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ORIGINAL ARTICLE

Frequency of ischaemic stroke and intracranial haemorrhage in patients with reversible cerebral vasoconstriction syndrome (RCVS) and posterior reversible encephalopathy syndrome (PRES) – A systematic review

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Abstract

Background: Posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS) may cause ischaemic stroke and intracranial haemorrhage. The aim of our study was to assess the frequency of the afore-mentioned outcomes.

Methods: We performed a PROSPERO-registered (CRD42022355704) systematic review and meta-analysis accessing PubMed until 7 November 2022. The inclusion criteria were: (1) original publication, (2) adult patients (≥18 years), (3) enrolling patients with PRES and/or RCVS, (4) English language and (5) outcome information. Outcomes were frequency of (1) ischaemic stroke and (2) intracranial haemorrhage, divided into subarachnoid haemorrhage (SAH) and intraparenchymal haemorrhage (IPH). The Cochrane Risk of Bias tool was used.

Results: We identified 848 studies and included 48 relevant studies after reviewing titles, abstracts and full text. We found 11 studies on RCVS (unselected patients), reporting on 2746 patients. Among the patients analysed, 15.9% (95% CI 9.6%–23.4%) had ischaemic stroke and 22.1% (95% CI 10%–39.6%) had intracranial haemorrhage. A further 20.3% (95% CI 11.2%–31.2%) had SAH and 6.7% (95% CI 3.6%–10.7%) had IPH. Furthermore, we found 28 studies on PRES (unselected patients), reporting on 1385 patients. Among the patients analysed, 11.2% (95% CI 7.9%–15%) had ischaemic stroke and 16.1% (95% CI 12.3%–20.3%) had intracranial haemorrhage. Further, 7% (95% CI 4.7%–9.9%) had SAH and 9.7% (95% CI 5.4%–15%) had IPH.

Conclusions: Intracranial haemorrhage and ischaemic stroke are common outcomes in PRES and RCVS. The frequency reported in the individual studies varied considerably.

KEYWORDS
intracranial haemorrhage, ischaemic stroke, posterior reversible encephalopathy syndrome, PRES, RCVS, reversible cerebral vasoconstriction syndrome

INTRODUCTION

Reversible cerebral vasoconstriction syndrome (RCVS)

RCVS is a neurovascular disease associated with characteristic angiographic and clinical features: (1) diffuse reversible segmental and multifocal vasoconstriction of the cerebral arteries, (2) severe headache ('thunderclap headaches'), (3) may or may not be accompanied by focal neurological deficits or epileptic seizures and (4) no evidence of an inflammatory cause (no vasculitis) [1]. RCVS was reported in patients aged 10–76 years, with a peak incidence of around 42 years, and women are more likely to be affected by RCVS than men. Diagnosis can be made based on angiographic evidence of segmental narrowing and dilation of one or more arteries [1, 2]. Concerning the pathophysiology, it is assumed that symptoms arise due to a transient disorder in the regulation of cerebral arterial tone [2]. The syndrome may occur spontaneously or may be provoked by certain triggering factors, such as exposure to vasoactive substances or being in the postpartum period [1]. Over 90% of patients experience a benign clinical course with self-limiting RCVS, which resolves within a few days up to a maximum of 3 months [1, 2]. A significant proportion of patients may develop intracranial haemorrhage or ischaemic stroke [3]. Neuroimaging including MRI may show white matter hyperintensities in fluid-attenuated inversion recovery (FLAIR) sequences [3, 4], indicating cortical and subcortical damage. Areas of hypoperfusion that may indicate cerebral infarction can be seen in perfusion-weighted imaging [2]. Due to the dynamic nature of RCVS (i.e., haemorrhage may occur several days after the first normal image) frequently multiple angiograms are required [2, 5]. However, it is not clear how lesions can be prevented or whether monitoring of vasoconstriction is useful [3].

Posterior reversible encephalopathy syndrome (PRES)

PRES is characterised by a constellation of clinical symptoms (whereby not all of the following must be present): (1) headache, (2) impaired mental status (ranging from confusion to coma), (3) visual impairment (ranging from vision loss to visual hallucinations) and (4) epileptic seizures and typical neuroradiological findings [6, 7]. Neuroimaging shows vasogenic oedema, usually in a bilateral pattern in the parieto-occipital region, or not uncommonly in the frontal or temporal lobes, brainstem, basal ganglia or cerebellum [8, 9]. FLAIR sequences detect characteristic lesion pattern of PRES [6]. The differential diagnosis comprises a variety of other diseases, such as infectious, autoimmune disorders or malignant diseases [8]. A triggering factor, such as pre-eclampsia, eclampsia or severe arterial hypertension, is often identified and described [7]. In terms of pathophysiology, it is assumed that alterations in relation to the control of cerebrovascular auto-regulation and the integrity of the blood–brain barrier (BBB) are the cause [10, 11]. The posterior brain regions can be particularly susceptible due to reduced sympathetic innervation of the posterior cranial fossa [7, 12]. The lesions resolve on their own within a few days to a few weeks in 75%–90% of cases, but patients may develop intracranial haemorrhage or ischaemic stroke [7, 8]. A correlation between contrast enhancement pattern due to the breakdown of the BBB, haemorrhage and cytotoxicity oedema was seen [13–15]. Diffusion-weighted imaging (DWI) may show ischaemic infarction, [13, 15].

