



Posterior Reversible Encephalopathy Syndrome with Angiogenesis Inhibitors for Solid Tumours: Clues from a Disproportionality Analysis of the FDA Adverse Event Reporting System and Pharmacodynamics

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Abstract

Background Posterior reversible encephalopathy syndrome (PRES) is a rare neurologic condition that may occur as an adverse drug reaction (ADR).

Objective We aimed to characterize post-marketing reporting of PRES related to angiogenesis inhibitors targeting the vascular endothelial growth factor and its receptor (VEGF/VEGFR) and to explore the underlying pharmacodynamic mechanisms.

Methods A disproportionality analysis was performed within the FDA Adverse Event Reporting System (FAERS) database. The Bayesian information component (IC) was calculated to detect signals of disproportionate reporting (SDRs), with subgroup analyses by treatment regimen, and coreported drugs as proxies for risk factors of PRES. A network analysis identified clusters of coreported events, and univariate regression models that interpolated disproportionality and receptor affinities (extracted from ChEMBL and IUPHAR/BPS databases) were performed.

Results We found 856 reports of PRES associated with anti-VEGF therapies (88.5% by healthcare professionals; 49% by tyrosine kinase inhibitors; 48% by monoclonal antibodies; 72% with immunotherapy in the 2021–2024 period). Patients were mainly females (68%), with a median age of 62 years (IQR 52–69). SDRs emerged for 12 drugs, notably bevacizumab [$N = 393$; $IC = 3.17$; 95% confidence interval (CI) 3.00–3.29] and lenvatinib (132; 3.27; 2.98–3.48). Hypertension, headache, confusional state, and proteinuria emerged in a coreported syndromic cluster. Only fibroblast growth factor receptor (FGFR) 4 emerged with a significant inverse association ($\beta = -0.107$, $p = 0.001$).

Conclusions Although causality cannot be established, these findings raise the hypothesis that PRES could be a class effect of angiogenesis inhibitors and call for ongoing epidemiological surveillance and timely multiprofessional management of hypertension as a risk-minimization strategy. The potential modulatory role of FGFR4 deserves further mechanistic translational studies.

Key Points

The consistency of disproportionality analyses raised the hypothesis that PRES could be a class effect of angiogenesis inhibitors.

The network analysis suggested timely recognition and management of hypertension as a key risk minimization strategy.

The unexpected inverse correlation with fibroblast growth factor receptor 4 deserves further translational mechanistic studies.

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1 Introduction

Molecular targeted therapies against the vascular endothelial growth factor (VEGF) and its receptor (VEGFR) are widely used as a single agent or with chemotherapy and immunotherapy in a variety of solid tumors, including breast cancer, non-small-cell lung cancer, thyroid, ovarian and colon cancer, and hepatocellular and renal cell carcinoma as well as prostate cancer, where angiogenesis has been implicated in disease progression [1–3]. These angiogenesis inhibitors (so-called anti-VEGF), including tyrosine kinase inhibitors (TKIs), monoclonal antibodies (mAbs), and the VEGF trap fusion protein (aflibercept), have been shown to be effective in inhibiting the formation, proliferation, and migration of new blood vessels [4].

In recent decades, anti-VEGF treatments have significantly improved the survival rates of patients with metastatic cancer, and ongoing studies are assessing their benefit–risk profile in various clinical settings.

Rare neurological adverse events have been reported [5–7], including posterior reversible encephalopathy syndrome (PRES) [8–10], which is characterized by headache, visual loss, seizures, focal neurological deficits and encephalopathy. The exact pathophysiology of PRES is not fully understood; however, hypertension and endothelial dysfunction appear to be strongly implicated. Although PRES is a rare condition [11], it can potentially alter the regulation of cerebral blood flow and may be fatal. The management strategy is primarily based on identifying and removing the provocative cause. Therefore, early clinical suspicion and etiological diagnosis are crucial to avoiding irreversible neurological damage. A wide variety of medical conditions have been implicated as causes of PRES, including hypertension, (pre)-eclampsia, autoimmune diseases, organ transplantation, infections, sepsis, and renal failure. Additionally, PRES may occur as an adverse drug reaction (ADR), particularly after anticancer and immunosuppressive medications [12]. Recently, several cases have been reported during treatment with bevacizumab [13–16], sunitinib [17–20], sorafenib [21–23], pazopanib [24–26], regorafenib [27, 28], and lenvatinib [29–33]. Accordingly, except for ranibizumab, PRES is reported in the Food and Drug Administration (FDA) and European Medicines Agency (EMA) labels of all mAbs and TKIs, albeit with variable description across product labels in the relevant sections (warning and/or undesirable effects) (Supplementary Table S1).

In an evolving context where anticancer regimens combining TKIs and mAbs are gaining clinical application at earlier stages of disease, the evaluation of the safety profile is crucial to support oncologists in patient monitoring and management.

Pharmacovigilance studies based on large adverse event reporting databases, such as the FDA Adverse Event Reporting System (FAERS), are particularly suited to characterize rare ADRs that might be incompletely captured during clinical trials, particularly for recently marketed medications through the accelerated conditional approval [34].

The study aims to: (1) analyze individual case safety reports (ICSRs) from the FAERS database to gain insights into the potential association between angiogenesis inhibitors and PRES, thus addressing the issue of a class effect, and (2) explore the underlying mechanisms by integrating pharmacovigilance with pharmacodynamic data. Since several TKIs blocking VEGFR are multitarget inhibitors, a more comprehensive understanding of the role of other molecular targets may support risk minimization strategies and drug repurposing [35].

