>et al.</i> 2020 [78]	1	1	1	1	1		0	1	1	7	Good
	Yampayon <i>et al.</i> 2017 [79]	1	1	1	1	1		0	1	1	7	Good
	Kwan <i>et al.</i> 2014 [80]	1	1	1	1	1		0	1	1	7	Good
PB	Su <i>et al.</i> 2019 [81]	1	1	1	1	1		0	1	1	7	Good
	Sun <i>et al.</i> 2014 [31]	1	1	1	1	1		1	1	1	8	Good
	Wang <i>et al.</i> 2014 [51,84]	0	1	0	1	1		1	1	1	6	Fair
	Manuyakorn <i>et al.</i> 2016 [83]	1	1	0	1	1		1	1	1	7	Good
	Cheung <i>et al.</i> 2013 [18]	0	1	0	1	2		1	1	1	7	Good

CBZ, Carbamazepine; LTG, Lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin.

Phenytoin and HLA-B*15:02

Three meta-analyses [56,70,82] investigated the association between HLA-B*15:02 and phenytoin-induced SJS/TEN as visually depicted in Figure 6a. All three studies found a positive association between HLA-B*15:02 and phenytoin induced SJS/TEN (OR, 1.99; 95% CI, 1.28–3.10 and 3.15 (95% CI, 1.67–5.94). The most

recently published meta-analysis by Rashid *et al.* 2022 [56] included a study that examined the association of all SCAR and not SJS/TEN alone, explaining the lower OR compared to the other two meta-analyses.

As this may potentially affect the result of the study, we repeated the meta-analysis from 13 case-control studies

Table 3 Characteristic of included studies included for Umbrella review of HLA-B*1502 and Stevens–Johnson syndrome/toxic epidermal necrolysis

Citations	Number of studies included	Sample size	Population type	AEDs involved	Quality of study (AMSTAR-2)
Yip 2012 [60]	23 case-control studies	2275	Asian	CMZ	Critically low
Tangamornsuan 2013 [59]	16 case-control studies	777	Thailand	CMZ	Low
Zeng 2015 [68]	4 case-control studies	140	Chinese	LTG	Low
Li 2015 [70]	9 case-control studies	480	All countries	PHT, LTG	Low
Chouchi 2018 [58]	9 case-control studies	929	All countries	CMZ	Critically low
Deng 2018 [72]	11 case-control studies	367	Asian (Chinese, Korean, Thai)	LTG	Moderate
Moutaouakkil 2019 [57]	23 case-control studies	960	China, Malaysia, Thailand	CMZ	Critically low
Sukasem 2021 [41]	Case-control study	309	Thailand	CMZ, LTG, PHT, PB	Critically low
Phung 2022 [82]	11 case-control studies	1389	All countries	PHT	High
Biswas 2022 [55]	46 case-control studies	3200	All countries	CMZ	High
Rashid 2022 [56]	21 case-control studies	3004	All countries	CMZ, PHT, LTG, PB	High

CBZ, Carbamazepine; LTG, Lamotrigine; PB, phenobarbital; PHT, phenytoin.

Table 4 Characteristic of studies included for meta-analysis of HLA-B*1502 and Stevens–Johnson syndrome/toxic epidermal necrolysis