PRES and RCVS

The pathophysiology of PRES and RCVS remains controversial and is still unknown. As the two syndromes share some risk factors and clinical features, a possible common origin or pathophysiological pathway has been considered and they are frequently associated [1, 4, 16]. But misdiagnosis may occur as they share clinical and radiological features and may overlap [4, 16]. PRES is a known complication (7%–38%) of RCVS and has been associated with the risk of ischaemic stroke in RCVS [4, 17, 18].

Frequency of ischaemic stroke and intracranial haemorrhage vary among published studies. The aim of our study was to perform a systematic review and meta-analysis to assess the frequency of ischaemic stroke and intracranial haemorrhage (for all intracranial haemorrhages, as well as divided into SAH and IPH) in patients with RCVS and PRES.

METHODS

We conducted a systematic review and meta-analysis. We ensured compliance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [19]. This review was pre-registered at PROSPERO (CRD42022355704).

Inclusion and exclusion criteria

We defined the following inclusion criteria: (1) original scientific papers, (2) adult patients (≥18 years), (3) enrolment of patients with PRES and/or RCVS, (4) studies in the English language and (5) information on the occurrence of ischaemic stroke and/or intracranial haemorrhage. The following exclusion criteria were applied: (1) imaging (computed tomography [CT]/magnetic resonance imaging [MRI]) to verify the presence of outcome (ischaemic stroke, intracranial haemorrhage) was unavailable/nor reported and (2) case reports (≤3 patients) or reviews.

Data source and search strategy

PubMed was used as the database for the literature search. We applied the following search strategy: ((Posterior reversible encephalopathy syndrome) OR (PRES) OR (Reversible cerebral vasoconstriction syndrome) OR (RCVS)) AND ((Imaging) OR (CT) OR (MRI)) AND (journalarticle[Filter]) NOT (review) NOT (case report)). The search was carried out by the one author (J.K.) from 26 August

2022 to 31 August 2022 and was repeated independently by a second author (D.S.) on 7 November 2022. All studies that fulfilled the inclusion criteria listed above were considered. First, the titles were evaluated and, where appropriate, the abstracts were read in more detail. Subsequently, relevant articles were read in their full-text version. In addition, the references of those studies were reviewed to find further basic literature describing the diseases.

Statistical analysis

Data were extracted into the MedCalc Program (MedCalc Version 20.215) by J.K. Proportional meta-analysis was used to quantify the occurrence in the included studies. A random effects model was applied [20]. All extracted proportions can be found in the forest plots.

Risk of bias

We used the Cochrane Risk of Bias tool (a tool to assess the risk of bias in cohort studies) to assess the risk of bias for each included study. The assessment was done by two reviewers independently (J.K. and D.S.) and disagreement was resolved by a third reviewer (P.B.).

Outcomes

For all the studies, the frequency of (a) ischaemic stroke and (b) intracranial haemorrhage (all intracranial haemorrhages, as well as SAH or IPH considered separately) was recorded, and the information extracted from the corresponding articles. If the information was available, we described the results as a frequency within the study (*n* events/*N* total population) and reported our results for each study setting (studies in a selected population or non-selective studies, which included all patients with RCVS or PRES). Data were pooled for each outcome and presented separately for PRES and RCVS.

Funding

This study had no specific funding.

Ethics

This was a systematic literature research and meta-analysis without any original data, thus no ethics approval was necessary.

Data sharing

All data used in this study are publicly available and can be obtained from the original papers listed in the reference list.

RESULTS

Literature search

Our searches returned 848 and 867 results, respectively (Figure 1). Following the selection of titles and abstracts, 760 and 777 articles were excluded as unsuitable for the review. In the case of the remaining 90 articles, the full text was read, and 10 studies were excluded since they had investigated only paediatric patients. A further 13 articles were excluded due to missing imaging details regarding haemorrhage or ischaemia. In addition, seven articles were excluded based on being a case report. Furthermore, seven studies were excluded due to duplicate publications and five studies due to not being available in the English language. Ultimately, 48 articles were included: 34 concerning PRES and 14 concerning RCVS (Tables 1 and 2).

Studies included: General findings and imaging used

Of the studies analysed, 41 of 48 (85.4%) used a retrospective design. Furthermore, over a third of all studies were carried out in the last decade (34 of 48 studies, 70.8%). All studies (100%) used MRI to confirm the diagnosis. In addition, the majority of the studies (20 of 47, 42.6%) also used CT. The study size ranged from 4 to 2020 subjects. Of these, 28 (58.3%), and therefore more than half of the

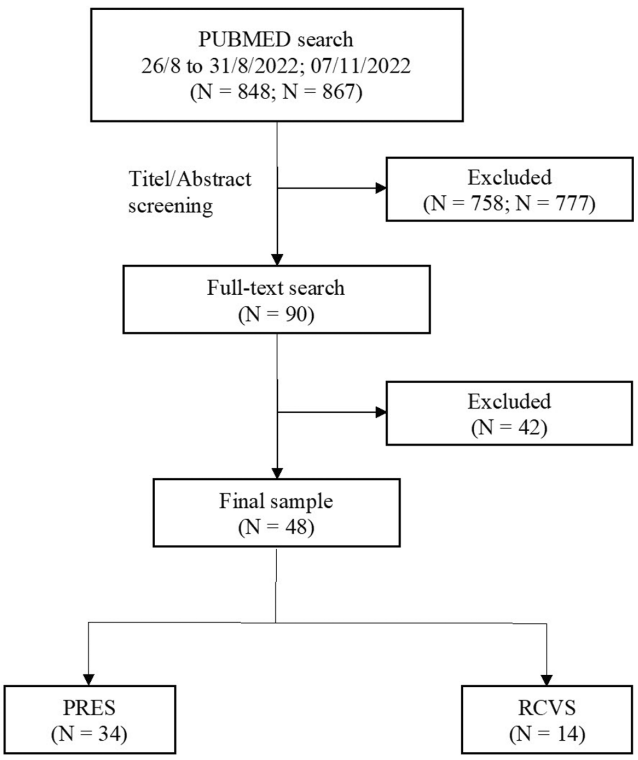

FIGURE 1 Literature search. PRES, posterior reversible encephalopathy syndrome; RCVS, reversible cerebral vasoconstriction syndrome.

