



Intracranial hemorrhage in posterior reversible encephalopathy syndrome: a systematic review and meta-analysis

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Background: Posterior reversible encephalopathy syndrome (PRES) is a clinical-radiographic phenomenon characterized by vasogenic edema, predominantly affecting the posterior regions of the brain. The hemorrhagic variant of PRES has been increasingly recognized, complicating the clinical picture and prognosis.

Methods: This meta-analysis was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Observational studies and case reports/series were included. Extracted data included demographics, clinical presentations, imaging findings, and outcomes. A random-effects model to pool the incidence rate of hemorrhagic PRES and heterogeneity was assessed using the I^2 statistic. The Joanna Briggs Institute scale for case reports/series and the Newcastle–Ottawa scale for cohort studies were used for quality and risk of bias assessment.

Results: A total of 63 individual records and 12 cohort studies were reviewed. Hypertension at arrival was seen in > 90% of cases. Overall, 60.3% of cases occurred in women and the average age was 39.3, with a 12.7% mortality rate. The incidence rate of hemorrhagic PRES was found to be approximately 17%, with significant heterogeneity among the included studies ($I^2 = 67\%$). Seizures (31.7%), headaches (33.3%), and altered mental status (30.1%) were the most reported symptoms. Hypertension (31.7%), immunosuppressive therapy (23.8%), and coagulopathy (11.1%) were identified as the most common risk factors. Hemorrhagic findings included intraparenchymal hemorrhage (77.7%), subarachnoid hemorrhage (15.8%), and microhemorrhages (6.3%).

Conclusions: Hemorrhagic PRES is a significant clinical concern, occurring in approximately 17% of PRES cases, and is often associated with poorer outcomes. We highlight the importance of early recognition, aggressive blood pressure control, and careful monitoring in high-risk patients.

Keywords: intracranial hemorrhage, posterior reversible encephalopathy syndrome (PRES), reversible posterior leukoencephalopathy syndrome (RPLS)

Introduction

Posterior reversible encephalopathy syndrome (PRES) is a neuroradiological disorder characterized by a unique set of

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HIGHLIGHTS

- Hemorrhagic transformation in PRES occurs in approximately 17% of cases, with significant variability across studies.
- Hypertension, immunosuppressive therapy, and coagulopathy are the most common risk factors for hemorrhagic PRES.
- Intraparenchymal hemorrhage is the most frequently observed hemorrhagic manifestation in PRES, affecting 77.7% of cases.
- Patients with hemorrhagic PRES experience poorer outcomes, with a 12.7% mortality rate observed in the review.
- Surgical intervention including craniectomy and external ventricular drain placement was seen in 11.1% of cases.

clinical and imaging findings^[1]. Clinically, it presents with symptoms such as headache, seizures, visual disturbances, and altered mental status. Radiologically, it is typically identified by the presence of vasogenic edema seen as an increased signal in T₂-weighted imaging (T₂WI), which predominantly affects the posterior regions of the cerebral cortex and subcortical white

matter. PRES is commonly associated with various conditions and factors, including hypertension, renal failure, autoimmune diseases, and the use of certain medications^[2].

Traditionally, PRES has been described as a reversible condition with a favorable prognosis when promptly recognized and properly managed. However, recent literature suggests a more complex spectrum of the disease, particularly regarding its potential for hemorrhagic transformation. The hemorrhagic variant of PRES, characterized by the appearance of hemorrhage in the areas of edema, adds a layer of complexity to the clinical management and prognostic assessment of these patients^[3]. Furthermore, the phenomenon of “conversion,” where initially non-hemorrhagic PRES evolves into a hemorrhagic form, presents additional clinical challenges. Despite increasing recognition, the hemorrhagic variant of PRES remains poorly understood, with limited data on their incidence, risk factors, and pathophysiology, which underscores the need for a comprehensive and systematic synthesis of existing evidence. This systematic review and meta-analysis aim to consolidate current knowledge about hemorrhagic PRES, providing a detailed overview of its epidemiology, clinical and radiological characteristics, associated risk factors, management strategies, and results.

Methods

Protocol and registration

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and adheres to the Assessing the Methodological Quality of Systematic Reviews 2 (AMSTAR2) criteria^[4]. The review protocol was registered with the International Prospective Register of Systematic Reviews to ensure transparency and minimize the risk of bias.

Information sources and search strategy

A comprehensive search was performed across several databases, including PubMed/PubMed Central/MEDLINE, ScienceDirect, Hinari. The search strategy incorporated a combination of keywords and Medical Subject Headings terms relevant to PRES, hemorrhage/hemorrhage, hemorrhagic transformation, and conversion. The results were queried from the inception of the database until November 2024. The search took place on November 15, 2024. The search included literature from the inception of the databases to the present to ensure comprehensive coverage. Gray literature was also conducted by reviewing the first 100 results on Google Scholar and OpenGrey. The search strings utilized for each database is included in Supplemental Digital Content, Table 1, available at: <http://links.lww.com/MS9/A904>. AMSTAR 2 information is provided in Supplemental Digital Content, Table 2, available at: <http://links.lww.com/MS9/A905>.

Eligibility criteria

The studies were selected based on the following criteria:

Inclusion Criteria: Studies reporting on hemorrhagic variant and conversion in PRES, including observational studies (cohort, case-control, and cross-sectional), clinical trials, case series, and case reports.

Exclusion Criteria: Studies not focusing on the hemorrhagic variant or conversion in PRES. Additionally, nonoriginal studies (e.g., reviews, commentaries, and editorials) were not included. Records not of the English language were excluded.

