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Analysis of Bevacizumab-Related Hypertension Using the Japanese Adverse Drug Event Report Database

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Bevacizumab, a humanized monoclonal antibody that targets vascular endothelial growth factor and inhibits angiogenesis, can cause hypertension. Although blood pressure generally rises in winter and falls in summer, seasonal patterns of bevacizumab-related hypertension (BRHT) remain unclear. We investigated these patterns using Japanese Adverse Drug Event Report data from July 2007 to June 2025. Cases where bevacizumab was reported as a "suspected drug" were identified using the Medical Dictionary for Regulatory Activities preferred terms "hypertension," "blood pressure increased," or "systolic blood pressure increased." Monthly relative BRHT frequencies were calculated by dividing BRHT reports by the total adverse event reports and compared with mean monthly temperatures obtained from the Japan Meteorological Agency. Seasons were defined as spring (March–May), summer (June–August), autumn (September–November), and winter (December–February), and were visualized using mosaic plots. Between April 2004 and September 2025, 985,999 reports were registered, of which 956 met the BRHT criteria. The median time-to-onset (TTO) was 21.0 days (interquartile range, 7.0–45.0). The Weibull scale parameter (α) was 40.8 (95% confidence interval [CI]: 37.4–44.5), and the shape parameter (β) was 1.06 (95% CI: 0.99–1.13). BRHT reports peaked in September and October and were least frequent in summer. No significant differences were observed in either TTO or clinical outcomes across seasons of adverse event onset. BRHT occurred more frequently in autumn, particularly in September and October, than in winter. Healthcare professionals should be aware of this seasonal risk and ensure appropriate blood pressure monitoring and preventive measures during autumn.

Key words bevacizumab, hypertension, seasonal variation, spontaneous reporting system

INTRODUCTION

Bevacizumab is a recombinant humanized monoclonal antibody that targets and specifically binds to the vascular endothelial growth factor (VEGF). VEGF, a cytokine that regulates the proliferation and survival of vascular endothelial cells, is involved in increased vascular permeability; its expression is upregulated in various tumors.[1,2] Bevacizumab inhibits the binding of VEGF to VEGF receptors on endothelial cells, thereby suppressing tumor angiogenesis and, consequently, tumor growth.[3,4] Moreover, bevacizumab may promote the delivery of concomitantly administered anticancer agents to tumor tissues by reducing vascular permeability and interstitial pressure within the tumor microenvironment.[4] Based on these pharmacological effects, bevacizumab was approved in the United States in 2004 as the first global anti-angiogenic agent[5,6] and has since been widely used in combination with cytotoxic chemotherapy and other therapies across multiple cancer types.

Major adverse events associated with bevacizumab include hypertension, bleeding, and proteinuria. Hypertension often develops within the first 1–2 months after therapy initiation, although it may occur at any time during the treatment course.[7,8] It is generally asymptomatic; however, when blood pressure increases rapidly, symptoms such as headaches, dizziness, and nausea may occur. Although rare, progression to hypertensive encephalopathy or hypertensive crisis can lead to severe and potentially fatal outcomes.[9] Hypertension associated with VEGF inhibitors is often reversible and can improve with temporary drug discontinuation, dose reduction, or anti-

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hypertensive therapy.[8] The proposed mechanisms include functional changes, such as reduced nitric oxide production in the vascular endothelium, and structural changes, including increased peripheral vascular resistance secondary to microvascular rarefaction.[10] Additionally, preexisting hypertension, age ≥ 60 years, and a body mass index ≥ 25 kg/m^2 are risk factors for VEGF inhibitor-associated hypertension.[7] Moreover, the development of hypertension during VEGF inhibitor therapy may correlate with treatment efficacy; therefore, continuing VEGF inhibitor treatment while appropriately controlling blood pressure is clinically important.[8]

Blood pressure exhibits seasonal variation, decreasing from spring to summer as temperatures rise and increasing from autumn to winter as temperatures fall.[11,12] Whether bevacizumab-related hypertension (BRHT) follows a similar pattern remains unclear. To investigate this, we analyzed the Japanese Adverse Drug Event Report (JADER) database, a spontaneous reporting system (SRS) managed by the Pharmaceuticals and Medical Devices Agency (PMDA) that aggregates cases from routine clinical practice, to evaluate seasonal variations in BRHT.

METHODS

Data Source The JADER database is fully anonymized to prevent the identification of individuals. Publicly available JADER data were downloaded from the PMDA website,[13] and adverse event reports registered between April 2004 and September 2025 were included. The JADER database comprises four tables: (1) DEMO (patient information, including age, sex, height, and weight); (2) DRUG (drug information, including generic name, start date of administration, indication, and drug involvement in the adverse event); (3) REAC (adverse event information, including event term, onset date, and outcome); and (4) HIST (primary disease and medical history). The four tables were integrated to construct a relational database. In the JADER database, drugs are classified as "suspect drug," "concomitant drug," or "interacting drug" in relation to an adverse event. Only reports listing the drug as "suspect drug" were included in this analysis. All statistical analyses were performed using JMP Pro version 18.0 (SAS Institute Inc., Cary, NC, USA).