TABLE 1 Overview of studies relating to reversible cerebral vasoconstriction syndrome (RCVS) – frequency of intracranial haemorrhage and ischaemic stroke.

General information				Outcomes			
Authors	**Study design**	**Imaging**	**Sample size (*n*)**	**Ischaemic stroke (*n* (%))**	**All intracranial haemorrhage (*n* (%))**	**SAH (*n* (%))**	**IPH (*n* (%))**
RCVS							
RCVS (unselected population)							
Rocha et al. 2019 [21]	Prospective, single tertiary centre	MRI, CT	30	4 (13.3)	19 (63.3)	14 (46.6)	5 (16.7)
Caria et al. 2019 [22]	Retrospective, multicentre	MRI, CT	102	12 (11.7)	19 (18.6)	16 (15.7)	3 (2.9)
Chen et al. 2012 [23]	Prospective, single centre (2002–2009)	MRI	95	6 (6.3)	0	0	0
Topcuoglu et al. 2016 [3]	Prospective, single centre	MRI	162	65 (40.1)	71 (43.8)	62 (38.3)	21 (13.0)
Chen et al. 2018 [24]	Prospective, single centre (2010–2012)	MRI	65	1 (1.5)	2 (3.1)	1 (1.5)	1 (1.5)
Singhal et al. 2011 [4]	Retrospective, two academic tertiary centres	MRI, CT	139	39 (28.1)	44 (31.7)	34 (24.5)	20 (14.4)
Ducros et al. 2007 [1]	Prospective, single centre	CT, MRI	67	2 (3.0)	19 (28.4)	15 (22.4)	4 (6.0)
Hathidara et al. 2022 [5]	Retrospective, single centre	CT, MRI	9	5 (55.6)	5 (55.6)	5 (55.6)	0
Itsekson-Hayosh et al. 2020 [25]	Retrospective, single centre	CT, MRI	21	6 (28.6)	NA	6 (28.6)	NA
Oliveira et al. 2022 [26]	Retrospective, single tertiary centre	MRI, CT	36	2 (5.6)	2 (5.6)	1 (2.8)	1 (2.8)
Patel et al. 2021 [27]	Retrospective, multicentre	NA	2020	345 (17.1)	NA	660 (32.7)	220 (11.0)
Total			2746	487	181/705	813	274/2725
RCVS (selected population)							
Xing et al. 2020 [28]	Retrospective, single tertiary centre (only patients with bleeding)	MRI	24	6 (24.0)	24 (100.0)	19 (79.7)	7 (29.1)
Ansari et al. 2011 [29]	Retrospective, single centre (only patients with any complication)	CT, MRI	11	3 (27.3)	9 (81.8)	9 (81.8)	0
Arandela et al. 2021 [30]	Retrospective, multicentre (only patients with coronavirus disease)	MRI	10	4 (40.0)	4 (40.0)	3 (30.0)	2 (20.0)

Abbreviations: CT, computed tomography; IPH, intraparenchymal haemorrhage; NA, not available; MRI, magnetic resonance imaging; RCVS, reversible cerebral vasoconstriction syndrome; SAH, subarachnoid haemorrhage.

TABLE 2 Overview of studies relating to posterior reversible encephalopathy syndrome (PRES) – frequency of intracranial haemorrhage and ischaemic stroke.