Data collection

First, the records from the initial search strategy were exported to EndNote X9 (*ver* 3.3) to remove duplicate records. The records were then uploaded to the Rayyan QCRI web platform for review by the authors. Two independent reviewers extracted data using a standardized data extraction form. The information extracted included study characteristics, demographics of the patient, clinical presentations, imaging findings, surgical interventions, medical management strategies, results, and follow-up data. Discrepancies between the reviewers were resolved through discussion or consultation with a third reviewer. Descriptive statistics, including reporting of mean and standard deviations (SDs) and ranges, were completed where appropriate. The narrative synthesis provided an overview of the findings, including study characteristics and qualitative data.

Meta-analysis

This meta-analysis was conducted to evaluate the incidence rate reported in multiple studies. The analysis was performed using RStudio (*version* 2023.06.0 + 421) specifically the “metafor” package, which is well suited for meta-analyses of proportions and other effect sizes. The primary data extracted from each study included the number of events (e.g., cases of outcome of interest) and the total sample size. From these data, the incidence rate for each study was calculated as the number of events divided by the total number of participants.

The meta-analysis was performed using a random effects model, given the expectation of heterogeneity among the included studies. The random-effects model accounts for both within-study and between-study variability, providing a more generalized estimate of the incidence rate. The “metafor” package was used to pool incidence rate, compute 95% confidence intervals, and assess heterogeneity between studies. Heterogeneity was evaluated using the I^2 statistic, which describes the percentage of variability in effect estimates that is due to heterogeneity rather than chance. An I^2 value greater than 50% was considered indicative of significant heterogeneity, justifying the use of the random effects model.

Quality and risk of bias assessment

The quality of the included studies was assessed using two established tools: the Joanna Briggs Institute (JBI) Critical Assessment Tools and the Newcastle–Ottawa scale (NOS). The JBI Critical Appraisal Tools were applied to the case reports included in the review. This tool assesses the methodological quality of studies in several domains, including clarity of patient descriptions, appropriateness of diagnostic tests, consistency of interventions, and comprehensiveness of follow-up. Each domain is scored as either “Yes,” indicating that the criteria were met, or “No,” indicating that they were not, leading to an overall assessment of the risk of bias classified as low, moderate, or high. For cohort studies, the NOS was used to evaluate the quality of the studies in three key areas: the selection of study groups (maximum of 4 points), the comparability of the groups

(maximum of 2 points), and the determination of outcomes (maximum of 3 points). The total score ranges from 0 to 9, with higher scores indicating higher quality. Studies that scored 7 or more points were considered to have a low risk of bias, while those with scores between 5 and 6 were considered to have a moderate risk of bias. These quality assessments were conducted independently by two reviewers, with discrepancies resolved by consensus or by involving a third reviewer. The results of these assessments provided a basis for evaluating the robustness of the evidence and were considered when interpreting the findings of the meta-analysis.

Results

After removing duplicates, 397 records have their abstracts and titles screened. A total of 316 records were reviewed and assessed for eligibility for inclusion in the qualitative and quantitative synthesis. A total of 52 records were obtained. A PRISMA guided flow-diagram of record assessment is provided in Figure 1. A complete list of individual patient records and observational studies is provided in Supplemental Digital Content, Table 3, available at: <http://links.lww.com/MS9/A906>

and Supplemental Digital Content, Table 4, available at: <http://links.lww.com/MS9/A907>, respectively.

Clinical and radiographic characteristics

A total of 63 patients were included in the analysis. The average age of reported cases was 39.3 with a SD of 19.45 and a range of 4–72. Twenty-one out of 63 (33.3%) cases occurred in men and 38/63 (60.3%) in women. Eight out of 63 (12.7%) individuals were < 18 years of age^[7,12,16,29,35].

Commonly reported past medical diagnoses included hypertension (14/63; 22.2% of cases)^[8,18,20,21,25,27,30,39,43,45], chronic kidney disease (4/63; 6.3%)^[8,30,34], 2 acute renal failure^[9], 2 acute liver failure^[9], 1 congestive heart failure^[9], 3 anticoagulation usage^[5,9,30], 3 acute myeloid leukemia (AML)^[34,36], 1 aplastic anemia^[34], 1 chronic cytarabine usage^[36], 1 type II cryoglobulinemia^[6], 1 Loeys–Dietz syndrome^[7], immunosuppressive therapy 14/63 (22.2%) (adalimumab, 7 tacrolimus, mycophenolate, 2 cyclosporine, pazopanib, ruxolitinib, antithymocyte globulin)^[9–11,16,17,29,32,33,35,37], 4 hematopoietic stem-cell transplantation (HSCT)^[9,12], 5 solid-organ transplantation (3 liver^[9,16], 2 kidney^[9,17]), HELLP syndrome^[9,13], pre-eclampsia^[15,39], cancer (colon^[9], T-cell lymphoma^[9],