Citation	Participants	Controls, phenotype	Population type	AEDs involved	Quality of study (NOS)
Locharernkul 2008 [29]	16 cases	Antiepileptic drug-tolerant controls	Thailand	PHT	Good
Hung 2010 [22]	50 controls	Antiepileptic drug-tolerant controls	China	PHT, LTG, OXC	Good
	35 cases				
Cheung 2013 [18]	273 controls	Antiepileptic drug-tolerant controls	Hong Kong Chinese	PHT, CBZ, LTG	Good
	55 cases				
Kwan 2014 [80]	275 controls	Antiepileptic drug-tolerant controls	Hong Kong Chinese	PHT, CBZ, LTG, PB	Good
	55 cases				
Wang 2014 [51,84]	275 controls	ADR-tolerant	China	CMZ, OXC, PHT, LTG, PB	Good
	10 cases				
Sun 2014 [31]	50 controls	32 Antiepileptic drug-tolerant controls	China	CMZ, OXC, PB, LTG	Good
	17 cases				
Tassaneeyakul 2016 [85]	70 controls	38 Healthy volunteers	Thailand	PHT	Good
	39 cases				
Manuyakorn 2016 [83]	92 controls I	PB-tolerant	Thailand	PB	Good
	47 cases				
Chen 2017 [75]	54 controls	OXC-tolerant	Taiwan Chinese and Thai	OXC	Good
	50 cases				
Chang 2017 [74]	110 controls	32 PHT-tolerant and 300 healthy control	Malay	PHT	Good
	16 cases				
Yampayon 2017 [79]	332 controls	PHT-tolerant	Thailand	PHT	Good
	15 cases				
Devi 2018 [21]	100 controls	PHT-tolerant	India	PHT	Good
	8 cases				
Su 2019 [81]	8 controls	PHT-tolerant	Asian	PHT	Good
	65 cases				
Manuyakorn 2020 [77]	367 controls	PHT-tolerant	Thai	PHT	Good
	22 cases				
Sukasem 2020 [78]	60 control	PHT-tolerant	Thai	PHT	Good
	88 cases				
Sabourirad 2021 [61]	70 control	Antiepileptic drug-tolerant controls	Iranian	PHT, LTG	Good
	36 cases				
	37 control				

CBZ, Carbamazepine; LTG, Lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin.

[18,21,22,29,61,74,77–81,86,85] from our database. All studies show a significant association found between HLA-B*15:02 and SJS/TEN in patients on phenytoin (OR, 3.00; 95% CI, 1.65–2.47; I^2 , 64%; $P < 0.01$) as depicted in Figure 6b. All the 13 studies were on Asian populations, including Thais, Han Chinese, Malays and Indians. There was moderate heterogeneity ($I^2 = 64\%$) for this analysis.

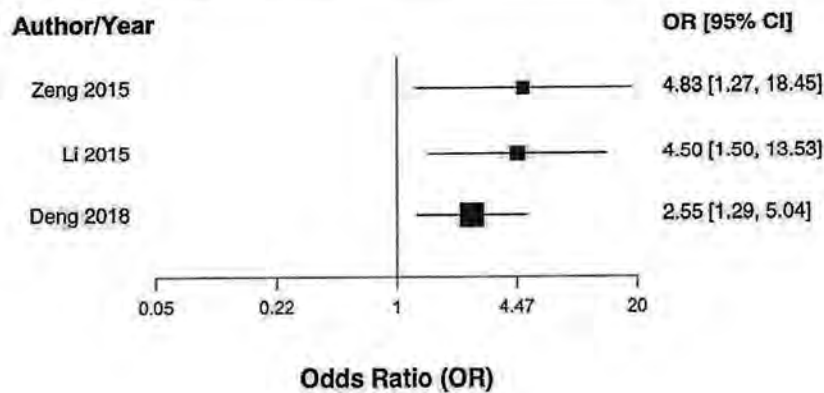
A subgroup analysis was performed for Han Chinese and Thai to explore the heterogeneity observed. This analysis found that for both Han Chinese and Thais,

HLA-B*15:02 was associated with SJS/TENS in patients administered phenytoin (Han Chinese—OR, 3.4; 95% CI, 1.39–8.43; $I^2 = 73\%$; $P = 0.01$; Thais—OR, 3.33; 95% CI, 1.04–10.66; $I^2 = 59\%$; $P = 0.04$).