General information			Outcomes				
Authors	Study design	Imaging	Sample size (*n*)	Ischaemic stroke (*n* (%))	All intracranial haemorrhage (*n* (%))	SAH (*n* (%))	IPH (*n* (%))
PRES							
PRES (unselected population)							
Pilato et al. 2019 [14]	Retrospective, single centre	MRI	25	NA	5 (20.0)	2 (8.0)	3 (12.0)
Pereira et al. 2015 [31]	Retrospective, single centre	MRI, CT	14	4 (28.6)	1 (7.1)	0	1 (7.1)
Faille et al. 2017 [32]	Retrospective, single centre	MRI, CT	37	NA	8 (23.0)	NA	NA
Raman et al. 2017 [33]	Retrospective, single centre	MRI	92	NA	9 (9.8)	NA	NA
Schweitzer et al. 2017 [34]	Retrospective, multicentre	MRI, CT	99	NA	37 (37.4)	10 (10.1)	36 (36.4)
Hiremath et al. 2017 [35]	Retrospective, single centre	MRI	35	NA	9 (25.7)	7 (20.0)	1 (2.9)
Kalaiselvan et al. 2017 [36]	Prospective, single centre	MRI	14	NA	2 (14.2)	1 (7.1)	1 (7.1)
Vanacker et al. 2015 [7]	Retrospective, single centre	MRI	4	0	0	0	0
Hinduja et al. 2017 [37]	Retrospective, single tertiary centre	MRI	100	NA	26 (26.0)	NA	NA
Bansal et al. 2020 [38]	Prospective, single tertiary centre	MRI	22	NA	5 (22.7)	1 (4.5)	1 (4.5)
Moon et al. 2013 [39]	Retrospective, multicentre	MRI	49	NA	8 (16.3)	1 (2.0)	7 (14.3)
Legriel et al. 2012 [40]	Retrospective, multicentre	CT, MRI	70	4 (5.7)	6 (8.6)	NA	NA
Liman et al. 2012 [41]	Retrospective, multicentre	MRI	96	7 (7.3)	31 (32.3)	4 (4.2)	11 (11.5)
Pande et al. 2006 [10]	Retrospective, multicentre	MRI	52	NA	2 (3.8)	2 (3.8)	0
Covarrubias et al. 2002 [13]	Retrospective, single centre	MRI	22	2 (9.1)	2 (9.1)	0	2 (9.1)
Bartynski et al. 2008 [18]	Retrospective, single centre	MRI	47	7 (14.9)	3 (6.4)	NA	NA
McKinney et al. 2007 [42]	Retrospective, multicentre	MRI	76	NA	13 (17.1)	10 (13.2)	5 (6.6)
Brubaker et al. 2005 [12]	Retrospective, single centre	MRI	8	1 (25.7)	NA	NA	NA
Gocmen et al. 2007 [43]	Retrospective, single tertiary centre	MRI	21	NA	5 (23.8)	NA	NA
Fugate et al. 2010 [44]	Retrospective, single centre	MRI, CT	120	NA	10 (8.3)	NA	NA
Li et al. 2012 [9]	Retrospective, single centre	MRI, CT	59	14 (23.7)	6 (10.2)	1 (1.7)	3 (5.1)
Mueller-Mang et al. 2009 [45]	Retrospective, single centre	MRI	30	1 (3.3)	6 (20)	1 (3.3)	5 (16.7)
Amornpojnimman et al. 2022 [46]	Retrospective, single centre	MRI	136	14 (10.3)	10 (7.4)	NA	NA
Ansari et al. 2021 [47]	Prospective, single centre	MRI	31	NA	2 (6.5)	NA	NA
Goyal et al. 2022 [48]	Retrospective, single centre	MRI	30	2 (6.7)	2 (6.7)	NA	NA
Hiremath et al. 2022 [49]	Retrospective, single centre	MRI	60	n/a	19 (31.7)	8 (13.3)	4 (6.7)

(Continues)

TABLE 2 (Continued)

General information			Outcomes				
Authors	**Study design**	**Imaging**	**Sample size (*n*)**	**Ischaemic stroke (*n* (%))**	**All intracranial haemorrhage (*n* (%))**	**SAH (*n* (%))**	**IPH (*n* (%))**
PRES							
Ugurel et al. 2005 [50]	Retrospective, single centre	MRI	13	2 (15.4)	3 (23.1)	NA	NA
Yadav et al. 2019 [51]	Retrospective–prospective, single tertiary centre	MRI	24	1 (4.16)	2 (8.33)	1 (4.16)	1 (4.16)
Total			1385	59/552	232/1377	49/680	81/628
PRES (selected population)							
Burnett et al. 2010 [52]	Retrospective, single centre (only patients with calcineurin inhibitor)	MRI, CT	75	4 (5.3)	14 (19)	NA	NA
Cruz et al. 2012 [53]	Retrospective, single centre (only liver transplant patients)	MRI, CT	19	NA	6 (31.6)	NA	NA
Li et al. 2013 [54]	Retrospective, single centre (only patients with hypertension)	MRI, CT	28	NA	7 (25.0)	5 (17.8)	4 (14.3)
Aranas et al. 2009 [55]	Retrospective, single tertiary centre (only patients with bleeding)	MRI, CT	7	NA	7 (100.0)	1 (14.3)	6 (85.7)
Keepanasseril et al. 2022 [56]	Prospective, single centre (only pregnant women presenting with seizures)	MRI, CT	51	10 (19.6)	11 (21.6)	NA	NA
Lallana et al. 2021 [57]	Retrospective, multicentre (only patients with coronavirus disease)	MRI, CT	8	NA	2 (25.0)	NA	NA

Abbreviations: CT, computed tomography; IPH, intraparenchymal haemorrhage; MRI, magnetic resonance imaging; NA, not available; PRES, posterior reversible encephalopathy syndrome; SAH, subarachnoid haemorrhage.

studies, investigated a sample size of ≤50. Conversely, only seven (14.6%) studies investigated a sample size of ≥100. The frequency of outcome assessment depends on the outcome being assessed. Ischaemic stroke was investigated in 29 (60.4%) studies. Intracranial haemorrhage was assessed in almost all studies, more specifically in 45 (93.8%) of the 48 studies. The subcategory SAH was measured in 32 (66.7%) and IPH in 31 (64.6%) studies.

The risk of bias was heterogeneous and moderate in most of the studies (Table 3). Some 41 (85.4%) of 48 studies drew exposed and non-exposed cohorts from the same population. But groups were not matched for variables associated with the outcome, or no statistical analysis was mentioned to adjust for these differences. Overall, we can be confident about the assessment of exposure, and the follow-up was done adequately as all studies reached a positive assessment (+ or ++). The assessment of outcomes was mainly rated negative (− or −−), more precisely for 34 (70.8%) of 48 studies.