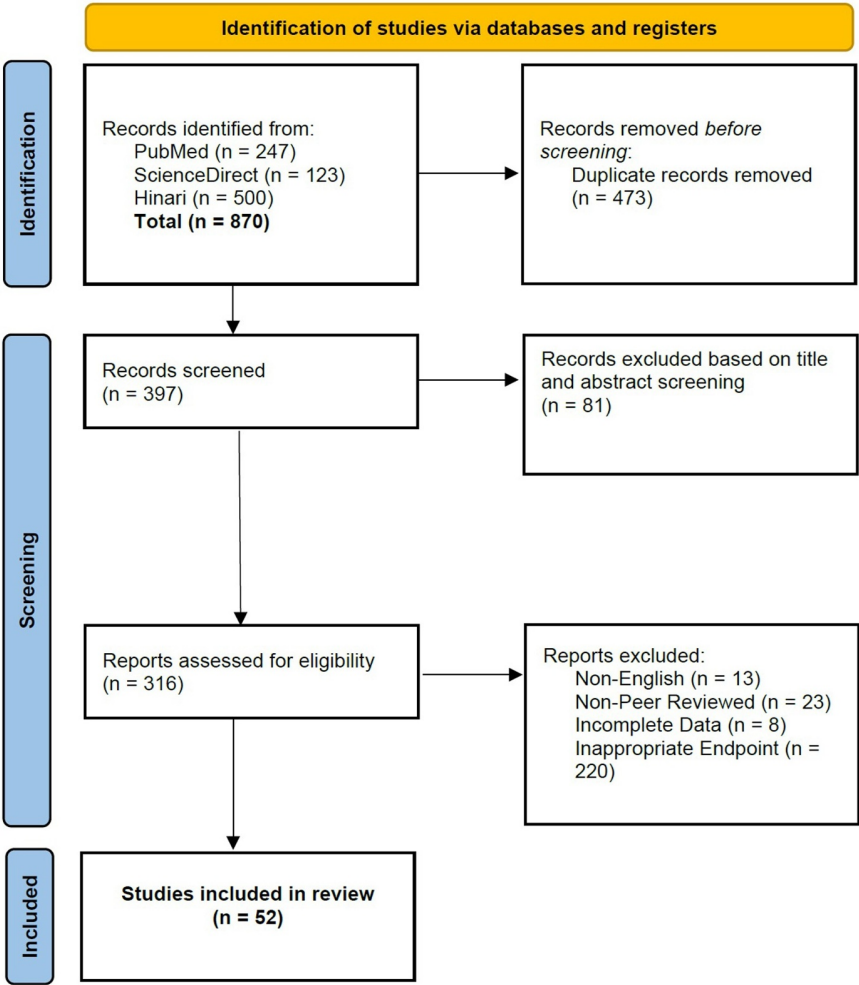


Figure 1. PRISMA flow diagram.

coronary artery disease^[20], type 2 diabetes mellitus (T2DM)^[21], systemic lupus erythematosus (SLE)^[23], 2 spinal cord injury^[45,46], Henoch-Schönlein purpura^[28], 1 Non-Hodgkin lymphoma^[41], phentermine abuse^[44].

The systolic blood pressure (SBP) on arrival ranged from 140 to 260 mmHg. A normal blood pressure was only noted in 4/63 (6.3%) cases^[5,6,10,30]. Mean arterial pressure (MAP) ranged from 100 to 120 mmHg^[5]. A SBP > 200 mmHg was noted in 12/63 (19.0%) case^[8,9,15,24,27,33,35]. Clinical symptoms of PRES included 20/63 (31.7%) cases of seizures^[7,9,12,16,17,28,29,34,38,40,44,46], 2 status epilepticus^[9,37], 21/63 (33.3%) non-thunderclap headache^[5-9,11,13,15,17,25,27-29,33,34,39,40,42,43,45], alteration in mental status in 19/63 (30.1%) cases^[5,9,13,16,17,20-22,30,32,34,41,43], 3 individuals reported a thunderclap headache^[11,14,26], 2 dysarthria^[27,36], 2 acute ataxia^[22,36], nausea/vomiting 7/63 (11.1%)^[11,25,30,42,43], 4 paresis^[6,9,27,42], visual disturbance 12/63 (19.0%)^[9-11,13,17,22,24,31,35,39,45], dizziness^[14], Anton-Babinski syndrome^[24].

Magnetic resonance imaging (MRI) of the brain showed evidence intraparenchymal hemorrhage (IPH) in 49/63 cases (77.7%): This includes 1 in the cerebellum (unilateral)^[30], 12/63 (19.0%) occipital lobe (unilateral)^[5,9,13,14,18,20,30,31,41,43,46], 3 frontal lobe (unilateral)^[9,28,38], 2 frontal lobe (bilateral)^[6,9], 5/63 (7.9%) parietal lobe (unilateral)^[9,10,21,29], 2 parietal lobe (bilateral)^[9,37], brain stem with intraventricular hemorrhage (IVH)^[9], 2 unilateral caudate hemorrhage with IVH^[22,42], 5/63 (7.9%) bilateral parieto-occipital lobes^[19,20,35,44], parietooccipital^[23], 3 bilateral occipital lobes^[24,26,32], 2 basal ganglia^[27,43], temporo-parieto-occipital lobe^[39], unilateral frontal and occipital lobes^[45]. Bilateral IPH was reported in 17/63 (27.0%) individuals. The most reported finding on MRI of the brain included an increased T₂-FLAIR signal representing vasogenic edema involving the parieto-occipital lobes, however sometimes involving the frontal lobes and deep white matter. One case reported contrast enhancement from metastatic disease^[33]. Subarachnoid hemorrhage (SAH) was noted in 10/63 (15.8%): 3 occipital lobe (bilateral)^[5,40], frontal lobe^[8], 2 temporal lobe (unilateral)^[13,17], 2 parietal lobe (unilateral)^[9,16], 1 R parasagittal sulcal region, and L perimesencephalic cistern^[25]. Subcortical microhemorrhages were seen in 4/63 (6.3%) individuals^[12,15]. One reported petechial hemorrhages involving the corpus callosum^[20]. Both IPH and SAH were noted in three individuals^[5,13,40]. Cortical or convexity subarachnoid hemorrhage (cSAH) was noted in three patients^[7,11,36]. Location of cSAH included one occipital lobe^[36] and two frontal lobe^[7,11]. Vessel imaging including magnetic resonance angiography showed two narrowing of the posterior cerebral arteries (PCAs)^[26,40], two middle cerebral arteries (MCAs)^[40,42], one internal carotid artery narrowing^[7], and one fetal-type posterior cerebral artery (fPCA) with an ipsilateral SAH^[17]. Cerebrospinal fluid analysis was rarely completed and was often normal^[10], one elevated red blood cell count^[14].

