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Review

Role of human leukocyte antigen in anti-epileptic drugs-induced Stevens–Johnson Syndrome/toxic epidermal necrolysis: A meta-analysis☆,☆☆

Muhammed Rashid [a], Asha K Rajan [a], Manik Chhabra [b], Ananth Kashyap [c], Viji Pulikkel Chandran [a], Rajesh Venkataraman [d], Sreedharan Nair [a], Girish Thunga [a,e,*]

[a] Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal, India
[b] Department of Pharmacology and Therapeutics, Max Rady College of Medicine, University of Manitoba, Winnipeg, Canada
[c] Department of Pharmacy Practice, Sarada Vilas College of Pharmacy, Mysuru, Karnataka, India
[d] Department of Pharmacy Practice, Sri Adichunchanagari College of Pharmacy, Adichunchanagari University, BG Nagara, Karnataka, India
[e] Coordinator, Centre for Toxicovigilance and Drug Safety, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal, India

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ABSTRACT

Purpose: Antiepileptic drugs (AEDs) are extensively used to manage epilepsy and other comorbidities associated with seizures. Human Leukocyte Antigen (HLA) has a strong association with AED-induced severe cutaneous adverse drug reactions.

Objective: We aimed to perform a systematic review and meta-analysis to identify, critically evaluate, and synthesize the best possible evidence on HLA-associated AED-induced Stevens–Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN).

Methods: MEDLINE/PubMed, Scopus, and the Cochrane Library were searched for literature from inception up to July 2022. We included case control studies analyzing association between HLA and AED-induced SJS/TEN. We assessed the studies' risk of bias in using Quality of genetic studies (Q-genie) tool. Outcomes focused on association (risk) between HLA and AED-induced SJS/TEN. The estimated risk was presented in the form of odds ratio (OR).

Results: We included 37 studies (51,422 participants; 7027 cases and 44,395 controls). There was a significantly higher risk of Carbamazepine-induced SJS/TEN with HLA-A (OR: 1.50; 95% CI: 1.03 to 2.17), HLA-B (OR: 1.94; 95% CI: 1.45 to 2.58), HLA-C (OR: 7.83; 95% CI: 4.72 to 12.98), and HLA-DRB1 (OR: 2.82; 95% CI: 1.94 to 4.12). Lamotrigine-induced SJS/TEN posed a higher risk with HLA-A (OR: 2.38; 95% CI: 1.26 to 4.46) and HLA-B (OR: 2.79; 95% CI: 1.75 to 4.46). Phenytoin-induced SJS/TEN showed a higher risk with HLA-A (OR: 3.47; 95% CI: 2.17 to 5.56), HLA-B (OR: 1.72; 95% CI: 1.38 to 2.15), and HLA-C (OR: 2.92; 95% CI: 1.77 to 4.83). Phenobarbital-induced SJS/TEN had a higher risk with HLA-A (OR: 6.98; 95% CI: 1.81 to 26.84), HLA-B (OR: 2.40; 95% CI: 1.39 to 4.17), and HLA-C (OR: 3.37; 95% CI: 1.03 to 11.01). Zonisamide-induced SJS/TEN was significantly associated with HLA-A*02:07 (OR: 9.77; 95% CI: 3.07 to 31.1), HLA-B*46:01 (OR: 6.73; 95% CI: 2.12 to 21.36), and HLA-DRB1×08:03 (OR: 3.78; 95% CI: 1.20 to 11.97). All other alleles of HLA were observed to have a non-significant association with AED-induced SJS/TEN. All included studies were of good quality, with a score of >50 and a mean score of 54.96 out of 77.

Abbreviations: ADR, Adverse drug reaction; AED, Anti-epileptic drugs; CBZ, Carbamazepine; CI, Confidence interval; DRESS, Drug reaction with eosinophilia and systemic symptoms; GBP, Gabapentin; HLA, Human leukocyte antigen; LTG, Lamotrigine; LVT, Levetiracetam; MHC, Major histocompatibility complex; MPE, Maculopapular exanthema; OR, Odds ratio; PB, Phenobarbital; PHT, Phenytoin; SCARD, Severe cutaneous adverse drug reaction; SJS, Stevens-Johnson Syndrome; TEN, Toxic epidermal necrolysis; VPA, Valproic acid; ZNS, Zonisamide.

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* Corresponding author at: Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal, India.
E-mail address: girish.thunga@manipal.edu (G. Thunga).

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Conclusion: Our study showed a significant association between few variants of HLA alleles and AED-induced SJS/TEN. Evidences from our study could help in population-based studies and in implementation of individualized treatment regimens. These findings could be part of translational research helping in precision therapy.

Research in context

Evidence before this study

Antiepileptic drugs (AEDs) are routinely used worldwide to treat epilepsy and other comorbidities associated with seizures. Severe cutaneous adverse drug reactions (SCADRs) presenting in the form of Stevens–Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are fatal and common with AEDs, NSAIDs, and certain antibiotics. However, in scientific literature there is a lag on the association as a group between human leukocyte antigen (HLA) and AED-induced SJS/TEN and the individual association between each allele and each drugs. With the large-scale global use of AEDs and reports of increase in induced SCADRs, there was a need for a systematic review and meta-analysis to synthesize the evidence in this important clinical area.

Added value of this study

This meta-analysis looks at AEDs commonly used to treat epilepsy and other comorbidities associated with seizures and AED-induced SCADRs. It assesses currently available evidence to guide the choice of appropriate AEDs in individualized therapy. We included case control studies that best described the research question to estimate, in comparison with a control group, the strong association of HLA on AED-induced SJS/TEN.

Implications of available evidence

Our findings have the potential to guide health care providers in the choice of the most appropriate antiepileptic drugs in individualized therapy for adults with epilepsy or other indications associated with seizures. Our findings can also improve early detection and early prevention of AED-induced adverse drug reactions, especially SCADRs, among the vulnerable. Our analysis observed higher genetic polymorphisms in SCADRs from Asian population. HLA genetic polymorphisms were highest with carbamazepine, followed by phenytoin, lamotrigine, and phenobarbital. Our study can serve as a reference for precision medicine based genetic assessment and treatment algorithms for better patient care.

1. Introduction

Antiepileptic drugs (AEDs) are the most important of the treatments available for the management of epilepsy [1]. AEDs are classified into conventional and newer AEDs. Conventional AEDs include carbamazepine (CBZ), clobazam, phenobarbital (PB), phenytoin (PHT), and valproic acid (VPA). Newer AEDs include felbamate, gabapentin (GBP), lamotrigine (LTG), levetiracetam (LVT), oxcarbazepine, tigabine, topiramate, vigabatrin, lacosamide, and zonisamide (ZNS) [1,2]. AEDs are used for the management of not only epilepsy but also neuropathic pain, bipolar disorders, and other comorbidities associated with seizures [1]. CBZ, PHT, and PB are potent enzyme inducers, which increase the risk of adverse drug reactions (ADRs), especially severe cutaneous reactions [2,3]. Despite the high risk of developing ADRs, they are widely used because of their low cost [4]. AEDs possess risk of developing severe cutaneous adverse drug reactions (SCADRs), with few showing clinical utility for non-epileptic disorders [5].

SCADRs have a notable impact on development of lifelong dystrophic scars and end organ failures. SCADRs range from minor ADRs such as maculopapular exanthema (MPE) to severe life-threatening ADRs such as drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens–Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN) [6]. SJS and TEN are differentiated based on the degree of skin detachment (percentage of body surface area). SJS–TEN overlap is characterized by skin detachment over 10%–30% of body surface area [3].

Human leukocyte antigen (HLA) genes code major histocompatibility complex (MHC) proteins, and differentiate between self and non-self-proteins [7]. Various studies have explored the role of highly polymorphic HLA on drugs, where HLA genotypes contribute to variability and unpredictability of SCADRs in different populations [8]. The common AEDs reported in HLA-associated SCADRs are CBZ, LTG, PHT, PB, LEV, and VPA [9,2,3].

HLA alleles linked to SCADRs act as biomarkers in pharmacogenomics-guided individualized therapy. Linkage disequilibrium patterns and frequencies at HLA loci vary across different ethnic groups. Ethnicity-specific HLA markers are important in individualized therapy [10]. The risk of SJS/TEN in AED-treated patients ranged from 0.0001% to 0.001%. Mortality rate for SJS ranged from 1% to 5%. Global mortality rate for TEN ranged from 25% to 35% [11].

Genetic risk of developing AED-induced ADRs varies with specific drugs and specific HLA alleles [12]. Researchers have explored ways to minimize risk of SCADRs in users of AEDs, non-steroidal anti-inflammatory drugs (NSAID), and antimicrobials. The study by Chung et al. identified the association between HLA-B*15:02 and CBZ-induced SJS/TEN in a Han Chinese population residing in Taiwan [13]. Similar associations were found between HLA-B*15:02 and HLA-B*15:11 alleles in CBZ-induced SJS and TEN in an Asian population [10]. HLA-A*31:01, HLA-B*51:01, and HLA-B*15:02 were strongly associated with CBZ- or oxcarbazepine-induced hypersensitivity reaction or MPE/DRESS among Asian, European, Chinese, and Thai populations [14–17].

In Korean and Indian populations, HLA-B*44:03 and HLA-B*13:01 were associated in LTG-induced SJS/TEN. In a Chinese population, HLA-B*13:02 was associated with LTG-induced MPE [18–21] and HLA-A*51:01 was associated with PHT- and PB-induced MPE/DRESS in Chinese population [21]. Causality of HLA-B*40:01, HLA-B*58:01, and HLA-A*11:01 was observed in LVT-induced MPE, SJS, and TEN, respectively, in a North-Indian population [22].

There is emerging evidence as well as previous systematic reviews and meta-analyses on associations of individual AEDs with SJS/TEN and of specific HLA alleles with SJS/TEN [10,23-33]. However, there is no meta-analysis on associations of HLA with AED-induced SJS/TEN till date. With this background, we performed an updated systematic literature review and meta-analysis to identify, critically evaluate, and synthesize the best possible evidence on association of HLA with AED-induced SJS/TEN.