Phenobarbital and HLA-B*15:02

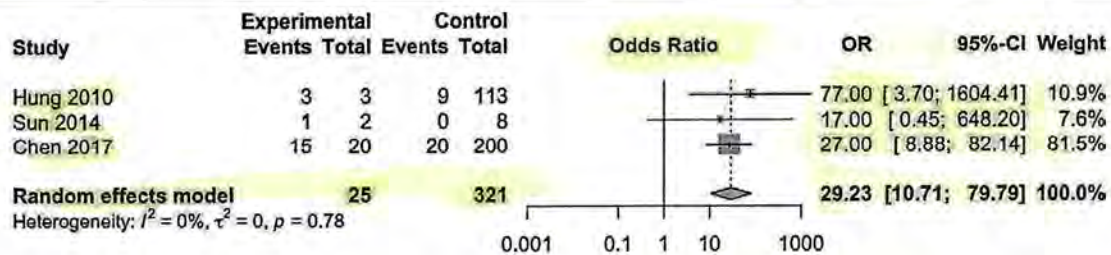
The study identified one meta-analysis [54] which examined the relationship between HLA-B*15:02 and SJS/TEN. However, as this study examined all cutaneous adverse reactions, the decision was made to repeat the meta-analysis.

Fig. 3



Umbrella review of carbamazepine, HLA-B*1502 and SJS/TEN. SJS/TEN, Stevens–Johnson syndrome/toxic epidermal necrolysis.

Fig. 4



Umbrella review of lamotrigine, HLA-B*1502 and SJS/TEN. SJS/TEN, Stevens–Johnson syndrome/toxic epidermal necrolysis.

This updated meta-analysis included three case-controlled studies involving a sample size of 67 patients and did not show an association between HLA-B*15:02 and phenobarbital-induced SJS/TEN (OR, 2.89; 95% CI, 0.36–22.97) as depicted in Figure 7. No significant heterogeneity was detected (I^2 test = 0%). However, this result should be interpreted with caution as there were limited studies [87].

Discussion

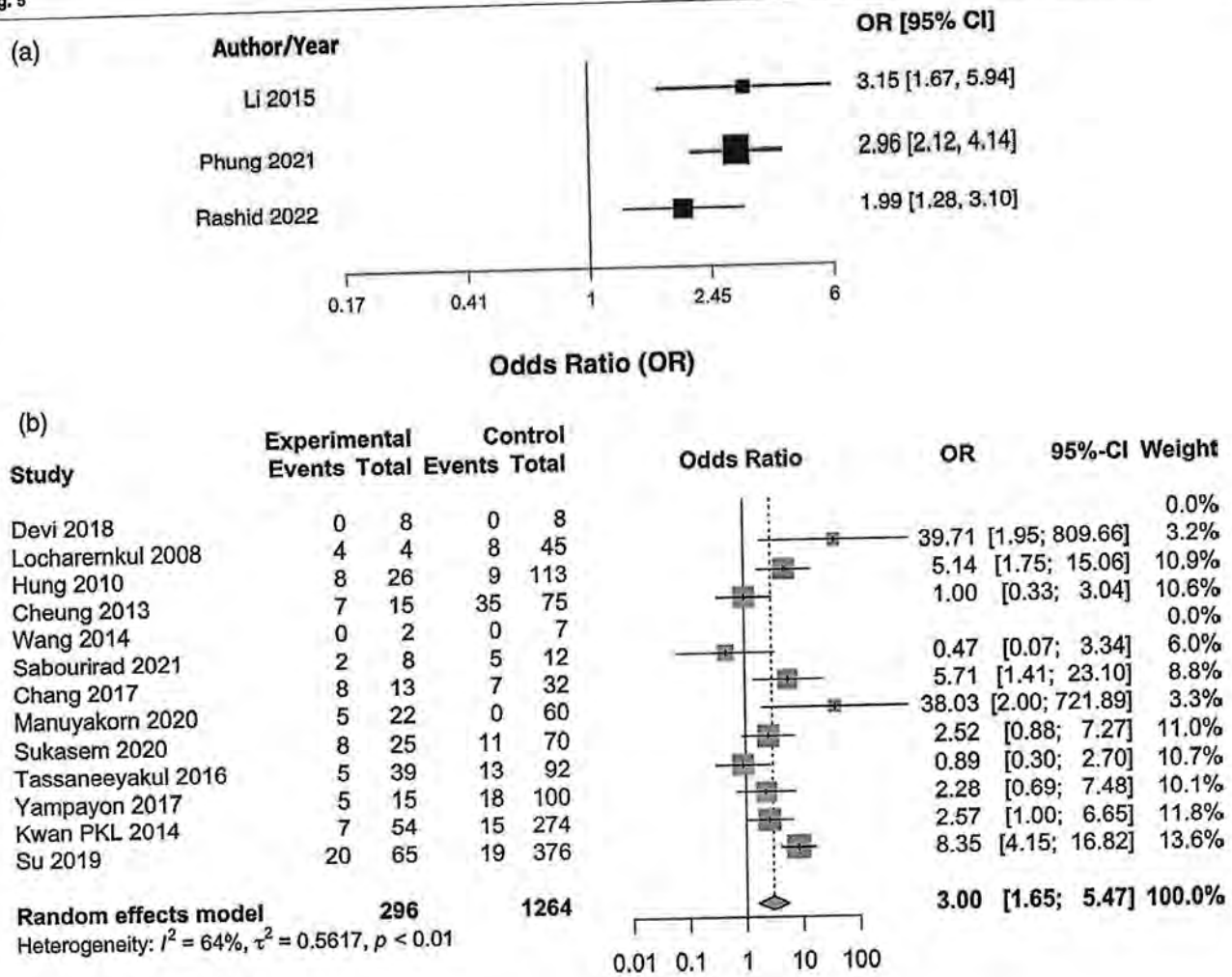
The findings of this study align with the established literature [81,84] that the presence of the HLA-B*15:02 allele is linked to an elevated risk of developing carbamazepine-induced SJS/TEN. In addition to carbamazepine, the study also identified a significant association between HLA-B*15:02 and SJS/TEN induced by other aromatic antiepileptic drugs, including lamotrigine, phenytoin and oxcarbazepine. Although no significant association was found for phenobarbital-induced SJS/TEN, it is likely that this is due to limited sample sizes in the studies analyzed. Consequently, the association between HLA-B*15:02 and SJS/TEN induced