Definition of Adverse Events Adverse events in the JADER database are coded using the Medical Dictionary for Regulatory Activities (MedDRA) (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, MedDRA version 27.0 Introductory Guide). In this study, hypertension-related events were identified using preferred terms (PTs) recorded in the REAC table. To ensure the validity of BRHT definitions, we first extracted all PTs related to blood pressure from cases where bevacizumab was reported as the suspected drug (Table S1). Among these, BRHT was defined as the occurrence of any of the following three PTs that directly indicate systemic arterial blood pressure elevation: "hypertension" (PT 10020772), "blood pressure increased" (PT 10005750), and "systolic blood pressure increased" (PT 10005760). In contrast, terms such as "pulmonary hypertension" and "hypertensive encephalopathy" were excluded due to differing clinical backgrounds and pathophysiology.

Handling of Duplicate Reports In the JADER database, multiple reports with the same identification ID may exist due to follow-up submissions or updates for a single case. To ensure case-level analysis and avoid potential duplication, reports sharing identical identification IDs were consolidated. When multiple records corresponded to the same identification ID, the record with the earliest adverse event onset date (i.e., the shortest time-to-onset) was retained for analysis. This approach was adopted to reflect the initial occurrence of the adverse event and to minimize bias arising from follow-up reports. Among the identification IDs with duplicate records, 1 case had five records, 4 cases had four records, 3 cases had three records, and 45 cases had two records.

Time-to-Onset (TTO) Analysis Since bevacizumab (Avastin®) was launched in Japan in June 2007,[14] TTO analysis was limited to reports from July 2007 to June 2025. TTO was calculated as the interval between the first administration date recorded in the DRUG table and the BRHT onset date recorded in the REAC table. Only reports with complete information for both dates were included, and those with a TTO ≥ 180 days were excluded to minimize the impact of outliers.

The median TTO and interquartile range (IQR) were calculated using descriptive statistics. To characterize the temporal pattern of BRHT onset, a Weibull distribution was fitted, and the scale (α) and shape (β; Weibull shape parameter [WSP]) parameters were estimated. Because SRS data lack a reference population, hazard time-dependency was assessed using β and its 95% confidence interval (CI). Specifically, an upper 95% CI bound for $\beta < 1$ indicated an early-failure pattern (decreasing hazard over time), a lower 95% CI bound for $\beta > 1$ indicated a wear-out pattern (increasing hazard over time), and a 95% CI including 1 indicated a random-failure pattern (approximately constant hazard).

Radar Chart For BRHT, the month of adverse event onset (January–December) was extracted, and the number of reports was summarized by month. Similarly, for all adverse events recorded in the JADER database, the onset month was extracted and monthly report counts were summarized. The monthly relative frequency (relative reporting frequency) was calculated by dividing the number of BRHT reports in each month by the total number of adverse event reports in the JADER database for the same month. Using these monthly relative frequencies, a radar chart with months (January–December) as the axes was constructed.

Monthly mean temperature data in Tokyo between July 2007 and June 2025 were obtained from the Japan Meteorological Agency website.[15] For each calendar month, the average temperature across the analytical period (i.e., the mean of the monthly means for the same month) was calculated. To visually compare seasonal patterns, the monthly relative frequency of BRHT and monthly mean temperature were overlaid on the same radar chart.

Monthly data on the daily maximum and minimum temperatures in Tokyo were obtained from the Japan Meteorological Agency website.[15] For each calendar month, the average diurnal variation was calculated as the mean difference between the monthly mean daily maximum and minimum temperatures over the study period.

Stratification by Adverse Event Onset Date Only reports from which the onset month could be extracted from the adverse event onset date were included; reports in which the onset date was recorded as "year only," "unknown," or "missing" were excluded. The season of onset for BRHT was defined based on the month of onset as follows: spring

(March–May), summer (June–August), autumn (September–November), and winter (December–February).

TTO was categorized as early (≤ 7 days), intermediate (8–30 days), late (31–90 days), or very late (≥ 91 days). A mosaic plot was constructed to visually assess the association between the season of onset (X) and TTO category (Y). A chi-square test was performed, and p-values < 0.05 were considered statistically significant.

Outcomes Among outcomes recorded in the REAC table, reports with an entered outcome were included; however, reports in which the outcome was recorded as "unknown" were excluded. A mosaic plot was constructed to visually assess the association between the season of onset (X) and outcome category (Y). A chi-square test was performed, and p-values < 0.05 were considered statistically significant.