2. Methodology

2.1. Study inclusion criteria

The research question for our systematic review was based on the association of HLA with AED-induced SJS/TEN. The protocol is registered in The International Prospective Register of Systematic Reviews (PROSPERO), with the registration ID: CRD42022316203. We broke down our research question into PECOS framework for inclusion of studies (P- Population that used any of the AEDs irrespective of its indication, E- AEDs, C- Control group not using AEDs, O- quantitative estimation of association of HLA with AED-induced SJS/TEN in case and control patients among various populations; Secondary outcomes included allele frequency of a variant HLA allele among groups, and S-Case-Control studies that considered cases as population with onset of

SJS/TEN following AED therapy and controls as patients with absence of SJS/TEN following AED therapy) and reported findings as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines [34]. Narrative reviews, systematic reviews, meta-analysis, letters to the editor, conference proceedings, non-English studies, descriptive studies, and clinical trials were excluded.

2.2. Literature search

A comprehensive literature search was performed without any restrictions on language, date or publication type from inception up to July 2019 for the keywords "antiepileptic", "Stevens–Johnson Syndrome, "toxic epidermal necrolysis", and "human leukocyte antigen", in PubMed/Medline, Cochrane library, and Scopus. The search was further updated up to July 2022. The detailed search strategy is provided in Supplementary file S1. The reference lists of all included articles were screened to identify any additional relevant citations along with a random search in Google, Google Scholar, and ResearchGate. One reviewer prepared the search strategy and another reviewer cross-checked its appropriateness before implementing the search.

Supplementary file S1: Search strategy for various databases

2.3. Study selection, data extraction, and quality assessment

All retrieved titles and abstracts were screened for eligibility. Eligible studies were retrieved in full text and assessed for inclusion based on inclusion criteria. All the relevant data such as country, population, number of participants, age, gender, study period, AED and HLA allele involved, duration of exposure, and the outcome characteristics were extracted to a standardized data extraction sheet. First author name and year of publication were used to identify the studies. Data were extracted directly from the articles or calculated from the available information. The quality of included studies was assessed using the Quality of genetic studies (Q-genie) tool [35]. The tool consists of 11 questions with a score of 7 each and a total score of 77. The quality was graded as poor, moderate, or good quality if the score was $\leq$35, >35 to $\leq$45, and >45, respectively [35]. Two independent reviewers were involved in the study selection, data extraction, and quality assessment. Any disagreements were resolved through discussion or by consulting a third reviewer.

2.4. Evidence synthesis and statistical analysis

A narrative synthesis was performed to summarize the extracted data and presented in a tabular form. Review manager software (RevMan, version 5.3 for windows, The Cochrane collaboration, Oxford UK) was used to conduct this meta-analysis [36]. The number of events and total number of participants were collected from the cases and controls to perform meta-analysis. Outcomes were presented in terms of odds ratio (OR) with 95% confidence interval (CI). Statistical heterogeneity of data was assessed using I^2 statistics. Fixed effects model was used for studies without significant heterogeneity ($I^2 \leq 50\%$; $P<0.10$) while random effects model was used for studies with substantial heterogeneity ($I^2>50\%$; $P \geq 0.10$). A subgroup analysis based on the type of HLA allele was performed to explore the sources of heterogeneity [37].

2.5. Publication bias and sensitivity analysis

Visual inspection of funnel plot (from Rev Man) was done to assess publication bias, which was further confirmed through statistical analysis by Egger's and Begg's test. Comprehensive meta-analysis software trial version was used to perform Egger's test and Begg's test [38]. A probability of $\leq$0.05 was considered to be statistically significant. Sensitivity analysis was performed by changing the random effects model to fixed effects model [39].

3. Results

3.1. Search characteristics

A total of 1560 citations were retrieved after searching different databases and considered for the initial screening (title and abstract). After the exclusion of 1276 records due to various reasons, 284 full-text articles were screened for eligibility. Finally, a total of 37 articles satisfied the inclusion criteria [11,14,15,17,20,21,30,40-69]. The study selection process is depicted in Fig. 1.

3.2. Characteristics of the included studies

A total of 37 studies [11,14,15,17,20,21,30,40-69] with 51,422 participants (7027 cases and 44,395 controls) were included in this review. Most of the studies were from Thailand (n = 10), followed by China (n = 5), India (n = 3), Malaysia (n = 3), Iran (n = 2), Hong Kong (n = 2), Vietnam (n = 2), Japan (n = 2), Indonesia (n = 1), Australia (n = 1), Taiwan (n = 1), Columbia (n = 1), Philippines (n = 1), Spain (n = 1), Germany (n = 1), and Ireland (n = 1). The studies were published between 2008 and 2022. The participants' age ranged between 3 and 91 years. The common AEDs involved in the reactions were LTG, LVT, PB, PHT, GBP, VPA, and CBZ, which are administered either alone or in combination. Among the included studies, the cases were defined as population with onset of SJS/TEN within days of initiation of AED therapy and controls were defined as patients with absence of SJS/TEN even when on therapy with AEDs for months. The diagnosis criteria was based on Roujeau's criteria, with the standard definition of skin detachment with >10% to <30% of body surface area [3].

Table 1: Characteristics of the included studies

3.3. Quality assessment

Quality of genetic studies (Q-genie) tool was used to assess the quality of included studies. All studies were of good quality, with a minimum score of 50 and an average score of 54.9 out of 77. All studies had excellent planned analysis, classification of outcome, and technical and non-technical classification of exposure. Most of the conclusions drawn by the authors were supported by results and appropriate methods. The quality assessment of included studies is provided in Supplementary file S2.

Supplementary file S2: Quality assessment of included studies using Q-Genie Quality assessment of genetic study

3.4. Quantitative estimation

A total of 37 studies [11,14,15,17,20,21,30,40-69] with 7027 cases and 44,395 controls were included for meta-analysis comparing association of HLA with AED-induced SJS/TEN. Among these, 26 studies provided data on CBZ, 14 studies on PHT, 8 studies on LTG, 4 studies on PB, and 1 study on ZNS, along with HLA-A, HLA-B, HLA-C, and HLA-DRB1 data.

3.4.1. HLA on CBZ-induced SJS/TEN

3.4.1.1. HLA-A on CBZ-induced SJS/TEN. A meta-analysis of 14 studies with 21,608 participants indicated HLA-A allele was significantly associated with the risk of CBZ-induced SJS/TEN (OR: 1.50; 95% CI: 1.03 to 2.17) in AED patients. Similarly, a significant association was observed with the sub alleles A*31:01 (OR: 2.88; 95% CI: 1.05 to 7.87; n = 9 studies; 10,457 participants), A*02:10 (OR: 10.40; 95% CI: 1.64 to 65.80; n = 1 study; 63 participants), A*31:1 (OR: 10.40; 95% CI: 1.64 to 65.80; n = 1 study; 63 participants), A*11:53 (OR: 86.64; 95% CI: 4.07 to 1844.52; n = 1 study; 560 participants), and A*24:07 (OR: 4.67; 95% CI: 1.32 to 16.53; n = 2 studies; 90 participants) [Supplementary file

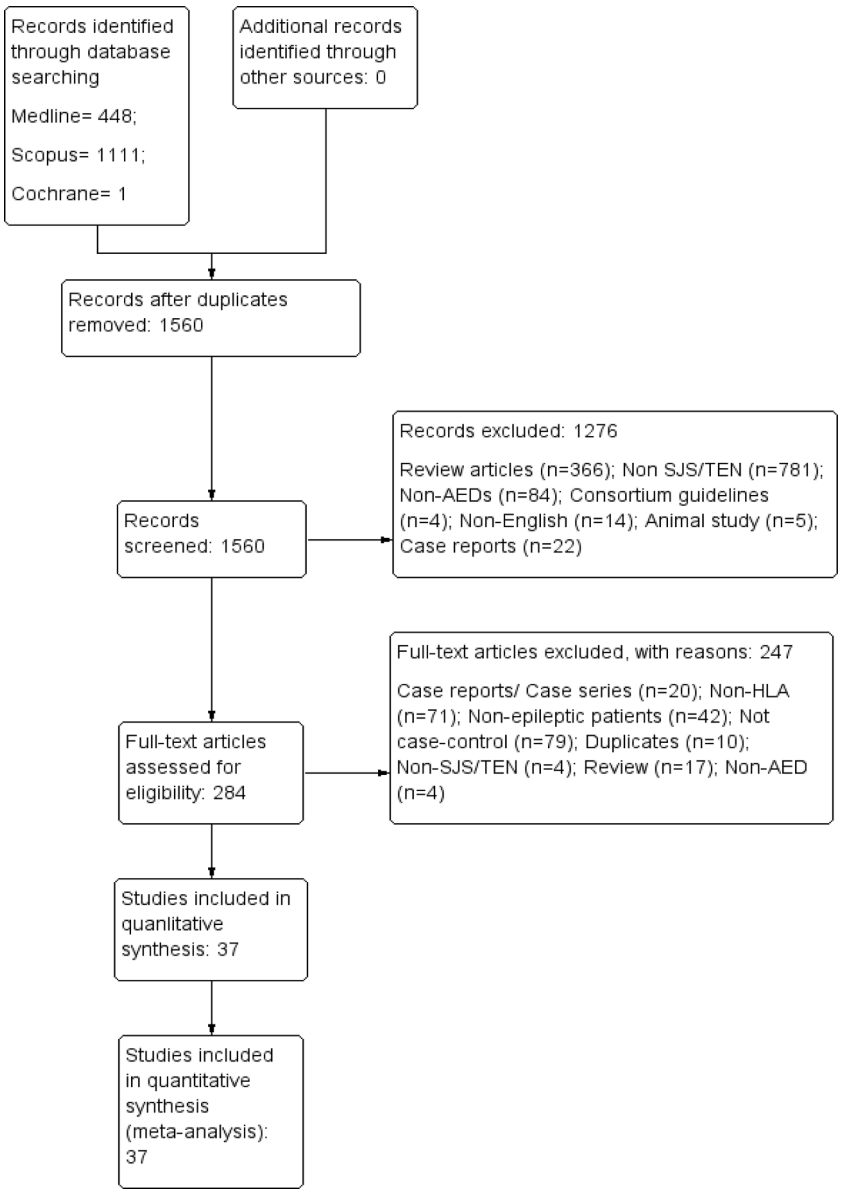

Fig. 1. PRISMA flow diagram for study selection.