2 Materials and Methods

2.1 Study Design and Data Sources

This is a hybrid study combining pharmacovigilance data (ICSRs obtained from the FAERS [36]) and pharmacodynamic affinity data from public databases (ChEMBL [37] and IUPHAR [38]). Integrating pharmacovigilance and pharmacodynamic data may help in the search for the pathogenetic mechanisms of drug-induced conditions and was recently applied to TKIs [39–41]. Pharmacovigilance analyses were conducted and reported in accordance with the READUS-PV guidelines [42, 43] for disproportionality analysis (checklist in Supplementary Materials), using FAERS data accessed via the DiAna R package [44] up to 31 March 2024. Through the well-known case/non-case study design, cases were defined as ICSR listings “posterior reversible encephalopathy syndrome” as preferred term (PT of the MedDRA terminology, version 27.1) [45] among events, with at least one anti-VEGF/VEGFR drug reported as suspect (primary or secondary suspect). Anti-VEGF/VEGFR drugs of interest were bevacizumab, ramucirumab, ranibizumab (mAbs), axitinib, cabozantinib, fruquintinib, lenvatinib, nintedanib, pazopanib, regorafenib, sorafenib, sunitinib, tivozanib, vandetanib (TKIs), and aflibercept (other), the recombinant fusion protein acting as a soluble decoy receptor for VEGF.

2.2 Descriptive Analysis

Clinical and reporting characteristics of cases were described for the overall sample and subgroups. Subgroups were defined

on the basis of the mechanism of action (mAbs, TKIs, and others) and the therapeutic regimen (monotherapy, cotherapy with chemotherapy, or cotherapy with immunotherapy). Statistical comparisons in the latter analysis were conducted to assess the homogeneity of distributions across the three groups, using the Wilcoxon–Mann–Whitney test for continuous variables and the chi-squared test for categorical variables. The Holm–Bonferroni correction was applied to account for multiple testing. Concomitant drugs and indications for VEGFR were described. Furthermore, co-occurring events with PRES were described graphically and explored using a network-based approach [46].

2.3 Disproportionality Analysis

Disproportionality analysis employed the Bayesian information component (IC); a signal of disproportionate reporting (SDR) was defined by the lower limit of 95% credibility interval of the IC ($IC_{0.25}$) > 0 to account for the small sample size of several drug–event pairs [47, 48]. In the primary analysis, VEGF(R) inhibitors were compared with all the other drugs reported in the FAERS (standard approach). Positive (calcineurin inhibitors) and negative (paracetamol and morphine) controls were identified to check the accuracy of disproportionality analysis. Subsequently, secondary active-comparator disproportionality analysis was performed by restricting to anticancer drugs to account for confounding by indication and channeling bias [49].

Two additional subgroup disproportionality analyses were then performed. The first was based on treatment regimen (monotherapy, cotherapy with chemotherapy, or cotherapy with immunotherapy) and the second on the presence of concomitant drugs considered proxies of pathological conditions associated with PRES (no concomitants, ≥ 1 concomitants, or ≥ 2 concomitants). The drugs selected as concomitants of interest included antihypertensives, anti-infectives, corticosteroids, and immunosuppressants.

2.4 Pharmacovigilance–Pharmacodynamic Analysis

For each molecular target, we performed linear regression models with affinity as the outcome and the median IC as the predictor, including all drugs for which affinity data were available. We considered receptors with a significant coefficient (p -value < 0.05) as plausible mechanistic targets [35].

3 Results

3.1 Descriptive Analysis

Out of 7207 cases of drug-related PRES reported in FAERS database, 856 were reported with an anti-VEGF/VEGFR as

a suspect drug. Specifically, 414 cases involved mAbs, 425 TKIs, and 26 aflibercept (Fig. 1).

The overall sample consisted mainly of female individuals (68%), with a median age of 62 years (IQR 52–69). Hospitalization was recorded in 46% of cases, and reports were primarily submitted by healthcare professionals (88.5%; 49% by physicians). Most reports originated from North America (383, 45%), followed by Europe (294, 34%) and Asia (151, 18%). The characteristics of the population across the different subgroups of drug classes are presented in Table 1.

Among cases, 425 reported monotherapy, 337 concomitant chemotherapy, and 103 concomitant immunotherapy (Table 2). The most reported drugs, alone or in combination, were bevacizumab for mAbs (393 cases) and lenvatinib for TKIs (132 cases) (Supplementary Fig. S1). The number of reports generally increased over time, with reports of monotherapy showing a roughly constant growth since 2005. By contrast, reports coreporting chemotherapy reached a plateau in recent years, while those coreported with immunotherapy (72% in 2021–2024 period) showed an increase (Supplementary Fig. S2).

Therapeutic indications were reported in 95% of cases and varied between reports involving mAbs and TKIs. The most reported indications for mAbs were lung cancer (15.5%), colon cancer (14.0%), and ovarian cancer (12.8%). For TKIs, the most frequently reported indications were renal cancer (46.8%), endometrial cancer (8.9%), and thyroid cancer (8.9%) (Supplementary Fig. S3).

Among concomitant drugs, the most reported classes were analgesics (23.6%), other anticancer agents (23.4%), and psycholeptics (14.4%). The most reported concomitant drugs were levothyroxine (6.1%), ondansetron (5.8%), and paracetamol (5.8%) (Supplementary Fig. S4).