Neurosurgical intervention was done in 7/63 (11.1%) cases: One individual required decompressive sub-occipital craniectomy^[30], two hemispherectomy^[41,47], two external ventricular drain (EVD)^[22,47] placed, and two surgical evacuation of ICH^[28,33]. Medical management most often included blood pressure reduction, seizure management, anticoagulation reversal in three cases^[5,9,30], one plasmapheresis (type II cryoglobulinemia^[6]), cessation of immunosuppressive therapy^[9-11,16], five osmolar

therapy (mannitol, hypertonic saline)^[16,28,31,33,41], four corticosteroids^[23,28,29,35], one azathioprine, one C-section^[42].

The most commonly reported cause of hemorrhagic PRES was hypertension (20/63; 31.7%)^[7-9,21-24,27,28,31,35,38,39,43,46], anticoagulation usage (3/63; 4.7%)^[5,9,30], immunotherapy 15/63 (23.8%) (cytarabine^[36], tacrolimus 7/63 (11.1%)^[9,10,16,17,29], adalimumab^[11], mycophenolate^[17], 2 cyclosporine^[32], 1 pazopanib^[33], 1 antithymocyte globulin^[37], ifosfamide, carboplatin, etoposide (ICE) therapy^[41], coagulopathy 7/63 (11.1%) (5 thrombocytopenia^[6,9,36], elevated PTT^[9], elevated INR^[9]) intravenous corticosteroids^[40], 2 HELLP syndrome^[9,13], kratom and dextroamphetamine ingestion^[14], 4 pre-eclampsia^[9,15], acute renal failure^[9], 4 COVID-19^[19,20], SLE^[23], phenylpropanolamine^[26], phentermine abuse^[44]. Invasive management with intubation and mechanical ventilation were reported in 9/63 (14.2%) individuals^[16,17,19-21,30,41,45]. One patient was discharged from the hospital with clinical improvement, however, died from septic shock 3 months later^[47]. One patient died 9 months after discharge (unknown reason)^[9]. Most patients showed clinical improvement within 2 months. A total of eight (12.7%) patients died. *Machinis et al.* (2006) described a case of left cerebellar hemorrhage secondary to anticoagulation who previously had a central-PRES variant involving the same area within the same year^[30].

Meta-analysis

A total of 11 studies were included in the meta-analysis, with publication years ranging from 2007 to 2023. The studies varied significantly in sample size, ranging from 9 to 188 participants, and the number of events (e.g., cases of the outcome of interest) ranged from 2 to 48 across the studies. The total number of participants across all studies was 786, with 140 events reported. A 17% incidence rate was determined using a random effects model. The heterogeneity of the studies was assessed using the I² statistic, which was found to be 67%, indicating substantial heterogeneity among the studies (Fig. 2). This justified the use of a random-effects model to provide a more generalized estimate of the incidence rate. A funnel plot was generated to assess the presence of publication bias. The plot showed a relatively symmetrical distribution of studies around the pooled estimate (Fig. 3). In addition, a Baujat plot was used to identify studies that might have a disproportionate influence on the overall meta-analysis results. The Baujat plot revealed that the studies by Hilal et al., Raman et al., and Ellis et al. had a significant impact on both the heterogeneity and the pooled effect size, indicating their high influence on the overall results (Fig. 4).

Observational studies

Akdağ et al. (2023)^[8] completed a retrospective study of 15 patients with PRES diagnosed from 2015 to 2020. Two patients (case 4 and 5) were found to have a SAH and IPH, respectively. Behfar et al. (2020) completed a prospective study assessing the clinical and radiographic findings of pediatric patients with Fanconi anemia who underwent hematopoietic stem cell transplantation and had PRES. A total of 41 patients were enrolled and 9 patients had PRES (21.95% of the full cohort). Of the nine patients with PRES, three were found to have evidence of hemorrhage (33.3%). The occurrence of PRES was greater in individuals who had a donor with a 1-locus mismatch. Foci of microhemorrhages were observed in three patients and one of whom