S3A].

Supplementary file S3A: HLA-A on CBZ-induced SJS/TEN

3.4.1.2. HLA-B on CBZ-induced SJS/TEN. A pooled estimation of 26 studies with 33,390 participants observed HLA-B was associated with significantly higher risk of CBZ-induced SJS/TEN (OR: 1.94; 95% CI: 1.45 to 2.58). A similar significant risk was observed with sub-alleles B*57:01 (OR: 10.75; 95% CI: 5.84to 19.80; $n = 3$ studies; 9281 participants), B*15:02 (OR: 24.51; 95% CI: 14.56 to 41.27 $n = 21$ studies; 3004 participants), B*15:21 (OR: 4.58; 95% CI: 2.14 to 9.80; $n = 6$ studies; 941 participants), B*18:15 (OR: 52.55; 95% CI: 2.06 to 1343.47; $n = 1$ study; 287 participants), B*56:04 (OR: 18.00; 95% CI: 1.07 to 302.03; $n = 1$ study; 287 participants), B*15:214 (OR: 61.70; 95% CI: 2.38 to 1598.92; $n = 1$ study; 248 participants), B*35:32 and B*44:13 (OR: 61.70; 95% CI: 2.38 to 1598.92; $n = 1$ study; 248 participants), B*15:11 (OR: 11.52; 95% CI: 2.83 to 46.95; $n = 4$ studies; 1079 participants), B*56:10 (OR: 44.66; 95% CI: 1.79 to 1116.24; $n = 1$ study; 564 participants), and B*15:06 (OR: 81.00; 95% CI: 4.20 to 1561.52; $n = 1$ study; 38 participants) [Supplementary file S3B; Table 2].

Supplementary file S3B: HLA-B on CBZ-induced SJS/TEN

3.4.1.3. HLA-C on CBZ-induced SJS/TEN. A pooled analysis of 3 studies with 622 participants recorded a significantly higher risk of CBZ-induced SJS/TEN (OR: 7.83; 95% CI: 4.72 to 12.98) among HLA-C active patients. A similar significantly high risk was observed with sub alleles CW*08:01 (OR: 12.27; 95% CI: 6.06 to 24.84 $n = 2$ studies; 257 participants), CW*03:02 (OR: 4.96; 95% CI: 1.26 to 19.48; $n = 1$ study; 145 participants), and CW*03:03 (OR: 47.00; 95% CI: 1.28 to 1722.11; $n = 1$ study; 25 participants) [Supplementary file S3C; Table 2].

Supplementary file S3C: HLA-C on CBZ-induced SJS/TEN

3.4.1.4. HLA-DRB-1 on CBZ-induced SJS/TEN. A meta-analysis of 4 studies with 1080 participants revealed a significantly higher risk of CBZ-induced SJS/TEN (OR: 2.82; 95% CI: 1.94 to 4.12) among DRB-1 active patients. A similar significant association was observed with sub-alleles DRB1*07:01 (OR: 5.20; 95% CI: 2.04 to 13.26; $n = 2$ studies; 220 participants), DRB1*12:02 (OR: 3.38; 95% CI: 1.79 to 6.36; $n = 1$ study; 230 participants), DRB1*03:03 (OR: 3.12; 95% CI: 1.14 to 8.54; $n = 1$ study; 145 participants), and DRB1*01:01 (OR: 14.00; 95% CI: 1.53 to 128.10; $n = 1$ study; 230 participants) [Supplementary file S3D; Table 2].

Table 1
Characteristics of included studies.

Author, year	Country	Population	Participants	Gender, n (%)	Age (in years) (Mean/ Median/ Range)	Study Period	AEDs involved	Allele involved in SJS/TEN	Duration of drug exposure (in days)
Mortazavi H et al; 2022	Iran	Iranian	5 cases; 90 controls	NR	NR	March 2018 to December 2019	LTG	B*38 DRB1*13	NR
Nakkam N et al; 2022	Thailand	Thai	88 cases; 144 controls	Case: Male: 31 Female: 47 Control: Male: 50 Female: 94	Mean: Case: 43.30 Control: 46.87	Retrospective: 1993–2007 Prospective: 2008–2020	CBZ	B*15:02 B*46:01 B*13:01 B*38;02 B*39:09 B*40:01 B*58:01 B*15:35 B*18:01 B*15:21 B*27:06 B*56:01 B*18:02 B*44:03 B*55:02 B*15:11 B*15:25	Case: 11.00 ±7.73 Control: 346.51 ±170.92
Capule F et al; 2021	Philippines	Filipino	10 cases; 40 controls	Case: Male: 7 Female: 3 Control: Male: 15 Female: 25	Mean: Case: 32.2 Control: NA	2000–2018	CBZ	A*24:07 B*15:02 B*15:21	Case: 12–68 Controls: 121–3651
John S et al; 2021	India	SouthIndian	Cases 25; controls 30	NR	NR	13 months	PHT	B*51:01	NR
Nguyen D et al; 2021	Vietnam	Vietnamese	35 cases; 72 controls	Case: Male: 23 Female: 8 Controls: Male: 65 Female: 9	Case: 55 Controls: 60.3	June 2015-February 2017	CBZ	A*31:01 B*15:02	NR
Sabourirad S et al; 2021	Iran	Iranian	LTG cases: 28; controls: 25 PHT cases: 8; controls: 12	LTG cases: male: 12; female:16; controls: male: 14; female:11 PHT cases: male: 3; female: 5; controls: male: 5; female: 7	LTG cases: 42.57; controls: 38.28 PHT cases: 38.25; controls: 39.25	March 2013-March 2019	LTG, PHT	B*15:02	NR
Manuyakorn W et al; 2020	Thailand	Thai	5 cases; 60 controls	Case: male: 3; female: 2	Case: 3–14	October 2016-December 2018	PHT	B*38:02 B*56:02 C*07:01	Median duration: 365
Capule F et al; 2020	Thailand	Thai	8 cases; 32 controls	Case: male: 5; female: 3; control: male: 12; female: 20	Case: 33.88; Control: NA	January 2020-May 2018	CBZ	Multiple alleles of HLA-A and B	Case: 29.13 Control: 1170.53
Huyen TT et al; 2020	Vietnam	Vietnamese	13 cases; 25 controls	NR	NR	July 2018–2019	CBZ	B*15:06 B*46:01	
Mockenhaupt M et al; 2019	Germany	European	28 cases; 8862 controls	NR	NR	NA	CBZ	B*57:01 A*31:01	NR
Kaniwa N et al; 2013	Japan	Japanese	PHT cases: 9; controls: 2878 ZNS cases: 12; controls: 2878 PB cases: 8; controls: 2878	NR	NR	June 2006-July 2012	PHT, ZNS, PB	B*51:01 A*02:07 B*46:01 DRB1*08:03 A*24:20 B*51:01 DRB1*04:10	PHT: 13.6 ZNS: 23.8
Ihtisham et al., 2018	India	North Indian	120 cases; 250 controls	**Case:** Male: 62 (51.7%) Female: 58 (48.3). **Control:** Male: 137 (54.8%)	Range: Cases: 6–72; Control: 5–72	February 2013 to August 2015	LTG; CBZ; PHT; LEV; VPA	B*13:01; A*31:01; B*51:01; DRB1*07:01; B*57:01; A*03:01; DRB1*14:01	Cases: 8.41 (3–18) days

(*continued on next page*)

Table 1 (*continued*)

Author, year	Country	Population	Participants	Gender, n (%)	Age (in years) (Mean/ Median/ Range)	Study Period	AEDs involved	Allele involved in SJS/TEN	Duration of drug exposure (in days)
				Female: 113 (45.2%).					
Sukasem et al., 2018	Thailand	Thai population	38 cases; 271 controls	Case: Male: 24 (63.15%) Female: 14 (33.84%) Control: 137 (50.6%) Female: 134 (49.4%).	Range: Cases: 44/ 24–64 Control: 32/ 10–54	2011 to 2016	CBZ	B*15:02; B*15:21; B*07:05; B*13:01; B*15:01; B*18:01; B*18:15; B*44:03; B*46:01; B*56:04; B*58:01	Cases:16±7 days
Koomdee N et al., 2017	Thailand	Thai population	15 cases; 50 controls	Case: Male: 4 (26.7%) Female: 11 (73.3%) Control: Male: 12 (24.0%) Female: 38 (76.0%)	Range: Cases: 36.2 Controls: 38.2	2011 to 2015	LTG	A*02:07; A*33:03; B*15:02; B*35:08; B*39:01	NR
Yuliwulandari R et al., 2017	Indonesia	Javanese and Sundanese population	12 cases, 17 controls	Case: Male: (47%) Female: (53%)	Range: Cases: 15–59 /34.25 years	2014–2015	CBZ	B*15:02; B*15:21; B*15:214; B*18:01; B*35:05; B*35:32; B*44:03; B*44:13	NR
Shi YW et al., 2017	China	Southern Han Chinese population	91 cases (56 CBZ-SJS/TEN; 22LTG-SJS; 13PHT-SJS), 322 controls (180 CBZ, 102 LTG, 40 PHT exposed)	NR	NR	2006–2015	CBZ, LTG, PHT	B*15:02; C*08:01; DRB1*12:02; A*24:02; B*15:11; DRB1*01:01; A*02:01;	NR
Nguyen et al., 2015	Australia	Vietnamese	38 cases; 25 controls	Cases: Male: 20 (52.6%) Female: 18 (47.3%) Controls: Male: 13 (52%) Female: 12 (48%)	Cases: 40.6 years Controls: 22.4 years	2011–2013	CBZ	B*15:02	Cases: 12.0 (2–30) Controls: NR
Kwan PKL et al., 2014	Hong Kong	Hong Kong Chinese	54 cases (26 CBZ-SJS/TEN; 15 PHT-SJS/ TEN; 6 LTG-SJS/ TEN), 274 controls (135 CBZ, 74 PHT, 30 LTG exposed)	Cases: 25 Male (45.4%) 30 Female (54.6%) Controls: Male 125 (45.4%) Female 150 (54.6%)	Cases: 10–85 range/44.1 years Controls: 10–90 range/44.1 years	2010–2011	CBZ, PHT, LTG	B*13:01; B*15:01; B*15:02; B*35:01; B*38:02; B*40:01; B*46:01; B*51:01; B*51:02; B*54:01; B*55:02; B*56:01; B*58:01	NR
He XJ et al., 2013	China	North-eastern Han-chinese	35 cases; 125 controls	Case: Male: 20 (57.1%) Female 15 (42.9%) Control: Male: 84 (67.2%) Female 41 (32.8%)	Case: 12–67/ 31.4 years Controls: 13–65/ 34.2 years	NR	CBZ	B*15:02; A*02:06; A*33:03; B*58:01; C*03:02; C*06:02; DQB1*03:01; DQB1*03:03; DRB1*07:01	Cases: 14 (1–24) days Controls: 86.5 (67–192) months
Hsiao YH et al., 2013	Taiwan	Han Chinese	194 Cases; 152 Controls	Case: Male: 102 (52.5%) Female: 92 (47.4%) Control:	Case: 7–88/ 49.2 years	NR	CBZ	B*15:01; B*15:02; B*27:04; B*40:01; B*48:01; B*51:01; B*54:01; B*55:02; A*02:01; A*02:03; A*02:06; A*11:01; A*24:02; A*26:01; A*30:01; A*31:01; A*32:01; A*33:03	NR
	Hong Kong	Han Chinese				1993–2009			NR