The most frequently coreported adverse events with PRES were hypertension (21.8%), headache (12.5%), and seizures (11.8%) (Supplementary Fig. S5). Hypertension and headache were also part of a cluster identified by the network analysis, along with confusional state and proteinuria. Headache linked this cluster to another one, including nausea, vomiting, and transient global amnesia (Fig. 2).

3.2 Disproportionality Analysis

The primary disproportionality analysis identified an SDR for 12 out of the 15 drugs under analysis. The remaining drugs did not show a signal owing to an insufficient number of cases to compute disproportionality (Supplementary Table S2 and Fig. 3). Ciclosporin [IC 4.75; 95% confidence interval (CI) 4.63–4.83], tacrolimus (4.55; 4.44–4.62), and voclosporin (1.65; 0.24–2.56) were confirmed as positive controls. Likewise, the negative controls paracetamol (-1.18 ; -1.66 to -0.84) and morphine (0.41; -0.05 to 0.74) were confirmed.

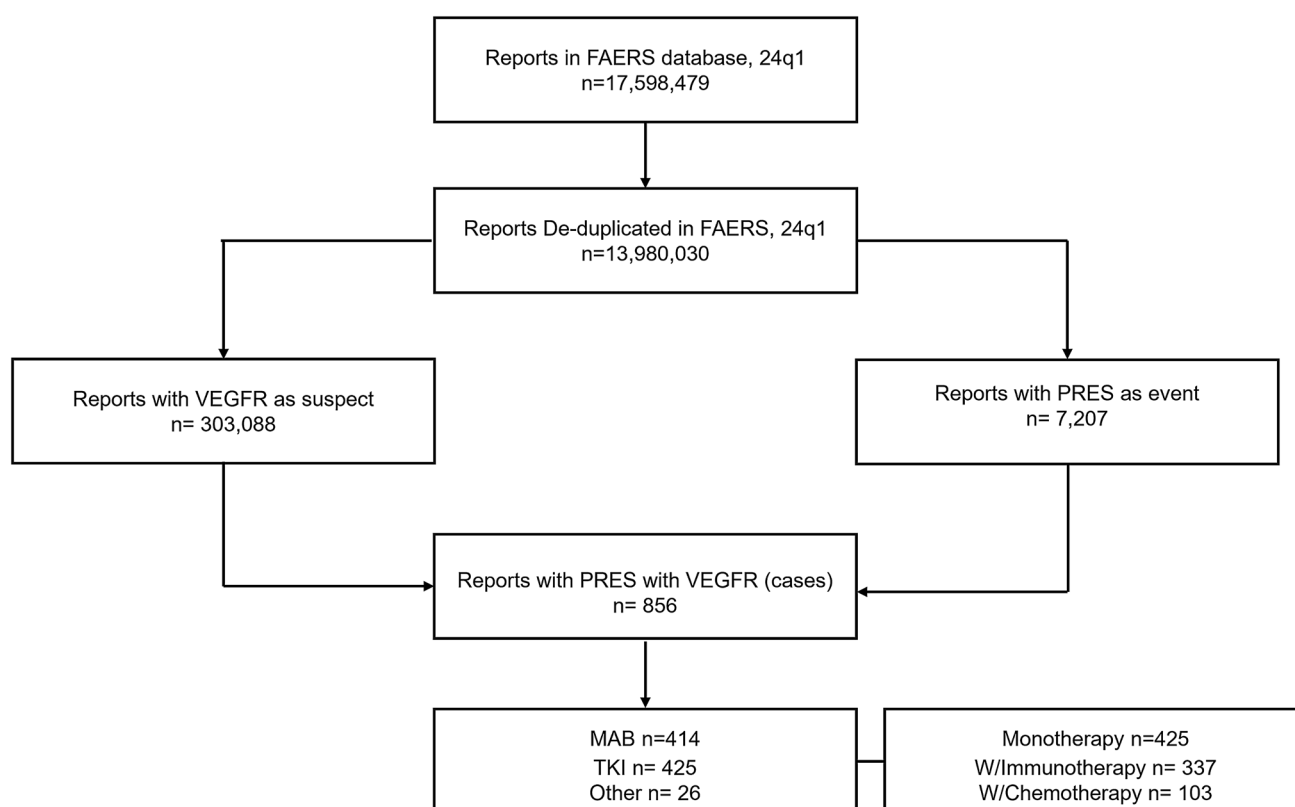


Fig. 1 Flowchart of cases retrieval. Note that the sum of the subsamples is higher than the total sample size because one case can involve more than one suspected drug from different classes

When restricting the comparison to anticancer drugs, SDRs remained for mAbs, bevacizumab and ramucirumab, and for axitinib, lenvatinib, pazopanib, and tivozanib among TKIs (Supplementary Table S3 and Fig. 3).

Among the 12 drugs with at least three cases overall, the subgroup disproportionality analysis based on treatment regimen showed SDR for nearly all drugs in monotherapy, except for ranibizumab, fruquintinib, vandetanib, nintedanib, and aflibercept. When chemotherapy was coreported, SDR emerged only for bevacizumab. Similarly, when immunotherapy was coreported, SDRs were found only for axitinib, lenvatinib, and sunitinib (Supplementary Table S4 and Fig. 4).

When performing the disproportionality analysis within subgroups defined by the presence of concomitant drugs considered proxies for pathological conditions associated with PRES, only bevacizumab generated consistent SDRs as monotherapy and with at least one and with two or more concomitant drugs of interest (Fig. 5).