Standardization by Prescribing Volume As a sensitivity analysis to account for potential confounding by monthly prescribing volume, bevacizumab prescription data were obtained from the 10th National Database Open Data,[16] using the "G injections" category for the period from April 2023 to March 2024. For each month, the proportion of the total annual prescription volume was calculated. The monthly relative frequency of BRHT (BRHT reports per all JADER adverse event reports) was standardized by dividing by the corresponding monthly prescription proportion (Supplementary Table S2). Following NDB Open Data guidelines, a hyphen is displayed when monthly injectable prescriptions are fewer than 400 cases; these months were excluded from the calculation, so the sum of monthly proportions may not equal 100%.

RESULTS

In total, 985,999 adverse event reports were registered in the JADER database between April 2004 and September 2025. Within the analytical period, 956 reports met the definition of BRHT. After excluding duplicate reports with identical identification IDs, 889 reports were included in the final analysis (Fig. 1).

Among 800 BRHT reports with available sex information, 305 (38.1%) were male and 495 (61.9%) were female (Table 1). Among 828 reports with available age data, the age distribution was as follows: ≤ 29 years, 1 (0.1%); 30–39 years, 6 (0.7%); 40–49 years, 70 (8.5%); 50–59 years, 141 (17.0%); 60–69 years, 285 (34.4%); 70–79 years, 244 (29.5%); and ≥ 80 years, 81 (9.8%) (Table 1).

Monthly information was extracted from the onset dates of 856 BRHT reports. The monthly relative frequency of BRHT was highest in September (1.27% [105/8243]) and October (1.22% [105/8572]) and lowest in July (0.56% [49/8684]) and August (0.51% [45/8825]) (Table 2, Fig. 2). Diurnal temperature variation was greater between January and May than in the remaining months.

The median TTO was 21.0 days (IQR, 7.0–45.0). The estimated Weibull parameters were a scale parameter α of 40.8 (95% CI, 37.4–44.5) and shape parameter β of 1.06 (95% CI, 0.99–1.13).

In the seasonal stratification analysis, no differences were observed in the distribution of TTO categories (early, intermediate, late, and very late) among seasons (Fig. 3). The proportions of reports by season were 21.7% in spring, 19.0% in summer, 34.2% in autumn, and 25.0% in winter, with no sig-

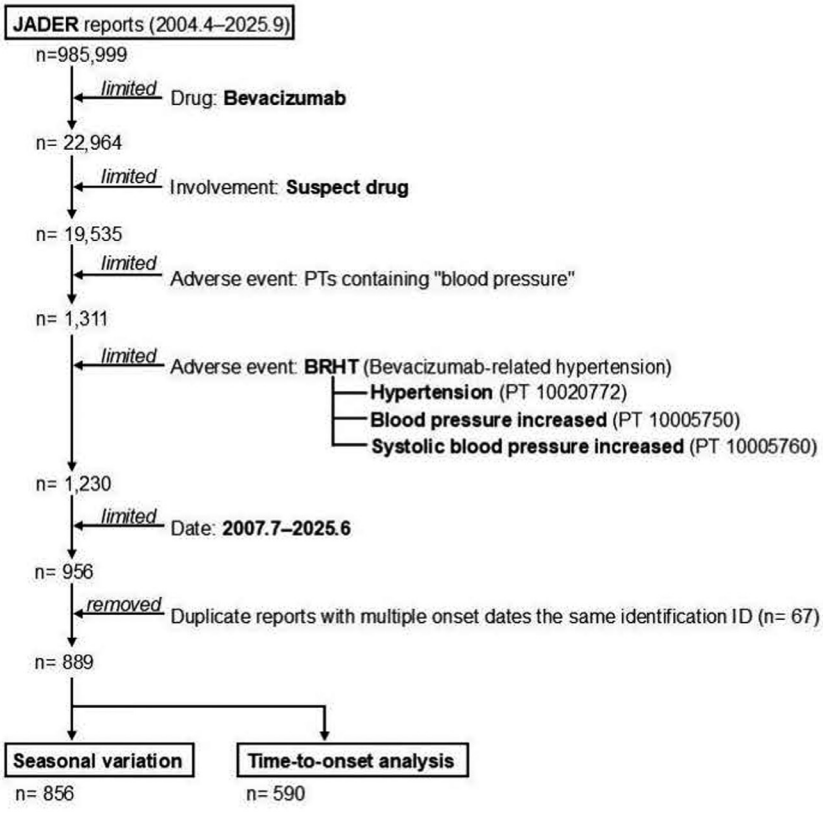

Fig. 1. Flowchart of Bevacizumab-Related Hypertension Analysis

Table 1. Reporting Rate of Bevacizumab-Related Hypertension by Sex and Age

Category		Case (n)	Reporting Rate (%)
Sex	Total*	800	100.0
	Male	305	38.1
	Female	495	61.9
Age	Total†	828	100.0
	≤ 29 years	1	0.1
	30–39 years	6	0.7
	40–49 years	70	8.5
	50–59 years	141	17.0
	60–69 years	285	34.4
	70–79 years	244	29.5
	≥ 80 years	81	9.8

* Total number of reports with sex input.
† Total number of reports with age input.