(*continued on next page*)

Table 1 (*continued*)

Author, year	Country	Population	Participants	Gender, n (%)	Age (in years) (Mean/ Median/ Range)	Study Period	AEDs involved	Allele involved in SJS/TEN	Duration of drug exposure (in days)
Cheung YK et al., 2013			54 Cases; 275 Controls	Case: Male: 25 (46.2 %) Female: 29 (54.5%) Controls: Male: 121 (44%) Female: 154 (56%)	Case: 6–77/ 38 years Controls: 10–90/44.1 years		CBZ, PHT, LTG, VPA, PB, GBP, LEV	B*15:02; B*13:01; B*15:01; B*38:02; B*39:01; B*40:01; B*46:01; B*51:01; B*54:01; B*55:02; B*58:01	
Amstutz U et al., 2013	Columbia	Canadian	42 Cases; 91 Controls	Case: Male 23 (55%) Female 19 (45%) Controls: Male: 48 (53%) Female 43 (47%)	Case: 0.64–16.9/ 9.9 years Control: 0.62–18.7/ 7.4 years	NR	CBZ	B*15:02; A*31:01	Cases: 14 (4–55) days Controls: 728 (58–6801) days
Shi YW et al., 2012	China	Southern Han Chinese population	18 Cases; 93 Controls	Case: Male: 11 (61%) Female: 7 (38.8%) Control: Male: 57 (61.2%) Female: 36 (38.7%)	Case: 27.83 years; Control: 25.46 years	2006–2011	CBZ	B*13:01; B*15:02; B*15:11; B*38:02; B*40:01; B*46:01; B*54:01; B*56:10; A*01:01; A*02:01; A*02:03; A*02:06; A*02:07; A*03:02; A*11:01; A*11:53; A*24:02; A*24:10; A*24:20; A*26:01; A*31:01; A*32:01; A*33:03	NR
Niihara H et al., 2012	Japan	Japanese	15 Cases; 33 Controls	NR	NR	2005–2011	CBZ	B*07:020; B*13:01; B*13:10; B*15:01; B*15:07; B*15:11; B*15:18; B*27:04; B*35:01; B*37:01; B*39:04; B*40:01; B*40::02; B*40:06; B*44:03; B*46:01; B*48:01; B*51:01; B*52:01; B*54:01; B*55:02; B*56:01; B*58:01; B*59:01; B*67:01	NR
Tassaneeyakul W et al., 2010	Thailand	Thai population	42 Cases; 42 Controls	Case: Male: 15 (35.7%) Female: 27 (64.2%) Control: Male: 15 (35.7%) Female: 27 (64.2%)	Cases: 42.36 years Controls: 44.07 years	NR	CBZ	B*15:02; B*15:21; B*15:35; B*13:01; B*18:01; B*18:02; B*27:06; B*35:05; B*38:02; B*39:09; B*40:01; B*46:01; B*51:01; B*51:02; B*55:02; B*56:01; B*58:01	NR
Khor AHP et al., 2017	Malayasia	Multiethinic Malaysian population	28 Cases (Malay- 16, Chinese- 6, Indian- 6); 227 Controls (Malay- 64, Chinese- 106, Indian- 57)	Cases: Male: 13 (46.4%) Female: 15 (53.6%) Controls: Male: 115 (50.7%) Female: 112 (49.3%)	Case: 9–71/ 36.6 years Controls: 14–78/37.3 years	2012–2015	CBZ	B*15:02; A*31:01	NR
Locharernkul C et al., 2008	Thailand	Thai population	10 Cases (6 CBZ-SJS; 4 PHT-SJS); 50 Controls	Cases: Male: 7 (70%) Female: 3 (30%)		1994–2007	CBZ, PHT	B*15:02	NR
Yampayon K et al.,2017	Thailand	Thai population	15 Cases; 100 Controls	Case: Male: 6 (40%)	Case: 57.9 years	2008–2015	PHT	B*13:01; B*15:02; B*56:02/04	Cases: 26 (7–65) days Controls:

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Table 1 (*continued*)

Author, year	Country	Population	Participants	Gender, n (%)	Age (in years) (Mean/ Median/ Range)	Study Period	AEDs involved	Allele involved in SJS/TEN	Duration of drug exposure (in days)
				Female: 9 (60%) Control: Male: 36 (36%) Female: 64 (64%)	Controls: 49 years				1008 (91–8972) days
Ramirez E et al., 2016	Spain	Spanish population	26 Cases (9 PHT-SJS; 3 LTG-SJS; 2 CBZ-SJS; 1 PB-SJS), 61 Controls	Case: Male: 10 (38.4%) Female: 16 (61.5%) Control: Male: 29 (47.5%) Female: 32 (52.5%)	Case: 3–91/ 50 years Control: 12–88/58 years	NR	PHT, LTG, PHT-LTG, CBZ	A*02:01; A*11:01; A*25:01; A*26:01; A*29:02; A*30:02; A*32::01; A*66:01; A*80:01; B*07:02; B*08:01; B*14:01; B*14:02; B*15:01; B*18:01; B*35:01; B*38:01a; B*44:02; B*44:03; B*49:01; B*51:01; B*53:01; Cw*03:03; Cw*04:01; Cw*05:01; Cw*07:01; Cw*08:02; Cw*12:03; Cw*15:02; Cw*15:05; Cw*16:01	NR
Manuyakorn W et al., 2016	Thailand	Thai Children population	27 Cases (4 SJS); 54 Controls	Case: Male: 1 (25%) Female 3 (75%) Control: Male: 34 (63%) Female: 20 (37%)	Case: 2–15/ 7.02 years Control: 0.17–18/ 8.36 years	NR	PB	A*01:01; B*13:01; B*13:02; B*15:02; B*51:01; C*03:04; C*06:02	Cases: 22 (21–53) days Controls: 591.5 (90–5930) days
Tassaneeyakul W et al., 2016	Thailand	Thai population	39 Cases; 92 Controls	Case: Male: 17(43.59%) Female: 22 (56.41%) Controls: Male: 52 (56.52%) Female: 40 (43.48%)	Case: 16–80/ 46.64 Controls: 16–78/ 40.32	2009–2015	PHT	A*02:01; A*33:03; B*13:01; B*15:02; B*38:02; B*46:01; B*51:01; B*56:02; B*58:01; C*14:02	Cases:18 (12.04) days Controls: >180 days
Chang CC et al., 2017	Malaysia	Malay population	13 Cases; 32 Controls	Case: Male: 7 (43.7%) Female: 9 (56.2%) Controls: Male: 22 (68.7%) Female: 10 (31.2%)	NR	NR	PHT	B*15:02; B*15:13	NR
Khor AHP et al., 2014	India	Indian population	5 Cases; 52 Controls	Case: Male: 4 (80%) Female: 1 (20%) Controls: Male: 27 (60%) Female: 25 (40%)	Case: 16–65/39.2 years Controls: 14–73/37.8 years	2012–2014	CBZ	B*15:02	NR
Wang WE et al., 2014	China	Chinese population	27 Cases; 64 Controls	Case: Male: 11(41%) Female: 16 (54%) Controls: Male: 35 (55%) Female: 29 (45%)	Case: 8–68/ 33 years Controls: 9–64/28 years	2009–2012	CBZ, PHT, PB, LTG	B*15:02; DRB1*15:01; A*33:03; B*58:01; DRB1*03:01	NR

(*continued on next page*)

Table 1 (*continued*)

Author, year	Country	Population	Participants	Gender, n (%)	Age (in years) (Mean/ Median/ Range)	Study Period	AEDs involved	Allele involved in SJS/TEN	Duration of drug exposure (in days)
McCormack M et al., 2011	Ireland	European population	12 Cases; 257 Controls	NR	NR	NR	CBZ	A*31:01	NR
Chang CC et al., 2011	Malayasia	Multiethinic Malayasian population	16 Cases; 300 Controls	NR	NR	1999–2007	CBZ	A1; A30; A33; A74; B*15:02;B27;B35; B*52:01;B*57:01; B75;DR11;DR12	NR
Hung SL et al., 2010	China	Han Chinese population	26 Cases; 113 Controls	Case: Male: 9 (34.6%) Female: 17 (65.4%) Controls: Male: 73 (64.6%) Female: 40 (35.4%)	Case: 83/ 57.9 years Controls: 59/38.8 years	2002–2008	PHT	Most subtypes under HLA*A,B,C,DRB1	Case: 21.1 (1–51) days Controls: 78.1 (3.5–273) months

CBZ: Carbamazepine; GBP: Gabapentin; HLA: Human Leukocyte Antigen; LTG: Lamotrigine; LVT: Levetiracetam; NR: Not reported; PB: Phenobarbitone; PHT: Phenytoin; SJS: Stevens–Johnson Syndrome; TEN: Toxic epidermal necrolysis; VPA: Valproic acid;.