3.3 Pharmacovigilance–Pharmacodynamic Analysis

Using ChEMBL and IUPHAR databases, complete data on affinity were retrieved for axitinib, cabozantinib,

fruquintinib, lenvatinib, nintedanib, pazopanib, regorafenib, sorafenib, sunitinib, tivozanib, and vandetanib (Supplementary Table S5).

From regression analyses, only fibroblast growth factor receptor 4 (FGFR4) showed a significant association between its affinity and IC ($\beta = -0.107$, $p = 0.001$) (Supplementary Table S6 and Supplementary Fig. S6). Specifically, higher FGFR4 affinity values were associated with a significant decrease in PRES reporting (Supplementary Table S6 and Fig. 6).

4 Discussion

Targeting VEGF/VEGFR has emerged as an effective therapeutic strategy in different cancers, especially in combination with immunotherapy. However, different life-threatening off-target toxicities have been described and characterized in the post-marketing real-life setting, including major adverse cardiovascular events [50, 51]. The available clinical evidence on PRES, a rare but life-threatening adverse event, by angiogenesis inhibitors is scant, jeopardized, and limited to case reports and small case series, especially on TKIs. This study is the largest collection of PRES cases

Table 1 Descriptive analysis of the cases of PRES with a VEGF inhibitor

	Total	mAbs	TKIs	Other
Number of cases	856	414	425	26
Primary suspect	617 (72.1%)	238 (57.5%)	367 (86.3%)	12 (46.1%)
Secondary suspect	239 (27.9%)	176 (42.5%)	58 (13.7%)	14 (53.8%)
Sex				
Female	533 (68.2%)	289 (76.2%)	241 (62.3%)	10 (43.5%)
Male	248 (31.7%)	90 (23.7%)	146 (37.7%)	13 (56.5%)
Missing	75 (–)	35 (–)	38 (–)	3 (–)
Age (years)				
Median (IQR) [min–max]	62 (52.00–69) [5.00–94]	60 (47.00–67) [5.00–84]	64 (56.00–71) [15.00–94]	65 (60.50–72) [38.00–81]
0–17	23 (3.1%)	16 (4.9%)	5 (1.5%)	–
18–29	3 (0.4%)	2 (0.6%)	1 (0.3%)	–
30–49	107 (16.0%)	72 (22.1%)	35 (10.7%)	2 (9.1%)
50–64	261 (39.1%)	129 (39.6%)	125 (38.1%)	9 (40.9%)
65–74	206 (30.8%)	82 (25.1%)	120 (36.6%)	8 (36.4%)
> 75	70 (10.5%)	25 (7.7%)	42 (12.8%)	3 (13.6%)
Missing	188 (–)	88 (–)	97 (–)	4 (–)
Reporter				
Consumer	95 (11.5%)	31 (7.8%)	65 (15.8%)	–
Healthcare practitioner	77 (9.4%)	38 (9.6%)	38 (9.2%)	1 (3.8%)
Other (unspecified)	177 (21.5%)	98 (24.8%)	74 (18%)	7 (26.9%)
Pharmacist	68 (8.3%)	28 (7.1%)	39 (9.5%)	2 (7.7%)
Physician	406 (49.3%)	200 (50.6%)	195 (47.4%)	16 (61.5%)
Missing	33 (–)	19 (–)	14 (–)	–
Reporter country				
North America	383 (44.7%)	184 (44.4%)	200 (47.1%)	6 (23.1%)
Europe	294 (34.3%)	142 (34.3%)	138 (32.5%)	16 (61.5%)
Asia	151 (17.6%)	77 (18.6%)	72 (17%)	2 (7.7%)
South America	9 (1.0%)	1 (0.2%)	7 (1.6%)	1 (3.8%)
Oceania	15 (1.7%)	7 (1.7%)	7 (1.6%)	1 (3.8%)
Africa	4 (0.5%)	3 (0.7%)	1 (0.2%)	–
Reporting year				
2004–2012	348 (40.7%)	76 (18.3%)	268 (63.1%)	4 (15.4%)
2013–2020	301 (35.2%)	63 (15.2%)	234 (55.1%)	4 (15.4%)
2021–2024	348 (40.7%)	76 (18.3%)	268 (63.1%)	4 (15.4%)
Outcome				
Death	117 (13.7%)	58 (14.0%)	61 (14.3%)	2 (7.7%)
Life threatening	107 (12.5%)	41 (9.9%)	60 (14.1%)	7 (26.9%)
Disability	19 (2.2%)	10 (2.4%)	9 (2.1%)	–
Required intervention	4 (0.5%)	3 (0.7%)	1 (0.2%)	–
Hospitalization	390 (45.6%)	187 (45.2%)	194 (45.6%)	12 (46.1%)
Other serious	215 (25.1%)	111 (26.8%)	100 (23.5%)	5 (19.2%)
Not serious	4 (0.5%)	4 (1%)	–	–

The “cases” column describes the entire sample, while the “MAB,” “TKI,” and “other” columns describe subsamples of cases divided by different types of VEGF inhibitors. Note that the sum of the subsamples is higher than the total sample size because one case can involve more than one suspected drug from different classes. Where not specified, data are reported as counts with valid percentages (without counting unknown values)

mAbs monoclonal antibodies, *TKIs* tyrosine kinase inhibitors, *IQR* interquartile range

Table 2 Descriptive analysis and statistical comparison of cases of PRES with a VEGFR inhibitor in monotherapy versus in combination with chemotherapy or immunotherapy