Frequency of ischaemic stroke and intracranial haemorrhage in patients with RCVS

In total, we included 14 studies in patients with RCVS: 11 of which reported on unselected RCVS patients; and three studies which only included patients suffering from coronavirus disease, with intracranial haemorrhage, and any complications, respectively. The 11 studies, which included all RCVS patients, provide reports on 2746 patients. Of these, 487 (15.9%, 95% CI 9.6%–23.4%) had suffered an ischaemic stroke, and 181 of 705 (22.1%, 95% CI 10%–39.6%) had an intracranial haemorrhage (Figures 2 and 3). In total, 813 (20.3%, 95% CI 11.2%–31.2%) patients suffered from SAH and 274 of 2725 (6.7%, 95% CI 3.6%–10.7%) suffered from IPH (Figures S1 and S2). For ischaemic stroke, the outcome varies from 1.5% to 55.6%. For intracranial haemorrhage, a variation of 3.1%–63.3% was found.

Frequency of ischaemic stroke and intracranial haemorrhage in patients with PRES

We have included 34 studies in relation to PRES. Of these, 28 studies included unselected patients with PRES. A further six studies were selected based on taking calcineurin inhibitors, having pre-existing hypertension, being recipients of liver transplants, having bleeding, being pregnant women and suffering from coronavirus disease. The studies reporting on all PRES patients (non-selectively) include 1385 patients. Intracranial haemorrhage was identified in 232 (16.1%, 95% CI 12.3%–20.3%) of 1377 patients (Figure 4). More precisely, 49 (7%, 95% CI 4.7%–9.9%) of 680 patients suffered from SAH, and 81 (9.7%, 95% CI 5.4%–15%) of 628 suffered an IPH (Figures S3 and S4). Additionally, 59 (11.2%, 95% CI 7.9%–15%) of 552 patients suffered from a stroke (Figure 5). For ischaemic stroke, the outcome varies from 3.3% to 28.6%. For intracranial haemorrhage, a variation of 3.8%–37.4% was found.

Frequency of of ischaemic stroke and intracranial haemorrhage in patients with PRES as a consequence of RCVS

Few papers report on the incidence of ischaemic stroke and haemorrhage associated with PRES in RCVS patients. One half to two thirds of the patients who developed an ischaemic stroke had concomitant PRES. [23, 58] In one study, PRES was reported more often in patients with haemorrhage [3].

DISCUSSION

Main findings

The main findings of our systematic review and meta-analysis are as follows. (1) A significant proportion of patients with RCVS and PRES suffer from ischaemic stroke and intracranial haemorrhage. (2) In patients with RCVS, haemorrhage is more frequent than ischaemic stroke and the majority of haemorrhages are SAH. (3) In patients with PRES, ischaemic stroke and intracranial haemorrhage seem equally frequent and SAH and IPH are equally common in patients with PRES.

PRES and RCVS

Previous studies have shown that PRES and RCVS can occur simultaneously or as overlapping phenomena in some cases [1–4]. Our findings advocate that both conditions – although per definition 'reversible' and thought to have a benign course – are not benign in a significant percentage of patients. They can indeed have a complicated course, leading to increased morbidity. Ischaemic stroke and intracranial haemorrhage are two well-known complications and the most common cause for an incomplete recovery [2, 8, 14, 37, 59]. We found that across all studies, up to a quarter of the patients studied suffer an outcome, either ischaemic stroke, intracranial haemorrhage, or both.

PRES is a known complication (7%–38%) of RCVS [4, 17, 18]. Shared pathophysiological mechanisms may explain the simultaneous occurrence of PRES and RCVS [1, 16]. Most of the haemorrhages occurred within the first week. PRES and the subsequent ischemia increased steadily within 2–3 weeks [1, 3]. This time pattern can be explained by the underlying dysfunction in the control of cerebral arterial tone. This may initially affect the small distal arteries responsible for haemorrhages and PRES, then progress to the medium and large arteries responsible for ischaemic stroke [1]. Patients with RCVS experienced prolonged vasoconstriction, which increased the risk for PRES and ischaemic strokes [58]. PRES was observed more frequently when haemorrhage occurred, but the result was not statistically significant [3]. It was found that patients with mild SAH had a significantly higher risk of PRES and ischaemic stroke than patients without these criteria [58]. As only a few papers reported on

TABLE 3 Cochrane Risk of Bias tool to assess the risk of bias in cohort studies.