Supplementary file S3D: DRB-1 on CBZ-induced SJS/TEN

3.4.2. HLA on LTG-induced SJS/TEN

3.4.2.1. HLA-A on LTG-induced SJS/TEN. A pooled analysis of 4 studies with 332 participants indicated a high risk of LTG-induced SJS/TEN among HLA-A active patients (OR: 2.38; 95% CI: 1.26 to 4.46). A similar significant association was observed with A*02:07 (OR: 10.44; 95% CI: 1.23, 88.44; $n = 1$ study; 55 participants) and A*24:02 (OR: 4.48; 95% CI: 1.66 to 12.11; $n = 1$ study; 124 participants). All other sub alleles were observed to have non-significant association [Supplementary file S4A; Table 2].

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

3.4.2.2. HLA-B on LTG-induced SJS/TEN. The meta-analysis of 6 studies with 798 participants indicated a significantly higher risk of LTG-induced SJS/TEN (OR: 2.79; 95% CI: 1.75 to 4.46) compared to the control group. A similar higher risk of LTG-induced SJS/TEN was observed in with sub-alleles B*15:02 (OR: 3.83; 95% CI: 1.49 to 9.86; $n = 4$ studies; 164 participants), B*51:02 (OR: 33.89; 95% CI: 1.39 to 826.08; $n = 1$ study; 36 participants), and B*38:01 (OR:37.08; 95% CI: 5.37 to 256.04; $n = 2$ studies; 108 participants) compared to the control group [Supplementary file S4B; Table 2].

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

3.4.2.3. HLA-C on LTG-induced SJS/TEN. Only one study with 52 participants recorded the effect of HLA-C on LTG-induced SJS/TEN. However, the association was non-significant (OR: 2.30; 95% CI: 0.53 to 10.03). Similarly, none of the other sub alleles showed a significant association [Supplementary file S4C; Table 2].

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

3.4.2.4. HLA-DRB-1 on LTG-induced SJS/TEN. A single study with 20 participants indicated a non-significant association between DRB1×15:01 and LTG-induced SJS/TEN (OR: 3.00; 95% CI: 0.45 to 20.15) [Supplementary file S4D; Table 2].

Supplementary file S4D: HLA-DRB1 on LTG-induced SJS/TEN

3.4.3. HLA on PHT-induced SJS/TEN

3.4.3.1. HLA-A on PHT-induced SJS/TEN. A meta-analysis of 4 studies with 736 participants reported HLA-A was significantly associated with higher risk of PHT-induced SJS/TEN (OR: 3.47; 95% CI: 2.17 to 5.56). A similar significant higher risk association was observed with sub alleles A*24:02 (OR: 6.00; 95% CI: 1.42 to 25.27; $n = 1$ study; 53 participants) and A*02:01 (OR: 4.33; 95% CI: 1.65 to 11.35; $n = 3$ studies; 221 participants) [Supplementary file S5A; Table 2].

Supplementary file S5A: HLA-A on PHT-induced SJS/TEN

3.4.3b. HLA-B on PHT-induced SJS/TEN. A pooled estimation of 14 studies with 6411 participants recorded a significant association between HLA-B and PHT-induced SJS/TEN (OR: 1.72; 95% CI: 1.38 to 2.15). A similar significant association was observed with sub-alleles B*15:01 (OR: 6.54; 95% CI: 1.04 to 41.16; $n = 2$ studies; 126 participants), B*15:02 (OR: 2.45; 95% CI: 1.52 to 3.95; $n = 8$ studies; 566 participants), B*38:02 (OR: 3.37; 95% CI: 1.53 to 7.41; $n = 3$ studies; 285 participants), B*56:02 (OR: 13.74; 95% CI: 2.03 to 93.17; $n = 3$ studies; 311 participants), and B*15:13 (OR: 11.28; 95% CI: 2.25 to 56.59; $n = 1$ study; 45 participants) [Supplementary file S5B; Table 2].

Supplementary file S5B: HLA-B on PHT-induced SJS/TEN

3.4.3.3. HLA-C on PHT-induced SJS/TEN. The summary estimate of 4 studies with 631 participants indicate HLA C was significantly associated with higher risk of PHT-induced SJS/TEN (OR: 2.92; 95% CI: 1.77 to 4.83) in patients. Similarly, sub alleles CW*08:01 (OR: 2.99; 95% CI: 1.15 to 7.80; 1 study; 139 participants) and CW*14:02 (OR: 6.49; 95% CI: 1.58 to 26.62; $n = 1$ study; 131 participants) also observed to have a significant association whereas other sub alleles did not have a significant association [Supplementary file S5C; Table 2].

Supplementary file S5C: HLA-C on PHT-induced SJS/TEN

3.4.3.4. HLA-DRB1 on PHT-induced SJS/TEN. A pooled estimate of studies recorded significant association of only one DRB1 sub allele DRB1×16:02 (OR: 4.26; 95% CI: 1.41 to 12.82; $n = 1$ study; 139 participants) with PHT-induced SJS/TEN.

DRB1 (OR: 2.19; 95% CI: 0.84 to 5.70; $n = 2$ studies; 157 participants) and its other alleles were not significantly associated with the PHT-induced SJS/TEN[Supplementary file S5D; Table 2].

Supplementary file S5D: HLA-DRB1 on PHT-induced SJS/TEN

3.4.4. HLA on PB-induced SJS/TEN

3.4.4.1. HLA-A on PB-induced SJS/TEN. A meta-analysis of 3 studies with 2974 participants reported significant association between the HLA-A and PB-induced SJS/TEN (OR: 6.98; 95% CI: 1.81 to 26.84) compared to the control group. A similar association was observed with

A*01:01 (OR: 12.05; 95% CI: 1.33 to 109.13; 1 study; 81 participants) and A*24:20 (OR: 20.08; 95% CI: 3.95 to 102.07; $n = 1$ study; 2886 participants) [Supplementary file S6A; Table 2].

Supplementary file S6A: HLA-A on PB-induced SJS/TEN

3.4.4.2. HLA-B on PB-induced SJS/TEN. A summary estimate of 3 studies with 3224 participants revealed HLA-B was significantly associated with higher risk of PB-induced SJS/TEN (OR: 2.40; 95% CI: 1.39 to 4.17). Similarly, sub-alleles B*13:01 (OR: 4.71; 95% CI: 1.48 to 14.91; $n = 1$ study; 81 participants) and B*51:01 (OR: 7.81; 95% CI: 2.38 to 25.65; $n = 2$ studies; 2967 participants) were significantly associated with higher risk of PB-induced SJS/TEN. Other sub-alleles B*15:02, B*58:01, and B*03:04 were not significantly associated with the risk of PB-induced SJS/TEN [Supplementary file S6B; Table 2].

Supplementary file S6B: HLA-B on PB-induced SJS/TEN

3.4.4.3. HLA-C on PB-induced SJS/TEN. Only one study recorded the effect of HLA-C on risk of PB-induced SJS/TEN, which indicated a significantly higher risk with sub allele C*06:02 (OR: 3.37; 95% CI: 1.03 to 11.01; $n = 1$ study; 81 participants) [Supplementary file S6C; Table 2].

Supplementary file S6C: HLA-C on PB-induced SJS/TEN

3.4.4.4. HLA-DRB1 on PB-induced SJS/TEN. A meta-analysis of two studies recorded DRB1 was not significantly associated with the risk of PB-induced SJS/TEN DRB1 (OR: 4.48; 95% CI: 0.87to 23.07; $n = 2$ studies; 2893 participants), whereas its sub-allele DRB1×04:10 was significantly associated with a higher risk of PB-induced SJS/TEN (OR: 8.08; 95% CI: 1.61 to 40.48; $n = 1$ study; 2886 participants) [Supplementary file S6D; Table 2].

Supplementary file S6D: HLA-DRB1 on PB-induced SJS/TEN

The overall findings of meta-analyses on association of HLA and alleles on AED-induced SJS/TEN are presented in Table 2.

3.4.5. HLA on ZNS-induced SJS/TEN

3.4.5.1. HLA-A on ZNS-induced SJS/TEN. Only one study recorded the effect of HLA-A on risk of ZNS-induced SJS/TEN, which indicated a significantly higher risk with A*02:07 (OR: 9.77; 95% CI: 3.07 to 31.1; $n = 1$ study; 2890 participants).

3.4.5.2. HLA-B on ZNS-induced SJS/TEN. Only one study recorded the effect of HLA-B on risk of ZNS-induced SJS/TEN, which indicated a significantly higher risk with B*46:01 (OR: 6.73; 95% CI: 2.12 to 21.36; $n = 1$ study; 2890 participants).

3.4.5.3. HLA-DRB1 on ZNS-induced SJS/TEN. Only one study recorded the effect of HLA-DRB1 on risk of ZNS-induced SJS/TEN, which indicated a significantly higher risk with HLA-DRB1×08:03 (OR: 3.78; 95% CI: 1.20 to 11.97; $n = 1$ study; 2890 participants).

3.5. Publication bias

Visual inspection of funnel plot indicates no obvious asymmetry, indicating absence of publication bias. This was statistically confirmed by Begg's test ($p = 0.03$); however, this was not confirmed by Egger's test ($p = 0.37$) . The funnel plot for publication bias is presented in Fig. 2.