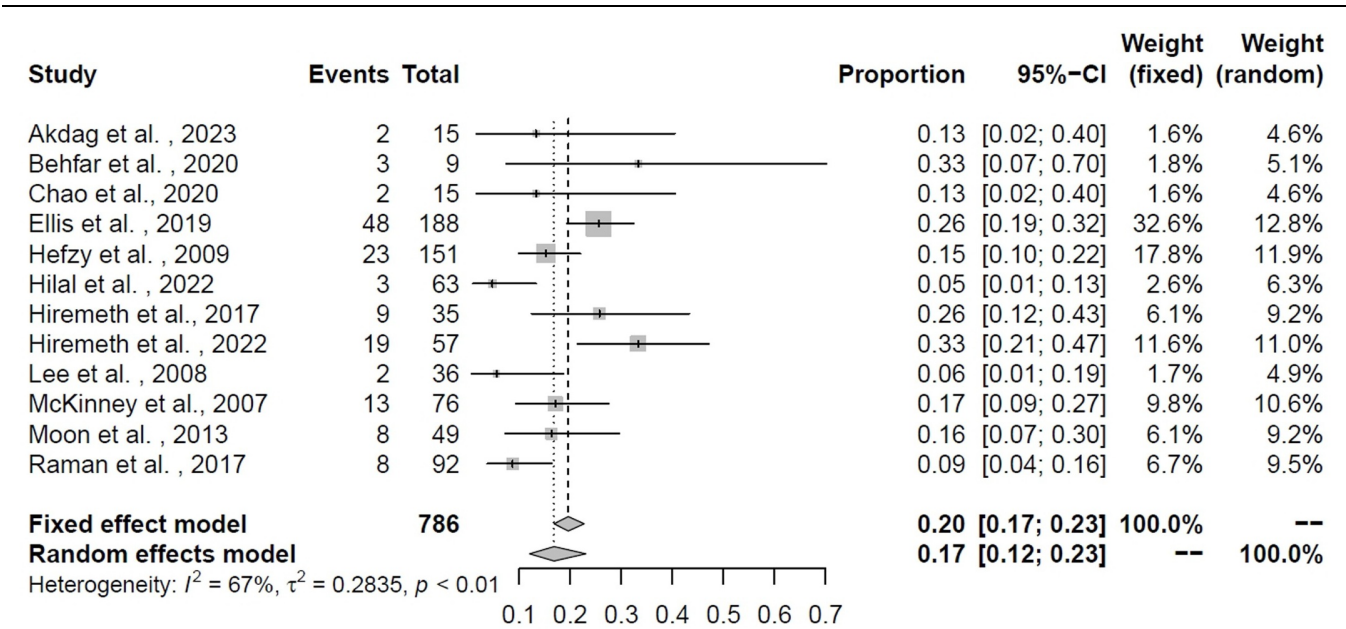


Figure 2. Forest plot showing the incidence rate of hemorrhagic PRES across the included studies.

developed a hemorrhagic infarct^[12]. *Chao et al.* (2020) completed a prospective study evaluating women with pre-eclampsia and found two women who clinical-radiographic evidence of PRES and susceptibility-weighted imaging (SWI) hypointensities consistent with microhemorrhages^[15]. *Ellis et al.* (2019) completed a retrospective analysis in 188 PRES patients. SAH was present in 6/188 (3%), and IPH in 42/188 (23%) of patients^[48]. *Hilal et al.* completed a retrospective study on 63 pediatric patients with PRES and found 3/65 (5%) incidence of hemorrhage. There was no statistical correlation between blood pressure and atypical imaging findings including intracerebral hemorrhage ($P = 0.33$)^[49]. *Hefzy et al.* completed a retrospective review of 151 patients with PRES and 23 individuals (15.2%) were found to have hemorrhage^[3]. *Hiremeth et al.* (2017) performed a retrospective analysis of 35 individuals with PRES. Nine out of

35 (25.7%) patients were found to have an intracranial hemorrhage. There was no statistically significant correlation between hemorrhage and blood pressure ($P = 0.403$). However, imaging severity was significantly associated with the presence of hemorrhage in PRES ($P < 0.001$)^[50]. *Hiremeth et al.* (2022) performed a retrospective imaging analysis of 57 patients with PRES. Hemorrhage was observed in 19 (35.7%) cases^[51]. *Raman et al.* (2017) completed a retrospective analysis of 92 patients with the clinical and radiographic presentation of PRES. They found a 9% incidence of hemorrhage as evidence on SWI^[52]. *McKinney et al.* (2007) completed a retrospective analysis of 76 PRES patients a determined a 17.1%^[53]. The study by *Lee et al.* (2008) investigates PRES through a retrospective analysis of 36 patients. The study found that patients often had comorbid conditions such as hypertension, renal disease, and malignancy and had undergone

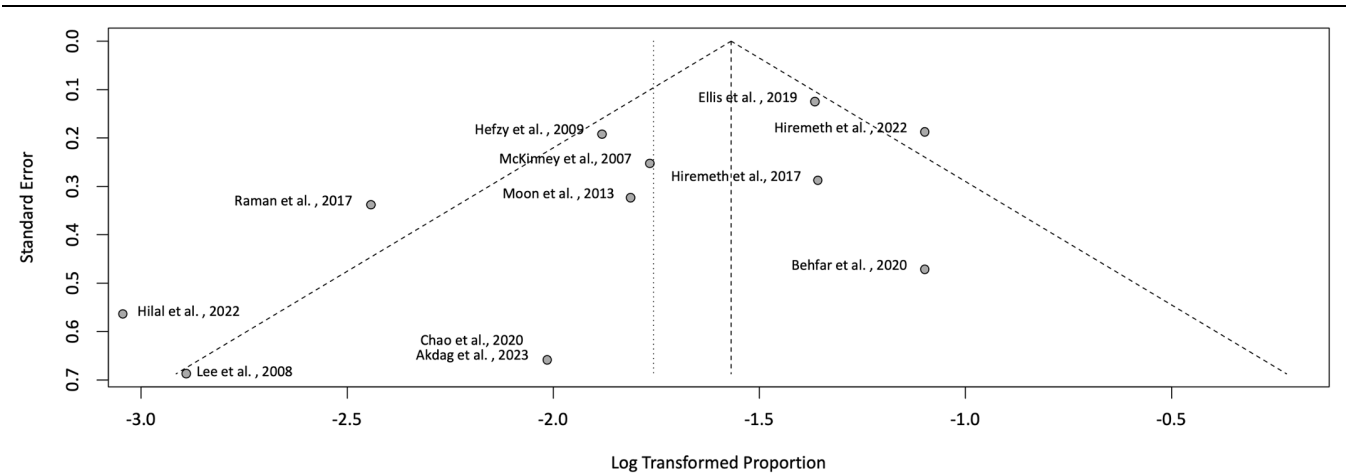


Figure 3. Funnel plot assessing publication bias among the included studies.