by aromatic antiepileptic drugs should be considered a class effect.

There are variations in the strength of association between HLA-B*15:02 and the different aromatic antiepileptic drugs. This association is most pronounced for carbamazepine and oxcarbazepine, with ORs of 26.3 (95% CI, 21.4–32.4) and 32.32 (95% CI, 11.36–91.95), respectively. In contrast, the association with lamotrigine and phenytoin is weaker, with ORs of 2.55 (95% CI, 1.29–5.04) and 3.00 (95% CI, 1.65–2.4), respectively. The impact of these associations on an individual's risk of developing SJS/TEN is depicted in Figure 8 by multiplying the OR obtained from our review by previously measured baseline risks [88,89].

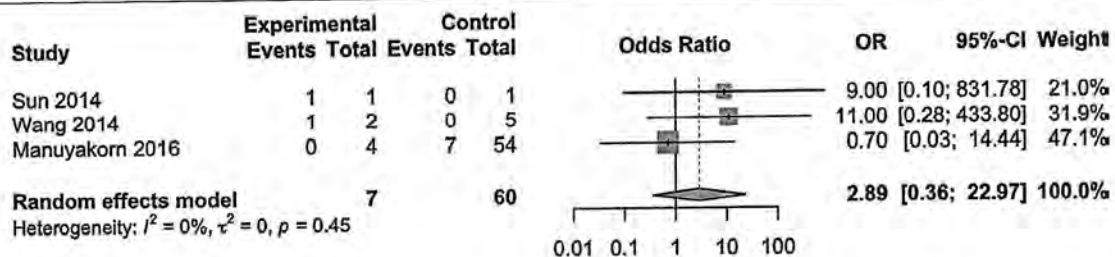
Based on these results, we support the current guidelines, which generally recommend that HLA-B*15:02 should be screened before initiation of carbamazepine/oxcarbazepine in individuals of Asian descent [90]. Previous studies have indicated that the prevalence of HLA-B*15:02 alleles in these populations, such as Han Chinese, Thai, Malays and some Southeast Asian populations can reach

Fig. 5



Meta-analysis of oxcarbazepine, HLA-B*15:02 and SJS/TEN. SJS/TEN, Stevens–Johnson syndrome/toxic epidermal necrolysis.