Authors	1	2	3	4	5	6	7	8
RCVS								
Rocha et al. 2019 [21]	++	++	++	−	++	−	++	−
Caria et al. 2019 [22]	++	++	++	−	++	−	++	−
Chen et al. 2012 [23]	++	++	++	−	+	++	++	−
Topcuoglu et al. 2016 [3]	++	++	++	+	++	−	++	−
Chen et al. 2018 [24]	−	++	++	−	+	++	+	−
Singhal et al. 2011 [15]	++	++	+	−	++	−	++	−
Ducros et al. 2007 [1]	+	+	++	−	++	−	++	−
Hathidara et al. 2022 [5]	+	++	++	−	++	−	+	−
Itsekson-Hayosh et al. 2020 [25]	+	++	+	−	+	−	+	−
Oliveira et al. 2022 [26]	++	++	+	−	++	−	−	−
Patel et al. 2021 [27]	+	++	++	−	+	−	+	−
Xing et al. 2020 [28]	+	++	++	−	+	++	++	−
Ansari et al. 2011 [29]	+	++	+	−	+	+	++	−
Arandela et al. 2021 [30]	−	++	++	−	+	−	+	−
PRES								
Pilato et al. 2019 [14]	+	++	+	+	+	++	++	−
Pereira et al. 2015 [31]	+	++	+	−	+	−	+	−
Faille et al. 2017 [32]	++	++	+	−	+	−	+	−
Raman et al. 2017 [33]	+	++	+	−	+	−	+	−
Schweitzer et al. 2017 [34]	+	++	++	−	++	++	++	−
Hiremath et al. 2017 [35]	+	++	++	−	++	++	++	−
Kalaiselvan et al. 2017 [36]	−	++	+	−	+	−	+	−
Vanacker et al. 2015 [7]	++	++	++	−	+	−	+	−
Hinduja et al. 2017 [37]	+	++	+	−	+	++	++	−
Bansal et al. 2020 [38]	+	++	+	−	+	−	+	−
Moon et al. 2013 [39]	+	++	+	−	+	+	+	−
Legriel et al. 2012 [40]	+	++	++	−	+	++	++	−
Liman et al. 2012 [41]	+	++	+	−	+	−	+	−
Pande et al. 2006 [10]	+	++	+	−	+	−	++	−
Covarrubias et al. 2002 [13]	+	++	++	−	+	−	++	−
Bartynski et al. 2008 [18]	+	++	++	−	+	++	++	−
McKinney et al. 2007 [42]	+	++	+	−	+	−	++	−
Brubaker et al. 2005 [12]	−	++	++	−	+	−	++	−
Gocmen et al. 2007 [43]	−	++	+	−	+	−	+	−
Fugate et al. 2010 [44]	+	++	+	−	+	++	++	−
Li et al. 2012 [9]	+	++	+	−	+	−	+	−
Mueller-Mang et al. 2009 [45]	−	++	+	−	+	−	++	−
Amornpojnimman et al. 2022 [46]	+	++	+	−	+	−	++	−
Ansari et al. 2021 [47]	+	++	+	−	+	−	++	−
Goyal et al. 2022 [48]	+	+	+	−	+	−	++	−
Hiremath et al. 2022 [49]	+	++	++	−	+	++	++	−
Ugurel et al. 2005 [50]	+	+	+	−	+	−	++	−
Yadav et al. 2019 [51]	+	++	+	−	+	−	+	−
Burnett et al. 2010 [52]	++	++	++	−	+	++	++	−

TABLE 3 (Continued)

Authors	1	2	3	4	5	6	7	8
Cruz et al. 2012 [53]	++	+	++	−	+	−	++	−
Li et al. 2013 [54]	+	+	+	−	+	−	+	−
Aranas et al. 2009 [55]	−	+	+	−	+	−	++	−
Keepanasseril et al. 2022 [56]	++	++	+	−	+	−	++	−
Lallana et al. 2021 [57]	+	+	++	−	+	−	++	−

Note: 1. Was selection of exposed and non-exposed cohorts drawn from the same population? 2. Can we be confident in the assessment of exposure? 3. Can we be confident that the outcome of interest was not present at the start of the study? 4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? 5. Can we be confident in the assessment of the presence or absence of prognostic factors? 6. Can we be confident in the assessment of outcome? 7. Was the follow-up of cohorts adequate? 8. Were co-interventions similar between groups?

Ratings: ++, definitely yes (low risk of bias); +, probably yes; −, probably no; −−, definitely no (high risk of bias).

Abbreviations: PRES, posterior reversible encephalopathy syndrome; RCVS, reversible cerebral vasoconstriction syndrome.

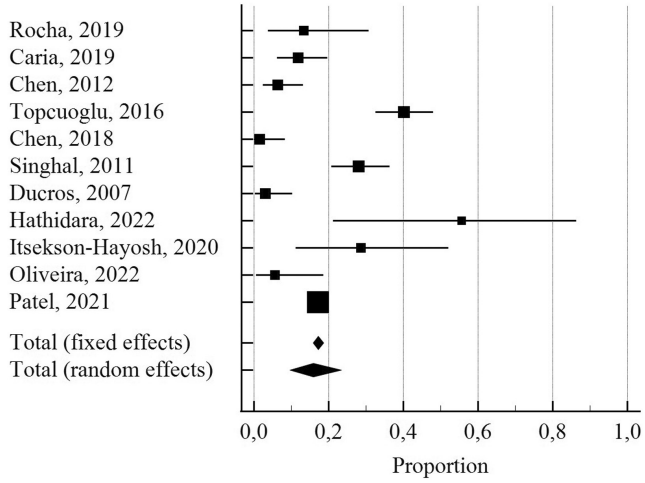

FIGURE 2 Frequency of ischaemic stroke in patients with reversible cerebral vasoconstriction syndrome (RCVS).

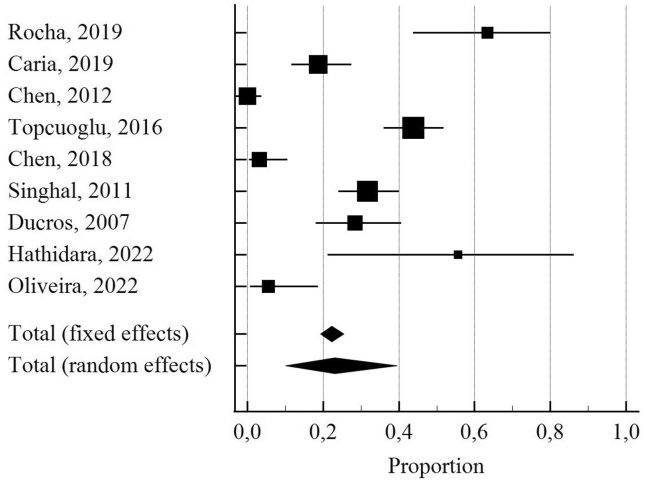

FIGURE 3 Frequency of intracranial haemorrhage in patients with reversible cerebral vasoconstriction syndrome (RCVS).

this topic, future research should be done to clarify the frequency of ischaemic stroke and/or haemorrhage in patients with PRES as a consequence of RCVS.