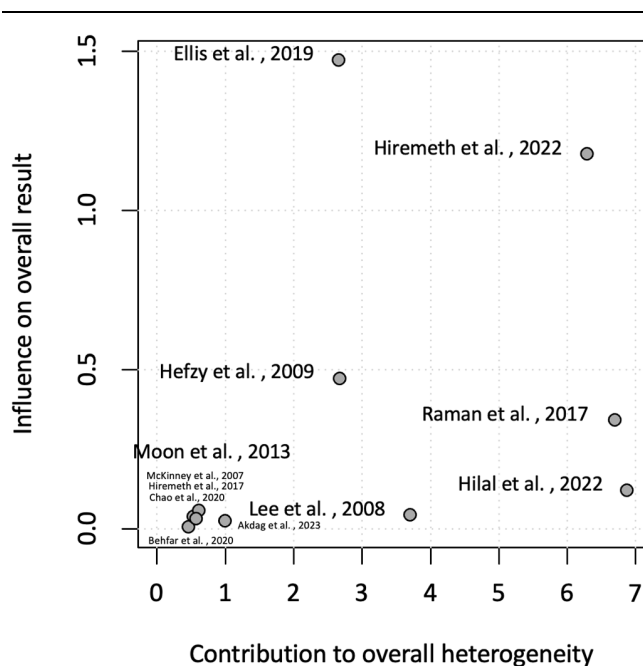


Figure 4. Baujat plot illustrating the influence of individual studies on the overall meta-analysis results.

transplantation. Clinical symptoms typically resolved within an average of 5.3 days. Neuroimaging revealed atypical features including frontal involvement, gray matter lesions, and brain-stem/cerebellar involvement. Hemorrhage was observed in 2 (5%) of patients^[54].

PRES after induced hypertension in subarachnoid hemorrhage

Although not included in the quantitative synthesis, PRES secondary to blood pressure augmentation or induced hypertension (iHTN) in SAH is a feared outcome. *Madaelil et al.* reported the case of a 55-year-old man diagnosed with a aneurysmal SAH of the superior cerebellar artery (Hunt and Hess score: 4). The patient was given phenylephrine for suspected delayed cerebral ischemia (DCI) and had MAP augmentation to 130–140 mmHg. Digital subtraction angiography (DSA) noted posterior circulation narrowing and intra-arterial verapamil was administered. The patient subsequently suffered from a generalized tonic clonic seizure and an MRI of the brain confirmed parieto-occipital T2/FLAIR lesions consistent with vasogenic edema seen in PRES with prominent bilateral thalamic involvement^[55].

Dhar et al. (2011) reported the case of a 47-year-old woman with a SAH due to a 4 mm posterior communicating artery aneurysm (modified Fisher grade 4). The patient was medically managed with a surgical clip ligation, right-sided craniotomy, and nimodipine. On day 6 of the hospital presentation, the patient developed severe vasospasm of the right MCA and bilateral anterior cerebral artery. Her blood pressure was raised from a MAP of 65–70 to 100 mmHg using a norepinephrine infusion. She was weaned off vasopressors on day 11. On day 13, she developed confusion and left-sided facial weakness, as well as weakness in the left upper and lower extremities. A CT scan of the head showed a hypodensity in the left temporal and

occipital-parietal cortex, and an MRI of the brain showed vasogenic edema involving the posterior left cerebral hemisphere consistent with PRES. The patient was slowly weaned off vasopressors and the neurological deficits resolved. On discharge, there was significant improvement in the vasogenic edema observed on MRI^[56].

Giraldo et al. (2011) reported a case series of three patients with PRES (two female and one male range: 62–70 years) after blood pressure augmentation due to aneurysmal SAH. In case one, the blood pressure was augmented to a MAP of 110 mmHg and developed alteration in mental status. A CT scan of the head showed bilateral posterior parietal-occipital regions. Management was supportive and the hypodensities resolved within 5 days. In case two, the blood pressure was augmented to SBP 200 mmHg, and the patient developed generalized tonic clonic seizures. A CT scan of the head showed parieto-occipital region hypodensities. The patient was managed with anti-seizure medications and blood pressure control and there was radiographic resolution of the hypodensities. In case three, the blood pressure was augmented to 160–180 mmHg and the hospital course was complicated by ventriculitis and cerebral salt wasting syndrome. On day 14 of hospitalization, the patient became more lethargic, and an MRI of the brain revealed vasogenic edema involving the bilateral temporal and occipital lobes as well as cerebellum consistent with PRES. The patient had an uncomplicated recovery and was discharged to an acute rehabilitation center^[57]. Similar cases of iHTN from SAH causing PRES have been reported by *Kuroda et al.* (2014)^[58].

Quality and risk of bias assessment

The quality and risk of bias of the included case reports were assessed using the JBI Critical Appraisal Checklist for Case Reports (Supplemental Digital Content, Table 5, available at: <http://links.lww.com/MS9/A908>). A total of 38 case reports were evaluated across eight quality domains, with each domain receiving a “Yes” (Y) or “No” (N) based on whether the criteria were met. The overall quality scores ranged from 5 to 8, with most of the case reports (36 out of 38) receiving the highest possible score of 8, indicating low risk of bias. These studies demonstrated consistent adherence to methodological rigor, including clear patient descriptions, comprehensive medical histories, thorough diagnostic assessments, and appropriate interventions and outcomes. Two case reports, specifically by Newey et al. and Miller et al., scored 5 out of 8, which placed them in the moderate risk of bias category. The lower scores for these reports were due to missing details in the diagnostic criteria and insufficient follow-up information, which could potentially affect the reliability of the conclusions drawn from these cases. Overall, the high quality and low risk of bias observed in most of the case reports underscore the robustness of the evidence presented. These findings provide confidence in the validity of the case reports’ contributions to the overall synthesis of evidence in this systematic review. The quality of the included cohort studies was evaluated using the NOS, which assesses studies across three domains: selection of the study groups (maximum of 4 points), comparability of the groups (maximum of 2 points), and the ascertainment of the outcome (maximum of 3 points). The total NOS scores for the studies ranged from 6 to 8, indicating a generally high level of methodological quality.