Fig. 6



(a) Umbrella review of phenytoin, HLA-B*15:02 and SJS/TEN. (b) Meta-analysis of phenytoin, HLA-B*15:02 and SJS/TEN. SJS/TEN, Stevens–Johnson syndrome/toxic epidermal necrolysis.

up to 15% [6]. If an individual tests positive for the allele, it is advisable to avoid carbamazepine/oxcarbazepine if alternative treatment options are available.

For patients who test positive for HLA-B*15:02, it is crucial to provide them with comprehensive information regarding their increased risk of developing SJS/TEN if

Fig. 7



Meta-analysis of phenobarbital, HLA-B*15:02 and SJS/TEN. SJS/TEN, Stevens–Johnson syndrome/toxic epidermal necrolysis.

lamotrigine or phenytoin is being considered. This enables informed decision-making and facilitates the exploration of alternative treatment strategies to minimize the risk of these adverse effects.

In addition to HLA-B*15:02, it is important to acknowledge that several other alleles have been found to be

associated with carbamazepine-induced SJS/TEN. Examples of these alleles include HLA-B*15:21 [55], HLA-B*15:11 [55], HLA-B*31:01 [55,91], HLA-B*58:01 and HLA-B*40:01 [18]. These findings indicate the complexity of genetic factors involved in the development of adverse drug reactions. To enhance the risk stratification of patients, it is crucial to conduct further research aimed at identifying additional relevant alleles. By expanding our understanding of the genetic variations that contribute to SJS/TEN susceptibility, it may be possible to develop polygenic risk stratification tools. Such tools could assist physicians in better assessing a patient's risk and making informed decisions about treatment options and medication selection.

Limitations

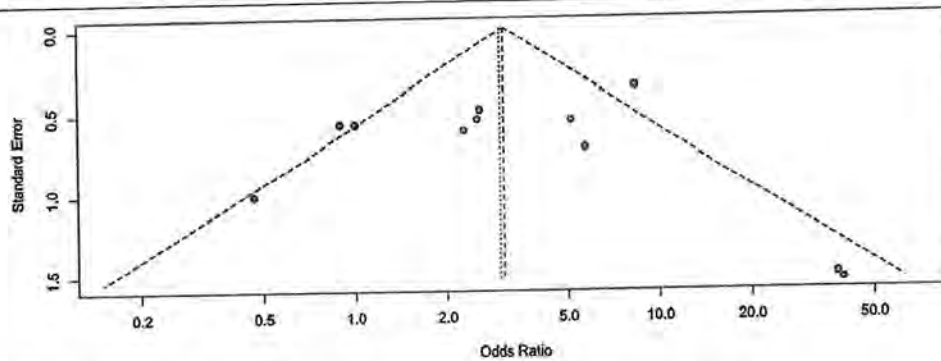
There are several limitations to consider for this study. First, the sample sizes for the analysis of antiepileptic drugs other than carbamazepine were small, potentially leading to heterogeneity, as well as under- or overestimation of the effect size. Further studies will be required to provide more reliable estimates of the strength of the association. Second, in delineating the scope of our research, we prioritized a specific inquiry into the association between HLA-B*15:02 and antiepileptic (AED)-induced SJS/TEN to ensure a more targeted examination of this particular genetic correlation and its clinical outcomes. While we acknowledge that there are other cutaneous adverse effects such as maculopapular exanthems and DRESS, these were not included within the remit of this study. Finally, it is worth noting that the results of this study are primarily applicable to individuals with Asian ancestries. This is due to the high prevalence of HLA-B*15:02 in Asian populations [92] and the inclusion of predominantly Asian study participants. However, this does not limit the generalisability of these results to other races.

In view of the nature of the study, heterogeneity is inevitable. When there are only a few studies, it is essential to interpret the I^2 statistic cautiously. With a small number of studies, it is possible that observed heterogeneity could be due to chance rather than true differences in study populations, interventions or outcomes. Additionally, the power of the test for detecting true heterogeneity decreases with fewer studies. Future studies should be added to these meta-analyses for us to draw more definite conclusions.

