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Neuroimaging in Drug-Induced Neurotoxicity and Posterior Reversible Encephalopathy Syndrome: An Independent Systematic Review and Meta-Analysis of MRI Pattern Distribution, Drug-Class Etiological Profiles, DWI/ADC Reversibility Predictors, and Clinical Outcome Stratification from January 2000 Through May 2026

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ADMINISTRATIVE INFORMATION

Support - Self-funded. University of Hail College of Pharmacy academic resources. No pharmaceutical industry or commercial funding received.

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202660046

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 9 June 2026 and was last updated on 9 June 2026.

INTRODUCTION

Review question / Objective What are the drug-class PRES etiological proportions, the prevalence of central-variant PRES, the DWI/ADC reversibility prediction performance, and the effect of drug cessation timing on complete MRI normalisation?

Rationale This systematic review addresses a critical evidence gap in radiological pharmacovigilance. No comprehensive synthesis with pre-specified pattern analyses exists for this topic. Prospective registration ensures transparency and minimises reporting bias.

Condition being studied Drug-induced posterior reversible encephalopathy syndrome (PRES), toxic leukoencephalopathy, and drug-induced encephalitis from any pharmacological agent including calcineurin inhibitors, chemotherapy, anti-VEGF agents, and immune checkpoint inhibitors.

METHODS

Search strategy PubMed/MEDLINE, Embase, Cochrane CENTRAL, Web of Science, and Scopus from January 1, 2000 to May 31, 2026. ClinicalTrials.gov and WHO-ICTRP on May 31, 2026. Key terms: posterior reversible encephalopathy syndrome, PRES, central-variant PRES, toxic leukoencephalopathy, drug-induced encephalitis, DWI, ADC, FLAIR, tacrolimus neurotoxicity, cyclosporine PRES, methotrexate leukoencephalopathy, ICI encephalitis, 5-fluorouracil leukoencephalopathy, DPD deficiency, uridine triacetate.

Participant or population Adults aged 18 years or above with confirmed drug-induced PRES (NARANJO ≥5 or clinical consensus), toxic leukoencephalopathy, or drug-induced encephalitis with brain MRI or CT data.

Intervention Brain MRI (FLAIR, DWI/ADC, SWI, gadolinium-enhanced T1) or CT for characterisation of drug-induced neurotoxicity

patterns, severity grading, reversibility assessment, and drug-specific attribution.

Comparator Clinical diagnosis as reference standard; DWI/ADC pattern as reversibility predictor versus clinical outcome; early drug cessation versus delayed cessation for MRI normalisation comparison.

Study designs to be included Prospective cohort studies (n≥10); retrospective cohort studies (n≥10 with MRI data); adequately sized case series (n≥5 with extractable MRI data); FAERS pharmacovigilance analyses for drug-PRES disproportionality.

Eligibility criteria Inclusion: Adults with confirmed drug-induced PRES (NARANJO ≥5 or consensus) or drug-induced toxic leukoencephalopathy; brain MRI or CT data with extractable imaging findings.Exclusion: Non-drug-induced PRES (eclampsia, hypertensive emergency without drug attribution); paediatric populations; studies without imaging data; case reports (n<5).

Information sources PubMed/MEDLINE, Embase, Cochrane CENTRAL, Web of Science, Scopus, ClinicalTrials.gov, WHO-ICTRP.

Main outcome(s) Drug-class PRES etiological distribution (pooled proportions); central-variant PRES prevalence (I^2); complete MRI normalisation rate by drug cessation timing (≤24h vs >24h); DWI/ADC cytotoxic admixture sensitivity and specificity for irreversible injury.

Additional outcome(s) SWI intracranial haemorrhage prevalence in PRES; diagnostic delay for central-variant PRES versus classic posterior PRES; 5-FU/DPD leukoencephalopathy specific pattern prevalence; drug-specific MRI pattern specificity for causative agent attribution.

Data management Data will be managed using Covidence for screening and Rayyan for deduplication. Extracted data stored in pre-piloted Excel forms. Two reviewers screen and extract independently; disagreements resolved by consensus.

Quality assessment / Risk of bias analysis Diagnostic accuracy studies: QUADAS-2 (four domains: patient selection, index test, reference standard, flow and timing). Cohort studies: Newcastle-Ottawa Scale (threshold ≥5 stars). Overall certainty of evidence rated using GRADE per primary outcome.

Strategy of data synthesis Freeman-Tukey double arcsine transformation for proportions under DerSimonian-Laird random-effects model. Bivariate random-effects modelling for diagnostic accuracy (Reitsma method) generating summary ROC curves. Heterogeneity quantified by Cochran Q and I^2. Egger regression and funnel plot inspection for publication bias where ≥10 studies contribute. PRES etiological proportions and reversibility rates via Freeman-Tukey. DWI/ADC performance via bivariate random effects. Cessation timing OR under DerSimonian-Laird. Subgroup analyses by drug class and DWI/ADC pattern.

Subgroup analysis Causative drug class (calcineurin inhibitors vs anti-VEGF vs chemotherapy vs ICI vs antibiotic); classic posterior vs central-variant PRES; DWI/ADC pattern (pure vasogenic vs cytotoxic admixture); drug cessation timing (≤24h vs >24h vs >72h).

Sensitivity analysis Restriction to prospective cohort studies only; restriction to MRI-confirmed PRES with DWI/ADC data; exclusion of case series; restriction to 3T MRI studies.

Language restriction No language restriction.

Country(ies) involved Saudi Arabia.

Other relevant information Neuroimaging; Neurology; Clinical Pharmacy; Oncological Imaging; Transplant Medicine.

Keywords PRES; posterior reversible encephalopathy syndrome; central-variant PRES; toxic leukoencephalopathy; DWI; ADC; tacrolimus; methotrexate; ICI encephalitis; drug-induced neurotoxicity; systematic review; meta-analysis.

Dissemination plans Peer-reviewed publication in a high-impact radiology, nuclear medicine, or clinical pharmacology journal; open-access preferred.

Contributions of each author

Author 1 - Abdulrahman Alanazi - Conceived and designed the study, drafted the protocol, will lead data extraction and synthesis, and drafted the manuscript and final manuscriptsubmission.
Email: aas2@hotmail.com
Author 2 - Basmah Alanazi - Contributed to the development of the selection criteria, will assist with data extraction and risk of bias assessment, and validity.
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