Discussion

PRES is a clinical radiographic phenomenon with multiple risk factors related to loss of cerebral autoregulation causing vasogenic edema and in some cases hemorrhage^[59]. The findings of this systematic review and meta-analysis underscore the complex and multifaceted nature of PRES, particularly when complicated by hemorrhagic transformation. The overall incidence of ICH in PRES, determined by the meta-analysis, is approximately 17%, with significant heterogeneity observed between studies. This variability highlights the diverse clinical and radiographic presentations of PRES and the challenges of predicting which patients are at higher risk of hemorrhagic complications.

Analysis of clinical data revealed that hypertension, immunosuppressive therapy, and coagulopathy were among the most frequently associated risk factors for hemorrhagic PRES. A significant proportion of patients presented with severe hypertension, which is consistent with understanding that blood pressure dysregulation plays a central role in the pathophysiology of PRES. The frequent involvement of vasogenic edema in the parieto-occipital regions, as observed on MRI, further corroborates the typical radiographic features associated with this syndrome.

The 17% pooled incidence of intracranial hemorrhage we derived sits squarely within – but toward the lower half of – the broad range reported by individual cohort studies over the past two decades. Early single-center series such as *McKinney et al.* (2007) found a virtually identical 17.1% frequency, whereas larger contemporary cohorts have varied from 9% on SWI (*Raman et al.*, 2017) to 25–36% in successive Hiremath cohorts that used more sensitive sequences and broader definitions of hemorrhage; pediatric data trend lower, with *Hilal et al.* documenting only 5%^[49,52,53]. Our estimate therefore confirms that the risk is neither as rare as the 5% figure sometimes quoted in obstetric-PRES literature nor as common as the one-in-three incidence suggested by highly selected tertiary-referral samples, supporting a middle-ground expectation for general practice. The relative predominance of intraparenchymal bleeds (~78%) and the strong association with presenting hypertension that we observed echo the study by *Hefzy et al.* (15% hemorrhage, 96% hypertensive at onset) while extending those findings to a more heterogeneous, multi-center population^[3]. Finally, our 12.7% mortality aligns with earlier estimates that hemorrhagic PRES roughly doubles the case-fatality rate compared with non-hemorrhagic forms, underscoring the need for vigilant blood pressure control and early neuroimaging follow-up.

Heterogeneity and implications for clinical practice

Significant heterogeneity identified in the meta-analysis, reflected by an I^2 value of 67%, suggests that the incidence of hemorrhagic PRES varies widely depending on the study population, the clinical setting, and the diagnostic criteria used. This heterogeneity could be attributed to differences in patient demographics, underlying comorbidities, imaging timing, and use of various therapeutic interventions in studies. Given this variability, it is crucial for clinicians to consider the clinical context of the individual patient when evaluating the risk of hemorrhagic complications in PRES. Tailored management strategies, including aggressive blood pressure control, hypomagnesemia management, and careful monitoring for signs of hemorrhage, are

essential in optimizing outcomes^[60]. The role of immunosuppressive agents and the potential contribution of their agents to hemorrhagic transformation also warrant further investigation, as this may influence treatment decisions in patients with PRES secondary to conditions such as transplantation or autoimmune diseases^[41,53]. *Srichawla et al.* previously reported on the potential implications of Circle of Willis variants on dynamic cerebral autoregulation and the development of severe unilateral vasogenic edema or hemorrhage in PRES^[41].

Our findings recast hemorrhagic PRES as a true neurocritical emergency – bleeding occurred in 17% of cases and doubled mortality – so early, protocolized blood pressure control, rapid reversal of coagulopathy, and prompt review of calcineurin-inhibitor or cytotoxic drug levels are imperative. Because heterogeneity is high ($I^2 = 67\%$) and nearly one-quarter of hemorrhages arise in immunosuppressed or transplant recipients, management must be individualized, with baseline susceptibility-weighted MRI to detect occult microbleeds and tailored hemostasis targets. Moreover, in subarachnoid-hemorrhage patients, iHTN meant to prevent DCI that can itself precipitate posterior vasogenic edema and bleeding, underscoring the value of autoregulation-guided CPP strategies and magnesium repletion. Prospective registries that track blood pressure trajectories, immunosuppressant levels, and serial SWI will be crucial for developing predictive models and integrating hemorrhagic-PRES prevention bundles into neurocritical care guidelines.

PRES in specific contexts: blood pressure augmentation in SAH

The review also highlighted the occurrence of PRES in the context of iHTN for the treatment of SAH. Although these cases were not included in the quantitative synthesis, they provide important information on the potential risks associated with aggressive blood pressure enhancement strategies. The reported cases demonstrate that while blood pressure elevation is a critical component in managing DCI in SAH, it can paradoxically lead to the development of PRES, particularly in the posterior circulation, which is more susceptible to vasogenic edema.

Niels A. Lassen first illustrated the cerebral autoregulatory curve in 1959 (Fig. 5)^[61]. Hyperperfusion and hypoperfusion events outside of the autoregulatory curve have been reported to cause vasogenic edema and PRES^[61]. Cerebral perfusion pressure (CPP) optimized for cerebral autoregulation (CPP_{opt}) is an emerging concept in the treatment of SAH, aimed at balancing the need to maintain adequate cerebral blood flow while minimizing the risk of secondary brain injury. CPP_{opt} involves continuous adjustment of CPP to an individualized target that optimizes autoregulatory function and reduces the probability of ischemia^[62]. This approach is particularly relevant in the context of iHTN, which is commonly used to prevent DCI after SAH. When blood pressure management is adapted to achieve CPP_{opt}, the risk of excessive cerebral perfusion and consequent vasogenic edema, hallmarks of PRES, may be mitigated^[63]. Therefore, the implementation of CPP_{opt} strategies may help prevent the development of PRES in patients undergoing iHTN, by avoiding extremes of perfusion that can disrupt the blood-brain barrier and lead to characteristic edema and hemorrhagic complications of PRES.