Conclusions

This study provides evidence supporting the association between HLA-B*15:02 and an increased risk of developing SJS/TEN induced by certain antiepileptics, namely, carbamazepine, oxcarbazepine, lamotrigine and phenytoin. However, no significant association was found between HLA-B*15:02 and phenobarbital-induced SJS/TEN, which could potentially be attributed to limited statistical power. These findings are clearly illustrated in

Fig. 8



Incidence of SJS/TEN for patients with positive HLA-B*1502 allele. SJS/TEN, Stevens–Johnson syndrome/toxic epidermal necrolysis.

Figure 8 (under ‘supporting information’). These findings indicate that the association between HLA-B*15:02 and SJS/TEN is likely a class effect, affecting aromatic antiepileptic medications. Further studies are required to enhance the precision of the current risk estimates and investigate the association between antiepileptic-induced SJS/TEN and other alleles, to refine the risk stratification process before initiation of treatment.

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Conflicts of interest

There are no conflicts of interest.

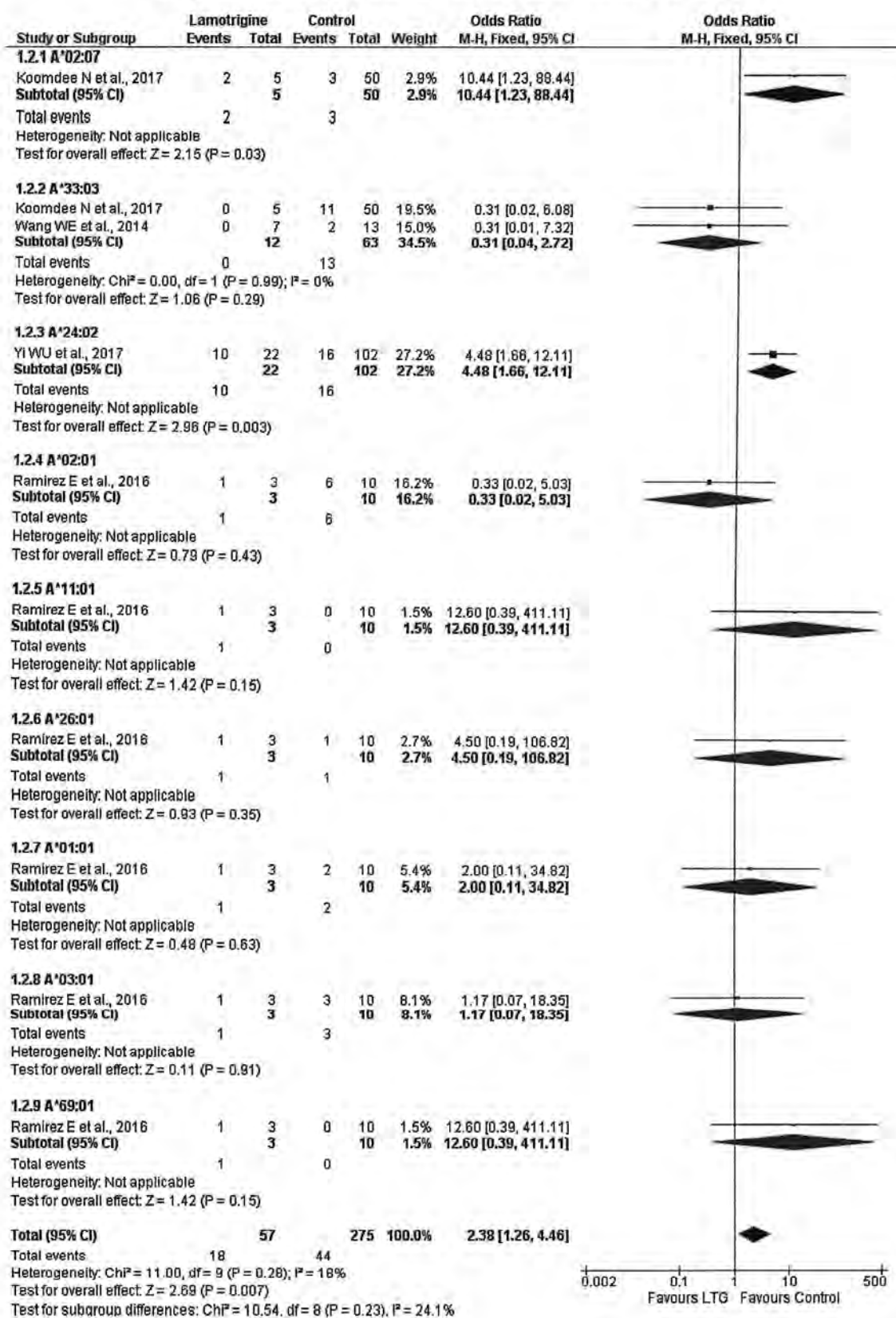
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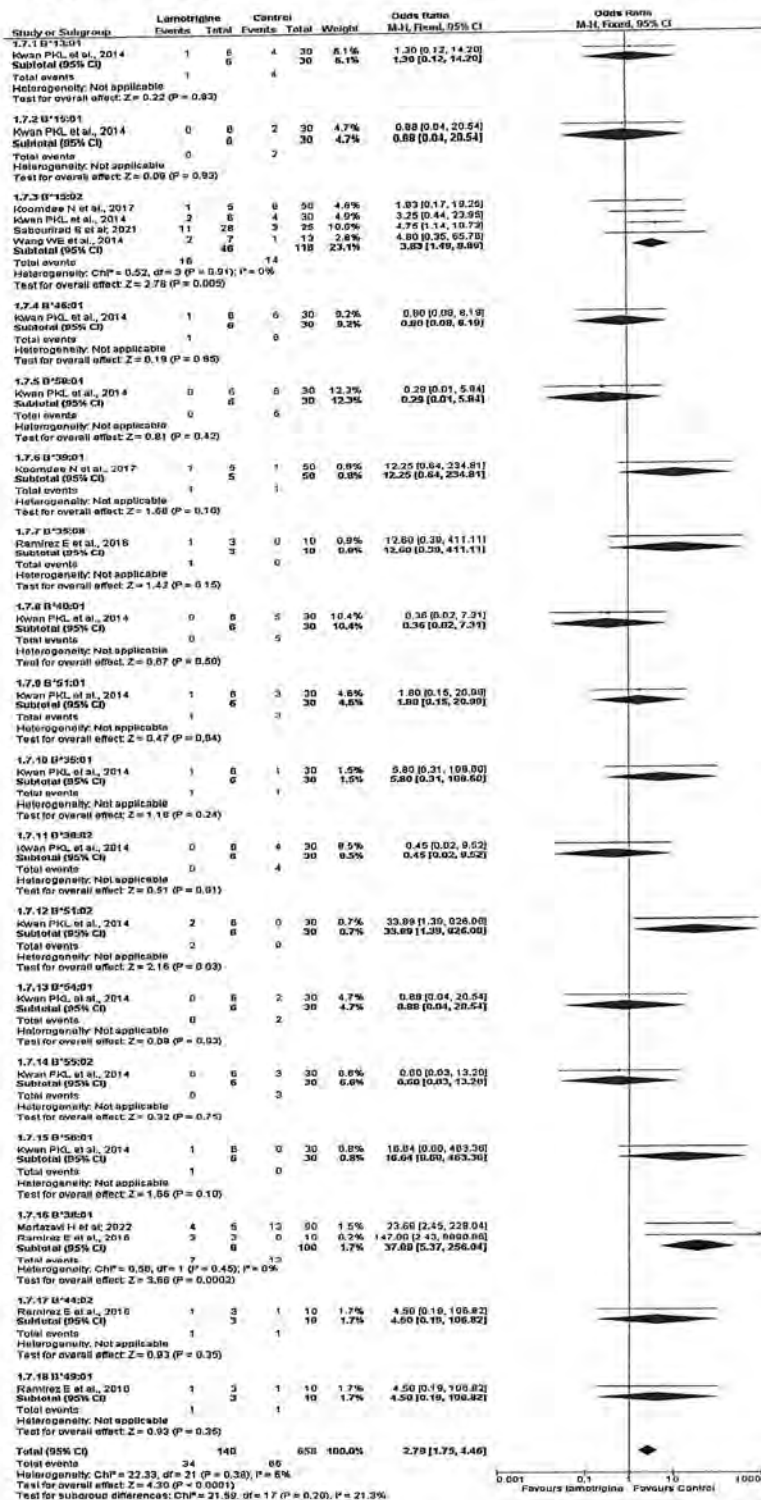
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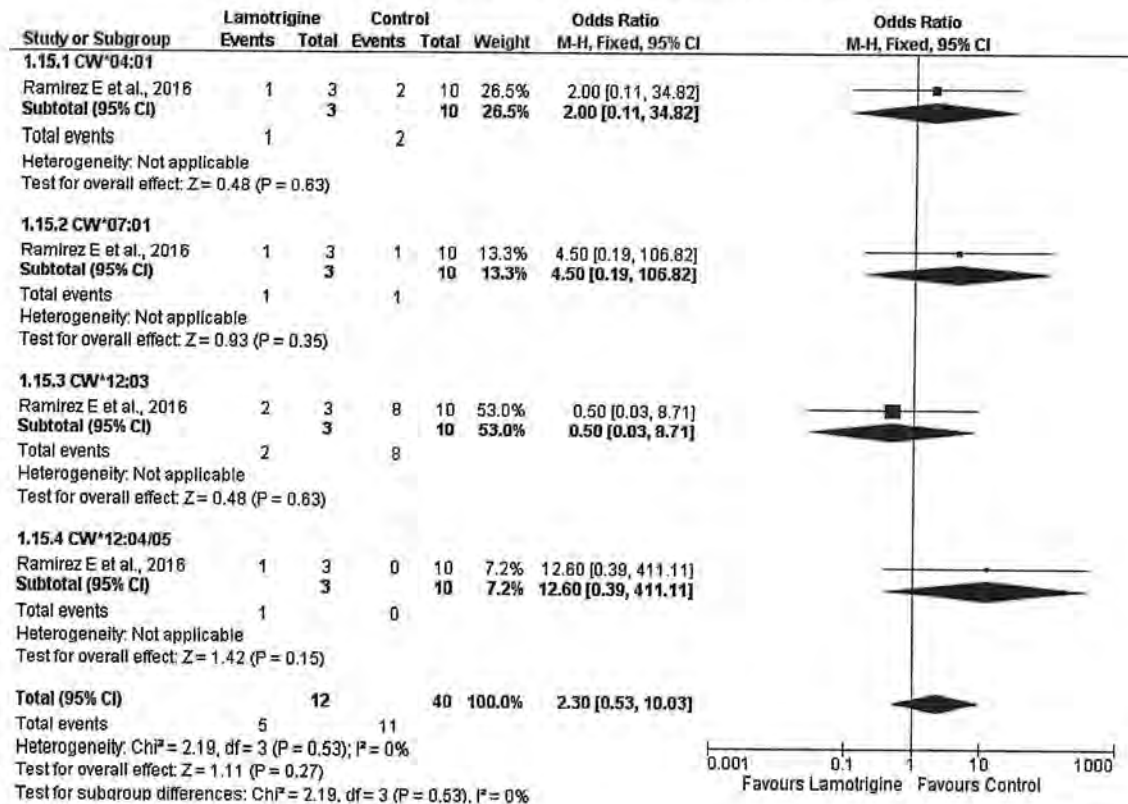
Supplementary file S4A: HLA-A on LTG induced SJS/TEN



Supplementary file S4B: HLA-B on LTG induced SJS/TEN



Supplementary file S4C: HLA-C on LTG induced SJS/TEN



Supplementary file S4D: DRB1 on LTG induced SJS/TEN