	Monotherapy	Chemotherapy	<i>p</i> -Value	<i>q</i> -Value	Immunotherapy	<i>p</i> -Value	<i>q</i> -Value
Number of cases	425	337	< 0.001	0.006	103	< 0.001	0.006
Primary suspect	394 (92.7%)	162 (48.1%)			72 (59%)		
Secondary suspect	31 (7.3%)	175 (51.9%)			50 (41%)		
Sex			0.050	0.200		0.095	0.475
Female	246 (64.4%)	221 (71.5%)			72 (73.5%)		
Male	136 (35.6%)	88 (28.5%)			26 (26.5%)		
Missing	43	28			5		
Age (years)			< 0.001	0.006		0.095	0.475
Median (IQR)	63 (55.00–70)	60 (48.00–67)	< 0.001		67 (58.00–71)	0.067	
[min–max]	[15.00–94]	[5.00–84]			[38.00–80]		
0–17	47 (14.6%)	21 (7.5%)			8 (10.5%)		
18–29	2 (0.6%)	1 (0.4%)			–		
30–49	47 (14.6%)	21 (7.5%)			8 (10.5%)		
50–64	122 (37.9%)	112 (40.3%)			31 (40.8%)		
65–74	106 (32.9%)	69 (24.8%)			34 (44.7%)		
> 75	42 (13.0%)	21 (7.5%)			8 (10.5%)		
Missing	103	59			35		
Reporter			< 0.001	0.006		< 0.001	0.006
Consumer	62 (15.2%)	21 (6.56%)			12 (11.7%)		
Healthcare practitioner	41 (10.0%)	23 (7.19%)			13 (12.6%)		
Other	82 (20.1%)	95 (29.7%)			2 (1.9%)		
Pharmacist	44 (10.8%)	15 (4.69%)			11 (10.7%)		
Physician	180 (44.0%)	166 (51.9%)			65 (63.1%)		
Missing	16	17			0		
Reporter country			< 0.001	0.006		< 0.001	0.006
North America	226 (53.2%)	127 (37.7%)			33 (32.0%)		
Europe	138 (32.5%)	124 (36.8%)			36 (35.0%)		
Asia	51 (12.0%)	75 (22.3%)			26 (25.2%)		
South America	5 (1.2%)	2 (1.0%)			3 (2.9%)		
Oceania	4 (1.0%)	6 (1.2%)			5 (4.9%)		
Africa	1 (0.2%)	3 (1%)			0 (0.0%)		
Reporting year			0.001	0.009		< 0.001	0.006
2004–2012	108 (25.4%)	117 (34.7%)			–		
2013–2020	237 (55.8%)	196 (58.2%)			34 (27.9%)		
2021–2024	80 (18.8%)	24 (7.1%)			88 (72.1%)		
Outcome			0.376	0.752		0.168	0.475
Death	61 (14.3%)	47 (13.9%)			10 (9.7%)		
Life threatening	53 (12.5%)	39 (11.6%)			18 (17.5%)		
Disability	5 (1.2%)	10 (3%)			5 (4.8%)		
Required intervention	4 (1%)	–			–		
Hospitalization	190 (44.7%)	157 (46.6%)			45 (43.7%)		
Other serious	110 (25.9%)	82 (24.3%)			25 (24.3%)		
Not serious	2 (0.5%)	2 (0.6%)			–		

Monotherapy is defined as the absence of both chemotherapy and immunotherapy

IQR interquartile range

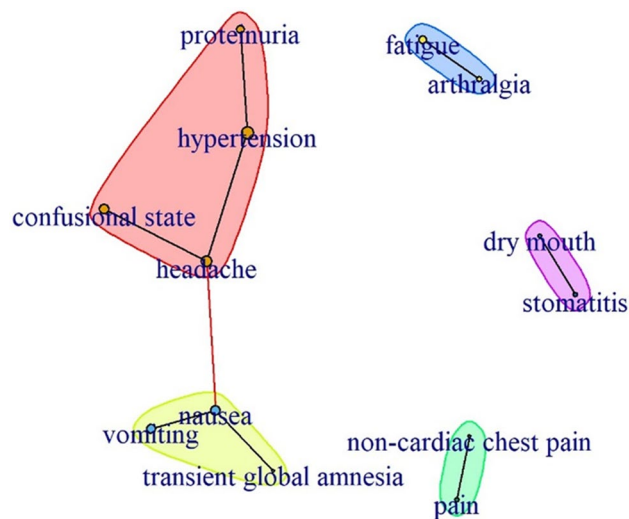


Fig. 2 Ising-based network of events co-occurring with PRES in the sample of interest

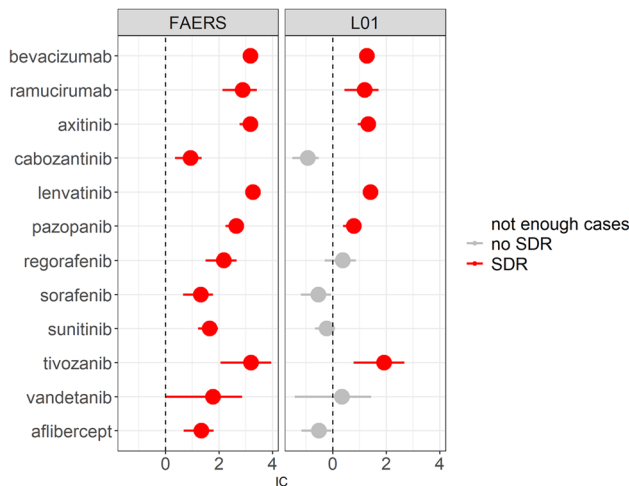


Fig. 3 Summary of signals from the main disproportionality analysis (FAERS) and from the analysis restricted to antineoplastic drugs (L01)

attributed to VEGF/VEGFR inhibitors from a large-scale pharmacovigilance database so far, and it strengthened the hypothesis that PRES should be considered a class effect of angiogenesis inhibitors. The vast catchment area of FAERS and the variegate geographic distribution of cases, including the USA (~ 45%), Europe (~ 34%), and Asia (~ 18%), supports the generalizability of findings across the globe.