RCVS

We found that in patients with RCVS, intracranial haemorrhage is much more frequent than ischaemic stroke and the majority of haemorrhages are SAH. This finding can be explained by the suspected pathophysiology of the disease involving vasoconstrictions of peripheral artery branches and subsequent rupture may result in SAH and IPH. SAH in RCVS patients is most likely to result from small leaks or ruptures of surface vessels [2–4]. According to a previous study, patients with RCVS typically have SAH as the most frequent complication. They often have concurrent IPH, PRES or develop ischaemic strokes [4]. A previous study suggests that a lower proportion of RCVS patients with haemodynamically significant vasoconstriction could explain the lower incidence of ischaemic stroke compared to SAH [58]. So far, however, SAH has not often been highlighted as a main feature of RCVS [1, 4]. The frequency of ischaemic stroke and intracranial haemorrhage in patients with COVID-19 has been reported in one study and is within the stated range of variation. It is possible that systemic disease and hyperinflammatory condition in COVID-19 contribute to the development of RCVS. This is supported by the fact that in about one third of the patients no other triggering disease or medication was present [30].

PRES

In PRES, we found that ischaemic stroke and intracranial haemorrhage seem equally frequent. Regarding intracranial haemorrhage, IPH was slightly more frequent than SAH. Therefore, the assumption that SAH occur more frequently in PRES than IPH cannot be confirmed [35]. FLAIR sequences are used to identify characteristic lesions of PRES. [6] However, caution should be taken in the interpretation of SAH on FLAIR due to its high sensitivity to other pathologies in the subarachnoid spaces [42, 60]. Previous

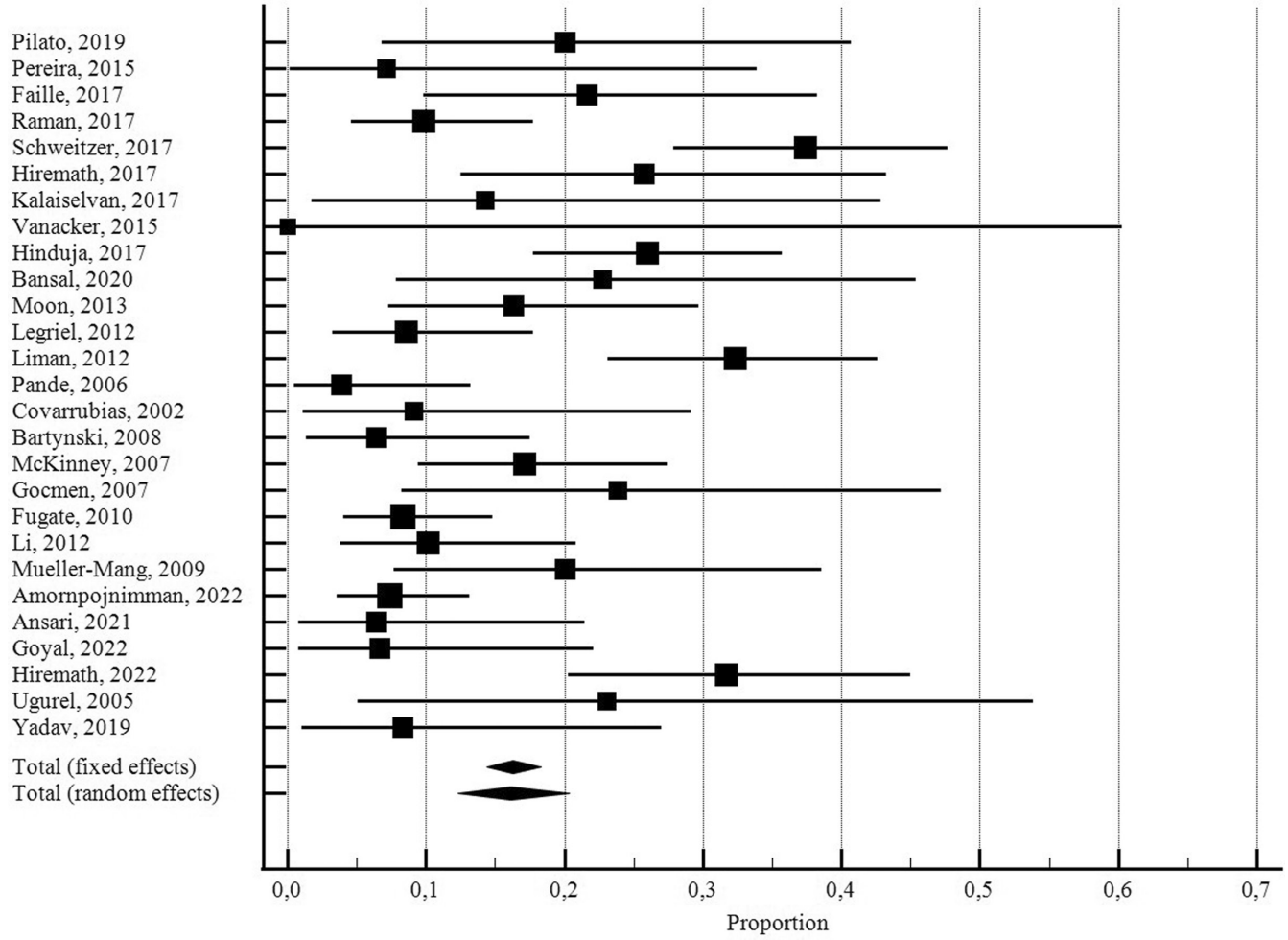

FIGURE 4 Frequency of intracranial haemorrhage in patients with posterior reversible encephalopathy syndrome (PRES).