3.6. Sensitivity analysis

A sensitivity analysis was performed by changing the random effects model to fixed effects model in the analysis of effect of HLA-B on CBZ-induced SJS/TEN. No change was observed in the overall effect measure (OR: 1.98; 95% CI: 1.79 to 2.20; $p<0.00001$; $n = 26$ studies). This indicates that our findings are robust. The funnel plot for sensitivity

Table 2
Meta-analysis results on association of HLA on AED induced SJS/TEN.

Name of allele and AED	No. of studies	Total Participants	Effect measure [95% CI]
HLA A Vs AED			
HLA A Vs CBZ			
HLA A Vs CBZ (Overall)	*14*	*21608*	*1.50 [1.03, 2.17]**
A*02:07 Vs CBZ	2	600	1.46 [0.47, 4.54]
A*33:03 Vs CBZ	5	1064	0.66 [0.10, 4.22]
A*24:02 Vs CBZ	4	1098	1.21 [0.48, 3.06]
A*02:06 Vs CBZ	4	1009	1.34 [0.67, 2.68]
*A*31:01 Vs CBZ*	*9*	*10457*	*2.88 [1.05, 7.87]*
*A*02:10 Vs CBZ*	*1*	*63*	*10.40 [1.64, 65.80]**
*A*31:1 Vs CBZ*	*1*	*63*	*10.40 [1.64, 65.80]**
A*32:01 Vs CBZ	2	1434	1.78 [0.35, 9.12]
A*01:01 Vs CBZ	1	560	5.65 [0.57, 55.86]
*A*11:53 Vs CBZ*	*1*	*560*	*86.64 [4.07, 1844.52]**
A*24:10 Vs CBZ	1	560	5.41 [0.22, 135.43]
A*30:01 Vs CBZ	1	264	0.22 [0.03, 1.85]
A*26:01 Vs CBZ	2	824	0.61 [0.18, 2.12]
A*11:01 Vs CBZ	4	889	0.76 [0.12, 4.65]
A*02:03 Vs CBZ	2	824	0.57 [0.28, 1.14]
A*02:01 Vs CBZ	4	889	0.95 [0.60, 1.50]
A*03:01 Vs CBZ	1	40	1.24 [0.05, 33.13]
A*11:04 Vs CBZ	1	40	0.37 [0.02, 7.64]
A*23:14 Vs CBZ	1	40	1.24 [0.05, 33.13]
A*24:03 Vs CBZ	1	40	1.24 [0.05, 33.13]
*A*24:07 Vs CBZ*	*2*	*90*	*4.67 [1.32, 16.53]**
A*24:17 Vs CBZ	1	40	13.00 [0.48, 351.63]
A*33:102 Vs CBZ	1	40	1.24 [0.05, 33.13]
A*34:01 Vs CBZ	1	40	1.53 [0.30, 7.79]
A*66:01 Vs CBZ	1	40	0.37 [0.02, 7.64]
A*68:01 Vs CBZ	1	40	1.24 [0.05, 33.13]
HLA-A Vs LTG			
HLA-A Vs LTG (Overall)	*4*	*332*	*2.38 [1.26, 4.46]**
*A*02:07 Vs LTG*	*1*	*55*	*10.44 [1.23, 88.44]**
A*33:03 Vs LTG	2	75	0.31 [0.04, 2.72]
*A*24:02 Vs LTG*	*1*	*124*	*4.48 [1.66, 12.11]**
A*02:01 Vs LTG	1	13	0.33 [0.02, 5.03]
A*11:01 Vs LTG	1	13	12.60 [0.39,411.11]
A*26:01 Vs LTG	1	13	4.50 [0.19, 106.82]
A*01:01 Vs LTG	1	13	2.00 [0.11, 34.82]
A*03:01 Vs LTG	1	13	1.17 [0.07, 18.35]
A*69:01 Vs LTG	1	13	12.60 [0.39,411.11]
HLA A Vs PHT			
HLA A Vs PHT (Overall)	*4*	*736*	*3.47 [2.17, 5.56]**
A*33:03 Vs PHT	2	140	2.31 [0.98, 5.41]
*A*24:02 Vs PHT*	*1*	*53*	*6.00 [1.42, 25.27]**
*A*02:01 Vs PHT*	*3*	*221*	*4.33 [1.65, 11.35]**
A*11:01 Vs PHT	1	37	1.04 [0.09, 11.47]
A*26:01 Vs PHT	1	37	3.38 [0.19, 60.24]
A*32:01 Vs PHT	1	37	6.50 [0.88, 47.90]
A*25:01 Vs PHT	1	37	10.06 [0.37,270.28]
A*29:02 Vs PHT	1	37	1.63 [0.13, 20.36]
A*30:02 Vs PHT	1	37	10.06 [0.37,270.28]
A*66:01 Vs PHT	1	37	3.38 [0.19, 60.24]
A*80:01 Vs PHT	1	37	10.06 [0.37,270.28]
A*03:01 Vs PHT	1	13	1.17 [0.07, 18.35]
A*69:01 Vs PHT	1	13	12.60 [0.39,411.11]
HLA A Vs PB			
HLA A Vs PB (Overall)	*3*	*2974*	*6.98 [1.81, 26.84]**
A*33:03 Vs PB	1	7	0.60 [0.02, 20.98]
*A*01:01 Vs PB*	*1*	*81*	*12.05 [1.33,109.13]**
A*24:20 Vs PB	*1*	*2886*	*20.08 [3.95, 102.07]**
HLA A vs ZNS			
*A*02:07*	*1*	*2890*	*9.77 [3.07, 31.1]**
HLA B Vs AED			
HLA B Vs CBZ			
HLA B Vs CBZ (Overall)	*26*	*33390*	*1.94 [1.45, 2.58]**
*B*57:01 Vs CBZ*	*3*	*9281*	*10.75 [5.84, 19.80] **
B* 07:05 Vs CBZ	2	327	2.29 [0.55, 9.44]
B*13:01 Vs CBZ	7	1416	0.70 [0.35,1.42]
B*15:01 Vs CBZ	5	800	0.56 [0.16, 1.98]
*B*15:02 Vs CBZ*	*21*	*3004*	

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Table 2 (*continued*)