Different key findings can be identified.

- (1) The mAb bevacizumab, having the longest history of reporting (since 2005), still received the highest number of reports in more recent years. In contrast, reports for lenvatinib began in 2014 but showed a

rapid increase in the following years. During the 2021–2024 period, a remarkable increase in PRES reports emerged for anti-VEGFR drugs in combination regimens, notably with immunotherapy. Taken together, these data call for constant epidemiological surveillance, especially considering their expanding use in combination with immune checkpoint inhibitors as first-line treatment in metastatic renal cell carcinoma (pembrolizumab plus axitinib/lenvatinib) and advanced hepatocellular carcinoma (bevacizumab plus atezolizumab). Notably, TKI monotherapy remains an appropriate first-line option for many patients ineligible for immunotherapy, as supported by the STAR trial; treatment interruptions in second-line settings may be considered with caution owing to shorter progression-free survival [52].

Although actual incidence and prevalence cannot be derived from ICSRs, on the basis of these data, PRES should be considered as an uncommon event of anti-VEGFR drugs, as classified in the vast majority of summaries of product characteristics, which could be potentially harmonized to describe PRES in the relevant section on warnings and precautions of use.

- (2) Among TKIs, axitinib, lenvatinib, pazopanib, and tivozanib generated consistent disproportionality across subgroup and sensitivity analyses (versus other anti-cancer drugs, as monotherapy, with immunotherapy, and without coreported drugs as a potential risk factor for PRES), thus supporting the existence of a plausible cause–effect relationship. Of note, these TKIs showed increased potency and higher selectivity for VEGFR-1, VEGFR-2, and VEGFR-3 tyrosine kinases [53].
- (3) The cluster analysis confirmed hypertension, headache, confusional state, and proteinuria as events coreported with PRES, thus confirming the notion that hypertension is a frequent plausible trigger event of PRES, and strengthening the need for increased awareness and optimal management of blood pressure as risk minimization strategies. Although hypertension is commonly observed with anti-VEGF therapy (and also positively correlated with clinical benefit), with an incidence up to 90% [54], there are no formal guidelines for the evaluation, diagnosis, monitoring, and management of hypertension [55]. Considering the beneficial effect on proteinuria, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers could be considered as first-line pharmacological approaches. We call for a tight multidisciplinary collaboration between oncologists, neurologists, cardiologists, nephrologists, and pharmacologists to implement dedicated guidelines for proactive management and monitoring of hypertension, especially in combination regimen with immunotherapy.

Fig. 4 Subgroup disproportionality analysis within mono-therapy, chemotherapy, and immunotherapy groups

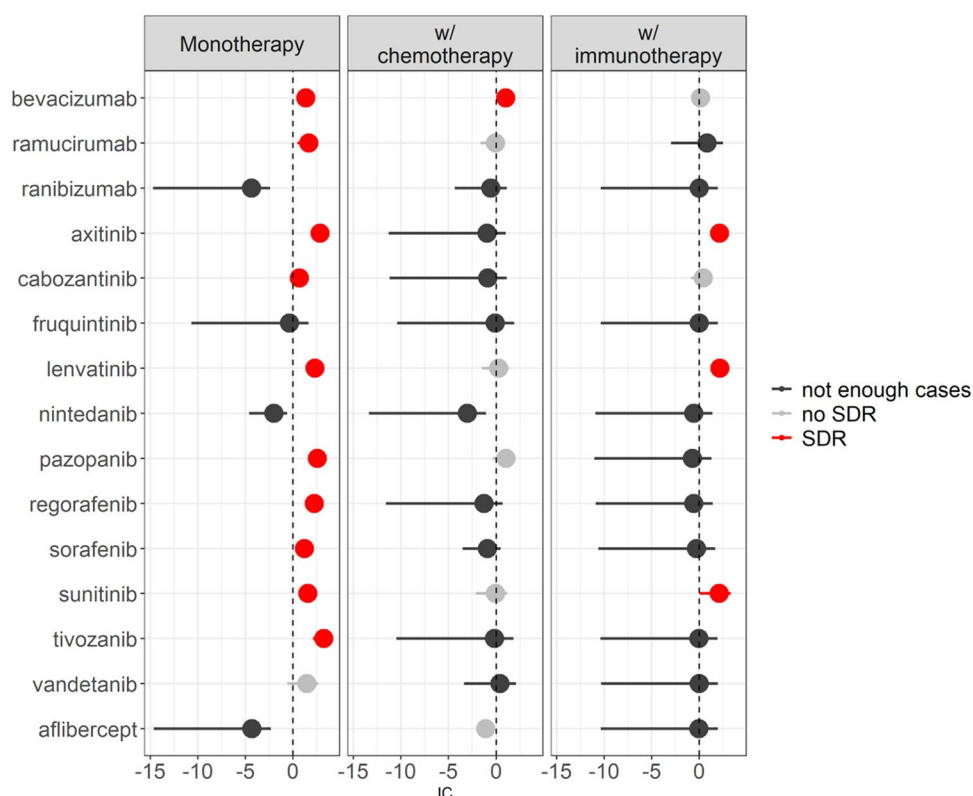
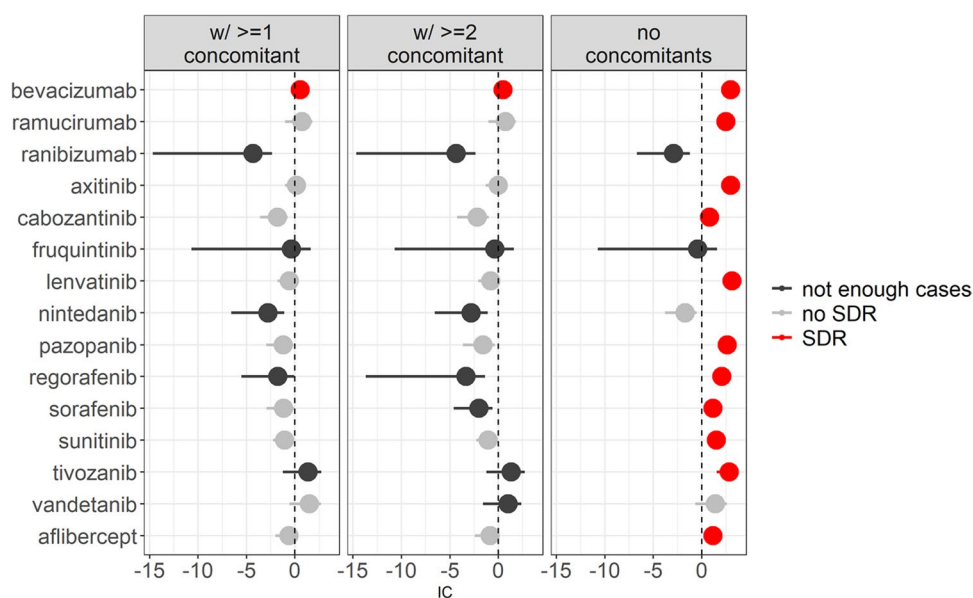