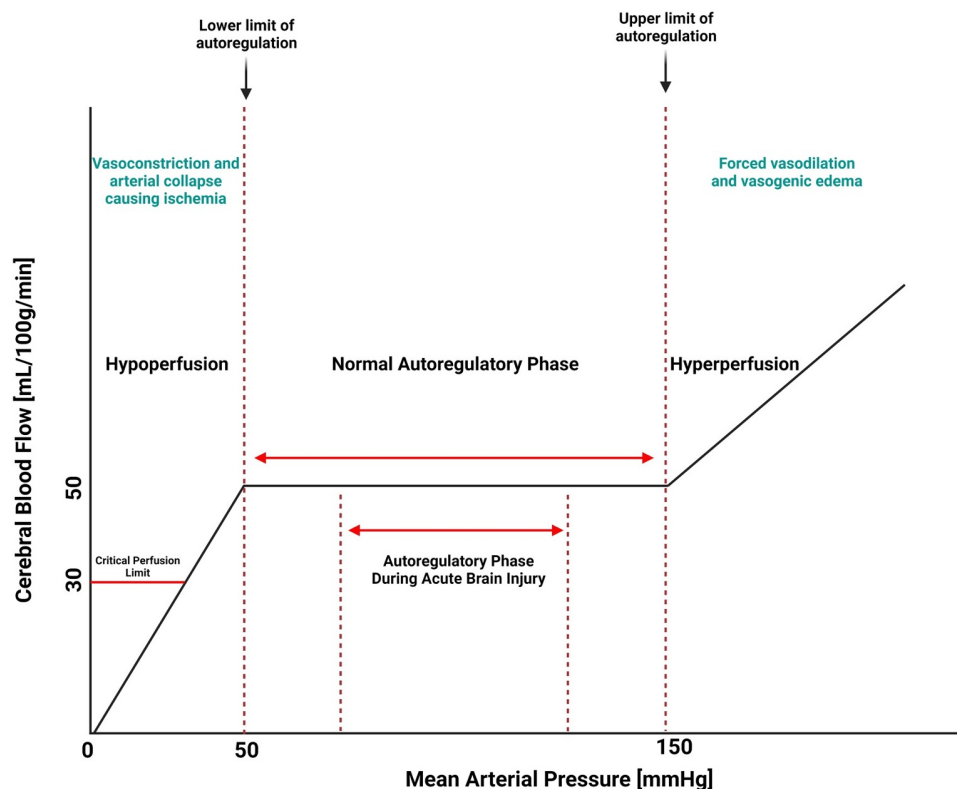


Figure 5. The cerebral autoregulatory curve. (BioRender Agreement: SE269MFWGB).

Limitations and future directions

While this systematic review and meta-analysis provide valuable information on the incidence and clinical characteristics of hemorrhagic PRES, several limitations must be acknowledged. First, the reliance on retrospective studies and case reports introduces a degree of selection and reporting bias, which can affect the generalizability of the findings. Furthermore, the heterogeneity observed in the studies highlights the need for standardized diagnostic criteria and reporting practices in future research to facilitate more accurate comparisons and meta-analyses. Future studies should focus on prospective data collection and the use of uniform imaging protocols to better understand the natural history of hemorrhagic PRES and to identify reliable predictors of hemorrhagic transformation. Furthermore, investigations of the underlying pathophysiological mechanisms, particularly the role of the disruption of the blood–brain barrier and the contribution of systemic inflammation, could lead to more targeted therapeutic interventions.

Conclusions

This systematic review and meta-analysis provide a comprehensive examination of the incidence, clinical characteristics, and outcomes associated with hemorrhagic PRES. A total of 63 single-patient records and 12 cohort studies were included in our analysis. Our findings showed that hemorrhage occurs in approximately 17% of PRES cases, with significant heterogeneity between studies ($I^2 = 67\%$). Most of the cases occurred in women and the most common risk factors included hypertension, renal

disease, and immunosuppressive therapy. Elevated blood pressure on arrival was seen in > 90% of cases. The most common location of hemorrhage was unilateral occipital or parietal lobe hemorrhage. Although IPH was the most reported, other types of hemorrhage include perimesencephalic SAH or cSAH and IVH. Treatment was more often supportive with regards to managing blood pressure. In 11.1% of cases, neurosurgical intervention with craniectomy and EVD placement was needed. Other emerging interventions including osmolar therapy for elevated intracranial pressure were also reported. The overall mortality rate was determined to be 12.7%. However, hemorrhage in PRES carries significant long-term neurological morbidity. PRES after iHTN in aSAH continues to be a reported phenomenon that points toward the need for individualized CPP goals. However, there should be reservation when interpreting these findings given the limitation of a meta-analysis. Prospective studies are warranted to better understand the pathophysiology of hemorrhagic PRES and to identify reliable predictors of hemorrhagic transformation.

Ethical approval

Ethics approval was not required for this systematic review/meta-analysis.

Consent

Written informed consent was deferred as there was no direct patient contact as this is a meta-analysis.

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Author contributions

B.S.S., M.A.G-D.: completed literature review, drafted the initial manuscript, generated illustrations/figures, provided intellectual verification of the topic, and edited the final manuscript. V.K., M.G. drafted the initial manuscript. H.C. provided intellectual verification on this topic. All authors reviewed the final draft of the manuscript.

Conflicts of interest disclosure

On behalf of all authors, the corresponding author states that there are no conflicts of interest.

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All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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