Name of allele and AED	No. of studies	Total Participants	Effect measure [95% CI]
			*24.51 [14.56, 41.27] * *
*B*15:21 Vs CBZ*	*6*	*941*	*4.58 [2.14, 9.80]**
B*18.01 Vs CBZ	5	800	0.56 [0.16, 1.98]
*B*18:15 Vs CBZ*	*1*	*287*	*52.55 [2.06, 1343.47]**
B*44:03 Vs CBZ	5	891	1.01 [0.42, 2.43]
B*46:01 Vs CBZ	7	1416	0.80 [0.54, 1.19]
*B*56:04 Vs CBZ*	*1*	*287*	*18.00 [1.07, 302.03] **
B*58:01 Vs CBZ	8	1052	0.64 [0.29, 1.44]
*B*15:214 Vs CBZ*	*1*	*248*	*61.70 [2.38, 1598.92]**
B*35:05 Vs CBZ	3	372	0.79 [0.10, 6.27]
*B*35:32 Vs CBZ*	*1*	*248*	*61.70 [2.38, 1598.92]**
*B*44:13 Vs CBZ*	*1*	*248*	*61.70 [2.38, 1598.92]**
*B*15:11 Vs CBZ*	*4*	*1079*	*11.52 [2.83, 46.95] **
B*40:01 Vs CBZ	7	1393	0.57 [0.23,1.40]
B*51:01 Vs CBZ	5	557	1.11 [0.25, 4.92]
B*15:25 Vs CBZ	2	393	0.49 [0.08, 2.91]
B*35:01 Vs CBZ	3	249	0.43 [0.07, 2.51]
B*38:02 Vs CBZ	5	1081	1.02 [0.48, 2.14]
B*51:02 Vs CBZ	3	285	0.72 [0.14, 3.65]
B*54:01 Vs CBZ	4	1037	0.64 [0.17, 2.44]
B*55:02 Vs CBZ	6	829	0.67 [0.25, 1.80]
B*56:01 Vs CBZ	4	525	1.54 [0.52, 4.55]
B*27:04 Vs CBZ	2	312	0.68 [0.15, 3.09]
B*48:01 Vs CBZ	2	312	0.43 [0.05, 3.96]
*B*56:10 Vs CBZ*	*1*	*564*	*44.66 [1.79, 1116.24]**
B*07:02 Vs CBZ	3	113	0.98 [0.20, 4.73]
B*13:02 Vs CBZ	1	48	0.70 [0.03, 18.16]
B*15:07 Vs CBZ	1	48	6.93 [0.27, 180.44]
B*15:18 Vs CBZ	1	48	0.41 [0.02, 8.99]
B*13:10 Vs CBZ	1	48	6.93 [0.27, 180.44]
B*37:01 Vs CBZ	1	48	0.70 [0.03, 18.16]
B*39:04 Vs CBZ	1	48	0.70 [0.03, 18.16]
B*40:02 Vs CBZ	2	88	1.12 [0.23, 5.59]
B*40:06 Vs CBZ	1	48	0.41 [0.02, 8.99]
B*52:01 Vs CBZ	3	404	0.95 [0.30, 2.98]
B*59:01 Vs CBZ	1	48	0.70 [0.03, 18.16]
B*67:01 Vs CBZ	1	48	1.11 [0.09, 13.25]
B*15:35 Vs CBZ	3	356	2.90 [0.68, 12.35]
B*18:02 Vs CBZ	1	84	0.23 [0.02, 2.17]
B*27:06 Vs CBZ	2	316	0.60 [0.20, 1.77]
B*39:09 Vs CBZ	2	316	1.85 [0.71, 4.84]
B*14:01 Vs CBZ	1	37	3.38 [0.19, 60.24]
B*14:02 Vs CBZ	1	37	3.38 [0.19, 60.24]
B*44:02 Vs CBZ	2	65	7.07 [0.19, 257.20] *
B*27:05 Vs CBZ	1	25	22.00 [0.72, 672.78]
B*18:02 Vs CBZ	1	232	0.35 [0.07, 1.65]
*B*15:06 Vs CBZ*	*1*	*38*	*81.00 [4.20, 1561.52]**
B*46:01 Vs CBZ	1	38	0.32 [0.06, 1.79]
B*15:09 Vs CBZ	1	40	1.24 [0.05, 33.13]
B*15:13 Vs CBZ	1	40	13.00 [0.48, 351.63]
B*15:139 Vs CBZ	1	40	1.24 [0.05, 33.13]
B*15:141 Vs CBZ	1	40	1.24 [0.05, 33.13]
B*15:345 Vs CBZ	1	40	1.24 [0.05, 33.13]
B*27:06 Vs CBZ	1	40	1.24 [0.05, 33.13]
B*39:02 Vs CBZ	1	40	13.00 [0.48, 351.63]
B*40:117 Vs CBZ	1	40	0.29 [0.01, 5.88]
B*48:29 Vs CBZ	1	40	1.24 [0.05, 33.13]
B*51:06 Vs CBZ	1	40	1.24 [0.05, 33.13]
B*51:37 Vs CBZ	1	40	1.24 [0.05, 33.13]
B*56:02 Vs CBZ	1	40	0.72 [0.03, 16.42]
HLA B Vs PHT			
HLA B Vs PHT (Overall)	*14*	*6411*	*1.72 [1.38, 2.15] **
B*13:01 Vs PHT	4	474	1.12 [0.62, 2.03]
*B*15:01 Vs PHT*	*2*	*126*	*6.54 [1.04, 41.16]**
*B*15:02 Vs PHT*	*8*	*566*	*2.45 [1.52, 3.95] **
B*18.01 Vs PHT	1	37	19.00 [0.82, 439.45]
B*44:03 Vs PHT	1	37	3.71 [0.44, 31.26]
B*46:01 Vs PHT	2	220	0.39 [0.18, 0.84]
B*58:01 Vs PHT	3	229	1.22 [0.54, 2.72]
B*40:01 Vs PHT	1	89	0.72 [0.15, 3.59]
B*51:01 Vs PHT	5	3199	1.64 [0.86, 3.13]
B*15:25 Vs PHT	1	89	5.21 [0.31, 88.37]
B*35:01 Vs PHT	2	126	2.22 [0.37, 13.15]
*B*38:02 Vs PHT*	*3*	*285*	*3.37 [1.53, 7.41] **
B*51:02 Vs PHT	1	89	3.64 [0.55, 23.97]
B*54:01 Vs PHT	1	89	0.66 [0.03, 13.42]
B*55:02 Vs PHT	1	89	5.21 [0.31, 88.37]
B*56:01 Vs PHT	1	89	2.57 [0.22, 30.33]
B*07:02 Vs PHT	1	37	1.04 [0.09, 11.47]
*B*56:02 Vs PHT*	*3*	*311*	*13.74 [2.03, 93.17] **
B*08:01 Vs PHT	1	37	1.63 [0.13, 20.36]
B*38:01 Vs PHT	1	37	3.71 [0.44, 31.26]
B*44:02 Vs PHT	1	37	1.04 [0.09, 11.47]
B*49:01 Vs PHT	1	37	2.38 [0.33, 17.17]
B*53:01 Vs PHT	1	37	10.06 [0.37, 270.28]
*B*15:13 Vs PHT*	*1*	*45*	*11.28 [2.25, 56.59]**
HLA B Vs LTG			
HLA B Vs LTG (Overall)	*6*	*798*	*2.79 [1.75, 4.46] **
B*13:01 Vs LTG	1	36	1.30 [0.12, 14.20]
B*15:01 Vs LTG	1	36	0.88 [0.04, 20.54]
*B*15:02 Vs LTG*	*4*	*164*	*3.83 [1.49, 9.86]**
B*46:01 Vs LTG	1	36	0.80 [0.08, 8.19]
B*58:01 Vs LTG	1	36	0.29 [0.01, 5.84]
B*39:01 Vs LTG	1	55	12.25 [0.64, 234.81]
B*35:08 Vs LTG	1	13	12.60 [0.39, 411.11]
B*40:01 Vs LTG	1	36	0.36 [0.02, 7.31]
B*51:01 Vs LTG	1	36	1.80 [0.15, 20.99]
B*35:01 Vs LTG	1	36	5.80 [0.31, 108.60]
B*38:02 Vs LTG	1	36	0.45 [0.02, 9.52]
*B*51:02 Vs LTG*	*1*	*36*	*33.89 [1.39, 826.08] **
B*54:01 Vs LTG	1	36	0.88 [0.04, 20.54]
B*55:02 Vs LTG	1	36	0.60 [0.03, 13.20]
B*56:01 Vs LTG	1	36	16.64 [0.60, 463.36]
*B*38:01 Vs LTG*	*2*	*108*	*37.08 [5.37, 256.04] **
B*44:02 Vs LTG	1	13	4.50 [0.19, 106.82]
B*49:01 Vs LTG	1	13	4.50 [0.19, 106.82]
HLA B Vs PB			
HLA B Vs PB (Overall)	*3*	*3224*	*2.40 [1.39, 4.17]**
*B*13:01 Vs PB*	*1*	*81*	*4.71 [1.48, 14.91]**
B*15:02 Vs PB	2	88	0.93 [0.24, 3.54]
B*58:01 Vs PB	1	7	0.60 [0.02, 20.98]
*B*51:01 Vs PB*	*2*	*2967*	*7.81 [2.38, 25.65]**
B*03:04 Vs PB	1	81	1.12 [0.36, 3.43]
HLA B Vs ZNS			
*B*46:01*	*1*	*2890*	*6.73 [2.12, 21.36]**
HLA-DRB1 Vs AED			
HLA-DRB1 Vs CBZ			
HLA-DRB1 Vs CBZ (Overall)	*4*	*1080*	*2.82 [1.94, 4.12]**
*HLA-DRB1*07:01 Vs CBZ*	*2*	*220*	*5.20 [2.04, 13.26]**
*HLA-DRB1*12:02 Vs CBZ*	*1*	*230*	*3.38 [1.79, 6.36]**
HLA-DRB1*03:01 Vs CBZ	1	145	2.05 [0.74, 5.66]
*DQB1*03:03 Vs CBZ*	*1*	*145*	*3.12 [1.14, 8.54]**
HLA-DRB1*03:01 Vs CBZ	1	55	0.09 [0.00, 1.55]
*HLA-DRB1*01:01 Vs CBZ*	*1*	*230*	*14.00 [1.53, 128.10] **
HLA-DRB1*15:01 Vs CBZ	1	55	3.98 [0.91, 17.46]
HLA-DRB1 Vs PB			
HLA-DRB1 Vs PB (Overall)	2	2893	4.48 [0.87, 23.07]
HLA-DRB1*15:01 Vs PB	1	7	1.50 [0.06, 40.63]
*HLA-DRB1*04:10 Vs PB*	*1*	*2886*	*8.08 [1.61, 40.48]**
HLA-DRB1 Vs LTG			
HLA-DRB1*15:01 Vs LTG	1	20	3.00 [0.45, 20.15]

(*continued on next page*)

Table 2 (*continued*)

Name of allele and AED	No. of studies	Total Participants	Effect measure [95% CI]
HLA-DRB1 Vs PHT			
HLA-DRB1 Vs PHT (Overall)	2	157	2.19 [0.84, 5.70]
HLA-DRB1*03:01 Vs PHT	1	9	0.26 [0.01, 7.27]
HLA-DRB1*15:01 Vs PHT	1	9	0.44 [0.01, 12.98]
*HLA-DRB1*16:02 Vs PHT*	*1*	*139*	*4.26 [1.41, 12.82]**
HLA-DRB1 vs ZNS			
*HLA-DRB1*08:03*	*1*	*2890*	*3.78 [1.20, 11.97]*
HLA C Vs AED			
HLA C Vs CBZ			
HLA C Vs CBZ (Overall)	*3*	*622*	*7.83 [4.72, 12.98]**
*CW*08:01 Vs CBZ*	*2*	*257*	*12.27 [6.06, 24.84]**
*CW*03:02 Vs CBZ*	*1*	*145*	*4.96 [1.26, 19.48]**
C*06:02 Vs CBZ	1	145	2.15 [0.63, 7.42]
*CW*03:03 Vs CBZ*	*1*	*25*	*47.00 [1.28, 1722.11]**
CW*07:02 Vs CBZ	1	25	2.83 [0.15, 52.74]
CW*05:01 Vs CBZ	1	25	22.00 [0.72, 672.78]
HLA C Vs PHT			
HLA C Vs PHT (Overall)	*4*	*631*	*2.92 [1.77, 4.83] **
*CW*08:01 Vs PHT*	*1*	*139*	*2.99 [1.15, 7.80]**
CW*03:03 Vs PHT	1	37	10.06 [0.37, 270.28]
CW*04:01 Vs PHT	1	37	0.86 [0.14, 5.13]
*CW*14:02 Vs PHT*	*1*	*131*	*6.49 [1.58, 26.62]**
CW*07:01 Vs PHT	2	102	2.29 [0.67, 7.80]
CW*08:02 Vs PHT	1	37	1.63 [0.13, 20.36]
CW*12:03 Vs PHT	1	37	4.17 [0.67, 26.02]
CW*15:02 Vs PHT	1	37	4.17 [0.67, 26.02]
CW*15:05 Vs PHT	1	37	10.06 [0.37, 270.28]
CW*16:01 Vs PHT	1	37	1.04 [0.09, 11.47]
HLA C Vs LTG			
HLA C Vs LTG (Overall)	1	52	2.30 [0.53, 10.03]
CW*04:01 Vs LTG	1	13	2.00 [0.11, 34.82]
CW*07:01 Vs LTG	1	13	4.50 [0.19, 106.82]
CW*12:03 Vs LTG	1	13	0.50 [0.03, 8.71]
CW*12:04/05 Vs LTG	1	13	12.60 [0.39, 411.11]
HLA C Vs PB			
*C*06:02 Vs PB*	*1*	*81*	*3.37 [1.03, 11.01]**

*indicates the significant association of HLA/HLA allele in AED induced SJS/TEN.

analysis is presented in Supplementary file S7.