Fig. 5 Subgroup disproportionality analysis within reports with no concomitant, ≥ 1 concomitant, and ≥ 2 concomitant



- (4) From a mechanistic perspective, PRES results from a failure of the blood–brain barrier to maintain the intra-vascular fluids compartmentalization, leading to vaso-genic edema and subsequent neuronal dysfunction. The VEGF signaling pathway is critical for microvascular homeostasis, and its disruption results in a decrease of nitric oxide availability, thereby promoting endothelial

dysfunction and increasing vascular permeability [56]. Nonetheless, we did not observe a correlation between disproportionality estimates and VEGFR affinity. This finding may be explained by the fact that highly potent TKIs (axitinib, lenvatinib) are those with more robust pharmacovigilance data.

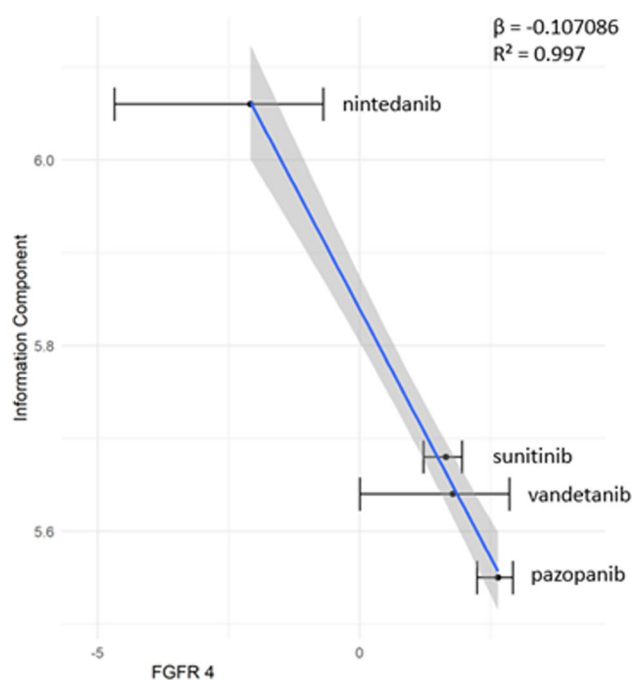


Fig. 6 Relationship between median IC (displayed with 95% CI) and FGFR4

The unexpected inverse correlation with FGFR4 (higher affinity was associated with a significant decrease in PRES reporting) should be interpreted very cautiously, and a relevant protective effect cannot be inferred. FGFR4 is a tyrosine kinase and cell surface receptor for fibroblast growth factors (FGFs). The encoded protein plays a crucial role in regulating various pathways, including cell proliferation, differentiation, migration, lipid metabolism, bile acid biosynthesis, vitamin D metabolism, glucose uptake, and phosphate homeostasis. Different small molecules inhibiting FGFR have been recently approved for treatment of urothelial carcinoma and cholangiocarcinoma, such as erdafitinib, infigratinib, futibatinib (inhibitors of FGFR1–FGFR4), and pemigatinib (inhibitor of FGFR1, FGFR2, and FGFR3), without data on PRES reported in the relevant summaries of product characteristics. The potential role of FGFR4 in modulating the occurrence of PRES remains speculative but, in our view, deserves dedicated mechanistic translational studies [57].