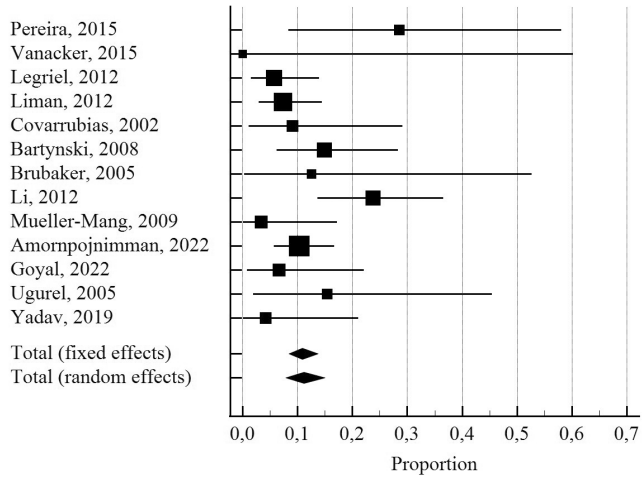

FIGURE 5 Frequency of ischaemic stroke in patients with posterior reversible encephalopathy syndrome (PRES).

studies reported a link between vasospasm and ischaemia [9, 35]. They also suggested that rupture of the cerebral vessels and altered cerebral autoregulation are responsible for haemorrhage. Furthermore, the studies describe that both haemorrhage and ischaemia may be caused by damage to the BBB due to prolonged cytotoxic oedema with subsequent cell death [9, 35, 41, 42]. The frequency of ischaemic stroke and intracranial haemorrhage in patients with COVID-19 has been reported in one study and is within the described range of variation. PRES can be triggered by a variety of causes, COVID-19 as a systemic disease with an inflammatory response and endothelial dysfunction can be a possible explanation [8, 57].

Strengths and limitations

Previous studies have reported diverging numbers of patients suffering an intracranial haemorrhage or ischaemic stroke, either alone or in combination [1, 3, 4, 42, 61]. Our study provides a condensed overview of the available published data giving the most precise estimates of these outcomes overcoming limitations from previous studies, which mostly included only small sample sizes of fewer than 50 patients. The review showed that outcomes (ischaemic stroke, intracranial haemorrhage) were investigated in many of the studies, but they varied considerably depending on the study site or setting. Imaging plays a central role in assessment. This

allows neurovascular changes to be visualised in order to record outcomes as well as to assess their course [1, 8, 14]. Interest in these syndromes in combination with imaging has increased exponentially in recent years. This can be seen from the fact that over two thirds of the works relevant to this study have been published over the past 10 years.

A limitation of the study is that the varying time point at which imaging was performed in the individual studies was not examined. In addition, the dynamics of the outcomes were not investigated although some of the studies report follow-up imaging. It is possible that certain outcomes, particularly ischaemic stroke, were unrecognised because they could have occurred after the time of imaging analysis. Previous studies suggested that ischaemia may follow a prolonged cytotoxic oedema [2, 35, 42]. Another limitation is the outcome of the risk of bias analysis. Many studies have biases (e.g., outcome assessment), use a retrospective design and take place in very heterogeneous settings. In contrast, the comprehensive analysis of the current state of research on the frequency of ischaemic stroke and intracranial haemorrhage can be regarded as a particular strength of this study. Through this holistic analysis, biases can be overcome. The systematic review provides a reasonable basis for finding information on general imaging with associated complications (ischaemic stroke, intracranial haemorrhage) in PRES and RCVS. In addition, the focus is placed on the similarities and differences of the studies conducted so far to assess comparability and identify research gaps. From this systematic review, it can be concluded that further research is needed to assess the time point of the afore-mentioned complications. If both ischaemic stroke and intracranial haemorrhage happen at onset of RCVS or PRES, we probably cannot prevent it. But if they happen after some days, protective approaches need to be investigated. In combination, a more precise understanding of pathophysiology could be important. Therefore, a possible area for future research could be prospective studies that use magnetic resonance angiography or perfusion imaging [4].

CONCLUSIONS

Both intracranial haemorrhage and ischaemic stroke are common events in both PRES and RCVS. The reported complication range varies depending on the study setting and population. This review provides a reasonable basis for obtaining information on the frequency of associated complications.

AUTHOR CONTRIBUTIONS

David Seiffge: Conceptualization; methodology; formal analysis; supervision; writing – original draft; investigation; validation. **Jana Kaufmann:** Investigation; writing – original draft; methodology; software; formal analysis; data curation. **Philipp Buecke:** Writing – review and editing. **Thomas Meinel:** Methodology; writing – review and editing; formal analysis. **Morin Beyeler:** Writing – review and editing. **Adrian Scutelnic:** Writing – review and editing. **Johannes Kaesmacher:** Writing – review and editing. **Adnan Mujanović:** Writing – review and editing. **Thomas Dobrocky:** Writing – review and editing. **Hakim Arsany:** Writing – review and editing. **Nils Peters:** Writing – review and editing. **Werner J. Z'Graggen:** Writing – review and editing. **Simon Jung:** Writing – review and editing; supervision.

CONFLICT OF INTEREST STATEMENT

No conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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