Supplementary file S7: Sensitivity analysis

4. Discussion

Our analysis indicated that HLA genetic polymorphisms were highest with CBZ, followed by PHT, LTG, PB, ZNS, and GBP. HLA alleles significantly associated with AED-induced SJS/TEN were A*01:01, A*02:01, A*02:07, A*02:10, A*11:53, A*24:02, A*24:07, A*24:20, A*31:1, A*31:01, B*13:01, B*15:01, B*15:02, B*15:06, B*15:11, B*15:13, B*15:21, B*15:214, B*18:15, B*35:32, B*38:01, B*38:02, B*44:13, B*46:01, B*51:01, B*51:02, B*56:02, B*56:04, B*56:10, C*06:02, CW*03:02, CW*03:03, CW*08:01, CW*14:02, DRB1*01:01, DRB1*03:03, DRB1*04:10, DRB1*07:01, DRB1*08:03 DRB1*12:02, and DRB1*16:02.

Our analysis observed higher genetic polymorphisms in SCADRs from developing countries (especially Asian) than developed countries. This might be due to variations in incidence of epilepsy, heterogeneity in genetic makeup, and diverse patient-related factors, such as race, ethnicity, population, and age. High rate of selection, mutation, and genetic hitchhiking can be associated with high HLA polymorphism [70]. Human MHC encoded glycoproteins, known as HLA, are specialized in presentation of short peptides to T cells and play a major role in the body's immune defense mechanism [71]. Globally, epilepsy is a commonly occuring neurological condition requiring multiple AEDs for its management, though AEDs are also used for other indications such as neuropathic pain, bipolar disorders, trigeminal neuralgia, migraine, and essential tremor and for other comorbidities associated with seizures [1,72,73]. The use of AEDs in patients with epilepsy is higher than in patients with other indications. Hence, HLA polymorphism screening would be beneficial among long-term users to identify HLA-associated AED-induced SCADRs. Prevalence of epilepsy is lesser in developed countries (5 to 8/1000 people) compared to developing countries (40/1000), varying significantly based on geographical location and age. AEDs are therapeutically used for symptomatic epilepsy to improve quality of life with lowest side effects and cost [74]. High cost of newer AEDs and sub-optimal management of epilepsy in developing countries is linked with higher mortality compared to that in developed countries [75].

Our findings indicate that HLA alleles A*31:01, A*02:10, A*31:1, A*11:53, A*24:07, B*57:01, B*15:02, B*18:15, B*56:04, B*15:214, B*35:32, B*44:13, B*15:11, B*56:10, B*15:06, DRB1×07:01 DRB1×12:02, DRB1×03:03, DRB1×01:01, CW*08:01, CW*03:02, and CW*03:03 were significantly associated with increased risk of CBZ-induced SJS/TEN. HLA-B*15:02 initially identified in a Han Chinese population in Taiwan had a stronger association with CBZ-induced SJS and TEN [13], and similar associations were observed in Malay population in Malaysia [56], Hong Kong Han Chinese patients [76], and European Asian ancestry population [77].

LTG-induced SJS/TEN was significantly higher among patients who had A*02:07, A*24:02, B*15:02, B*51:02, and B*38:01 alleles of HLA. Studies conducted by An DM et al., [18] and Hung SI et al., [57] also observed a significantly higher risk of LTG-induced SJS/TEN in patients with B*15:02 polymorphism.

HLA sub-alleles A*24:02, A*02:01, B*15:01, B*15:02, B*38:02, B*56:02, B*15:13, DRB1×16:02, CW*08:01 and CW*14:02 were found to be significantly associated with PHT-induced SJS/TEN. A study by Locharernkul C et al., in a Thai population also found a significant association between allele HLA-B*15:02 and PHT- and CBZ-induced SJS/TEN; however, these studies did not observe a significant association with other SCADRs such as MPE [50]. Case studies of two patients by Hu FY et al., indicated HLA-B*46:01/B*51:02 and HLA-B*370:1/B*46:01 alleles could contribute to PHT-induced SJS, thereby providing insights into the potential role of non-genetic factors or other genetic factors [78].

This clearly indicates the role of HLA-B, specifically allele HLA-B*15:02, in CBZ-, PHT-, and LTG-induced SJS/TEN. Interestingly, this association was seen with only SJS/TEN but not with other types of SCADRs [25,56]. More evidence is needed to define the exact role of the HLA-B gene in the pathogenesis of SJS/TEN, although gene mapping studies have observed a significant relationship between them [78]. While studies have observed significant associations in different Asian populations, except Japanese and South Koreans, compared to other populations, studies with larger populations (as study subjects) are needed to confirm these associations [56].

HLA sub-alleles A*01:01, A*24:20, B*13:01, B*51:01, DRB1×04:10, and C*06:02 were significant in causing PB-induced SJS/TEN. A study by Manuyakorn W et al., recorded that alleles A*01:01 and B*13:01 were significantly associated with PB-induced SJS/TEN in Thai children [52]. HLA sub-allele A*02:07, B*46:01, and DRB1×08:03 polymorphisms were significantly associated with ZNS-induced SJS/TEN. The evidence by Vivar KL et al., indicates that HLA alleles can be used as predictors of susceptibility to ZNS-induced SJS/TEN [79].

The Clinical Pharmacogenetics Implementation Consortium and the Dutch Pharmacogenetics Working Group guidelines assessed the diagnostic accuracy of HLA genotyping in AED-induced SJS/TEN. HLA-B*1502 was observed to have high sensitivity (67%–100%) and high specificity (73%–100%) in CBZ-induced SJS/TEN. HLA-B*1502 was observed to have low sensitivity (0%–33.3%) and high specificity (81.4%–100%) in LTG-induced SJS/TEN. HLA-B*1502 was observed to have a sensitivity of 12.8%–100% and a specificity of 77.5%–94.9% in

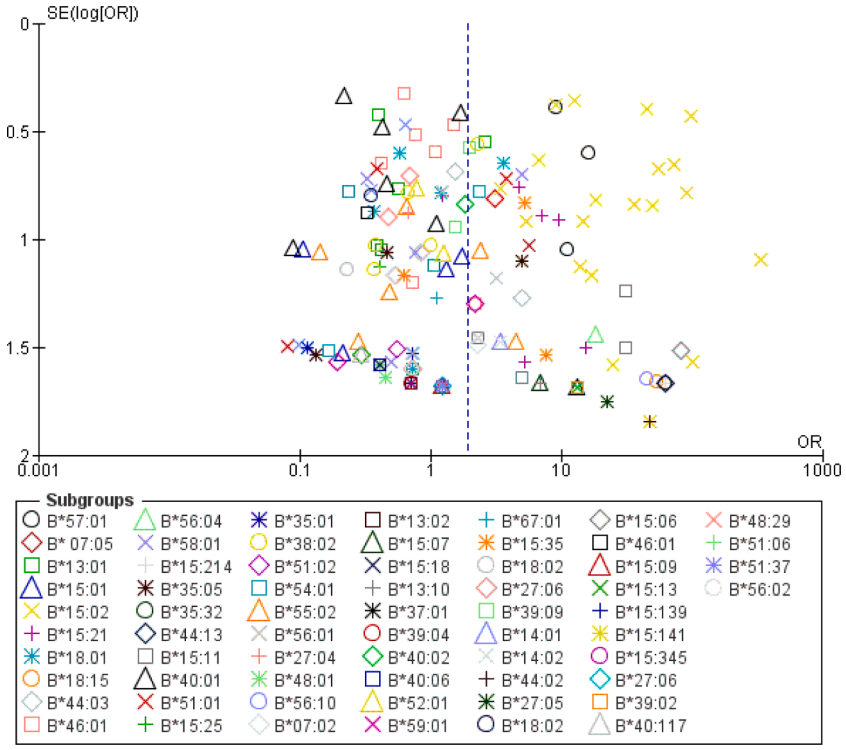

Fig. 2. Funnel plot for publication bias.

PHT-induced SJS/TEN [80]. Screening tests such as HLA typing and lymphocyte toxicity assays should be recommended for patients having high risk of developing AED-induced SJS/TEN [79].

The English language restriction to the inclusion criteria was a limitation of this study. This meta-analysis gives a comprehensive understanding of the role of various HLA alleles on AED-induced SJS/TEN. In addition to existing literature on this topic, further studies are needed on genetic links, similar immune response of HLA by different AEDs, pharmacogenomics testing of highly allergic drugs, and pathophysiological characters. The evidence from these findings can be extrapolated to further research in different populations. As translational research is growing, these findings could be incorporated in planning individualized therapy.

5. Conclusion

In conclusion, our meta-analysis indicated a significant association between HLA alleles and AED-induced SJS/TEN. Screening for HLA alleles prior to initiating AED therapy may help avoid AED-induced severe cutaneous adverse drug reactions. Clinicians could advise screening for HLA polymorphisms in patients suspected to have or having higher risk of severe cutaneous adverse drug reactions.

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Availability of data and material

The primary data related to this work has not been deposited in any repository. However, it will be available from the corresponding author on request (while following appropriate guidelines).

CRediT authorship contribution statement

Muhammed Rashid: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Software, Writing – original draft. **Asha K Rajan:** Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Writing – original draft. **Manik Chhabra:** Conceptualization, Data curation, Project administration, Supervision, Writing – original draft. **Ananth Kashyap:** Investigation, Visualization, Writing – review & editing. **Viji Pulikkel Chandran:** Methodology, Resources, Validation, Writing – review & editing. **Rajesh Venkataraman:** Resources, Visualization, Writing – review & editing. **Sreedharan Nair:** Resources, Validation, Writing – review & editing. **Girish Thunga:** Conceptualization, Project administration, Supervision, Writing – review & editing.

Declaration of Competing Interest

None of the authors have any conflicts of interest to declare. The listed authors are solely responsible for the originality and content of the manuscript. The authors have no relevant affiliations or financial involvements with any organizations or entities with a financial interest in or financial conflict with the subject matter discussed in the manuscript.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2022.09.011.

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