As a final consideration, we would like to compare and contrast PRES and progressive multifocal leukoencephalopathy (PML). Apart from significant clinical and neuroradiological similarities, both conditions may occur as complications of immunosuppressive or cytotoxic therapies, making the differential diagnosis challenging. Despite these similarities, PRES and PML have distinct pathogenetic mechanisms: PRES is primarily associated with disruption of the blood–brain

barrier, whereas PML results from infection of oligodendrocytes by the JC virus, typically in the setting of profound immunosuppression [58]. In addition, PML has been linked to specific genetic risk variants [59], most of which are involved in immune system function, whereas no established genetic risk variants associated with the occurrence of PRES have been identified to date [60]. It is worth mentioning that pharmacovigilance played a pivotal role in the timely identification and evaluation of PML as a plausible ADR by drugs for multiple sclerosis and other immunomodulators/immunosuppressants [61–64].

A collaboration between stakeholders, including public–private initiatives, may fill the knowledge gaps on genetics, biomarkers, and risk stratification, thus supporting actionable risk minimization strategies for PRES.

We acknowledge limitations and pitfalls of pharmacovigilance data, comprising the FAERS database, submitted ICSRs, and relevant disproportionality analysis. The lack of certainty on causality, missing denominator (exposed population), underreporting (only an unquantifiable fraction of treatment-related adverse events are actually reported), and the suboptimal quality/completeness of information provided in ICSRs make this kind of study hypothesis-generating [65].

Our analysis likely underestimated the total number of cases, as we included only reports explicitly containing a diagnosis of PRES. Those describing PRES-related symptoms and related imaging abnormalities without a formal diagnosis were not captured. Moreover, missing information on the date of events and drug exposure precluded a reliable assessment of the time to onset of PRES following treatment with anticancer therapy anti-VEGF.

Similarly, disproportionality analyses cannot establish a causal relationship between PRES and anti-VEGF agents; the absence of reliable exposure data in FAERS does not allow the estimation of incidence rates or the quantification of risk. Furthermore, as discussed, confounding factors constitute a major methodological challenge, and all confounders cannot be ruled out with certainty.

Nevertheless, when expected confounders are taken into account, the accuracy and validity of disproportionality analysis have been demonstrated in various settings (especially for rare life-threatening ADRs) [47, 66] and, in several cases, disproportionality measures are in line with estimates from meta-analyses [67]. To partially address confounding by indication and channeling bias, we performed a secondary active-comparator disproportionality analysis restricted to anticancer drugs, as well as two additional subgroup analyses to account for treatment regimens and potential pathological conditions associated with PRES.

Pharmacodynamic databases are often affected by issues such as incomplete records, variability in reported affinity

values (which depends on parameter selection and the reference compound), and duplicate records. For this reason, we systematically compiled affinity data by prioritizing the most reliable sources (ChEMBL and IUPHAR database), in which duplicated activity entries and potential transcription errors in activity records from publications are carefully detected [37]. The negative association observed with FGFR4 (where stronger binding affinity corresponded to a lower frequency of PRES reports) should be interpreted with great caution, and pharmacovigilance data alone are not sufficient to hypothesize a protective effect.

5 Conclusions

This study is the largest collection of PRES cases attributed to VEGF/VEGFR inhibitors from the public FAERS archive, a worldwide pharmacovigilance database. The consistency across disproportionality analyses for mAbs (e.g., bevacizumab) and TKIs (e.g., axitinib and lenvatinib) raised the hypothesis that PRES could be a class effect of angiogenesis inhibitors.

Notwithstanding the limitations, the rising reporting of PRES calls for constant epidemiological surveillance, especially considering their expanding first-line use in combination with immune checkpoint inhibitors.

We call for increased awareness by healthcare professionals to timely manage hypertension, a frequently coreported event, thus minimizing the occurrence of PRES. The potential modulatory role of FGFR4 deserves further mechanistic translational studies.

Considering the expanding uses of TKIs in combination regimens, especially immunotherapy, pharmacovigilance plays a key role in promoting targeted clinical surveillance and safer prescribing, especially for rare but life-threatening syndromes such as PRES.

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Declarations

Conflict of Interest Monia Donati, Chiara Cancellerini, Valentina Giunchi, Simone Rossi, Francesco Massari, Francesco Gelsomino, Elisabetta Poluzzi, and Emanuel Raschi declare that they have no conflicts of interest that might be relevant to the contents of this manuscript.

Ethical Approval, Consent to Participate, Consent to Publish Not applicable.

Data Availability The datasets generated and/or analyzed during the current study are publicly available in the FDA Adverse Event Reporting System (FAERS) database (<https://fs.fda.gov/extensions/FPD-QDE-FAERS/FPDQDE-FAERS.html>). The algorithm for cleaning FAERS data is open-source at <https://github.com/fusarolimichele/DiAna>, and the cleaned database is available on an OSF repository (<https://osf.io/zqu89/>) and through the R package DiAna (https://fusarolimichele.github.io/DiAna_package/). The code generated and/or analyzed in the current study is available from the corresponding author on reasonable request.

Code Availability Not applicable.

Author Contributions Francesco Gelsomino and Emanuel Raschi contributed to the study conception. Monia Donati, Chiara Cancellerini, and Emanuel Raschi contributed to the study design. Monia Donati and Chiara Cancellerini contributed to data collection. Valentina Giunchi performed the analysis. Monia Donati and Chiara Cancellerini drafted the manuscript. All authors contributed to the writing and editing of this paper. All authors contributed to interpreting the results and read and approved the final version submitted for publication.

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