Table 2. Bevacizumab-Related Hypertension, JADER Adverse Events, Average Temperature, and Diurnal Variation for Each Month

	Reports*	JADER *		Temperature*	Diurnal variation*
Month	Case (n)	Case (n)	Ratio (%)	(°C)	(°C)
January	67	8303	0.81	5.6	8.14
February	61	7640	0.80	6.3	8.47
March	66	8514	0.78	9.9	8.94
April	57	8547	0.67	14.2	8.97
May	70	8418	0.83	18.6	8.42
June	62	9206	0.67	21.5	7.22
July	49	8684	0.56	25.3	6.98
August	45	8825	0.51	26.5	7.23
September	105	8243	1.27	23.1	6.81
October	105	8572	1.22	17.8	6.90
November	82	7780	1.05	12.8	7.49
December	87	8530	1.02	7.9	7.91

* 2007.7–2025.6

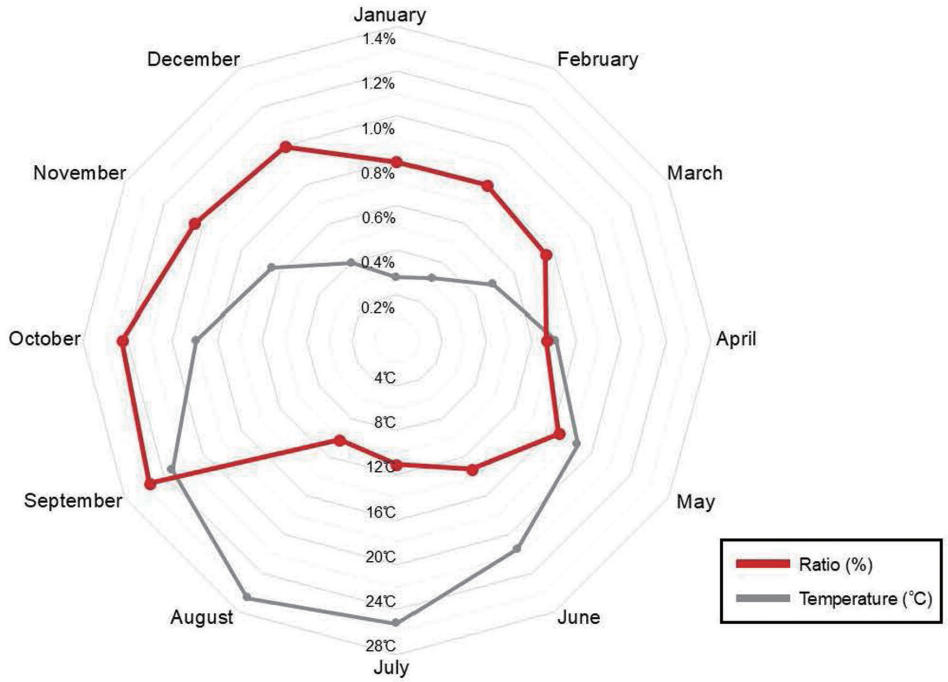

Fig. 2. Radar Chart of the Monthly Relative Frequency of Bevacizumab-Related Hypertension

nificant differences ($p > 0.05$).

Regarding outcomes, "sequelae" were reported only in summer. The most frequently reported outcome was "not recovered" in spring and summer (24.4% and 21.3%, respectively), whereas it was "recovered" in autumn and winter (36.7% and 28.1%, respectively) (data not shown). The distribution of outcomes within each season is shown (Fig. 4). However, seasonal differences in outcome distributions were not significant ($p > 0.05$).

DISCUSSION

In a Japanese home blood pressure dataset,[17] blood pressure was highest in December and January and lowest in July and August. In contrast, BRHT reports peaked in September and October, indicating a seasonal pattern that differed from that observed for blood pressure in the general population. Consistent with the general tendency of blood pressure to decrease during warmer summer months, the relative reporting frequency of BRHT in our study was also lower in summer. However, although blood pressure is generally higher in winter in the general population, our results showed a shift in the BRHT peak, with the highest relative reporting frequency occurring in September and October rather than in winter.

One possible explanation for this discrepancy is the increase in diurnal temperature variations during early autumn in Japan,[18] which may increase sympathetic nervous system activity.[19] Hypertension associated with VEGF inhibitors, including bevacizumab, is thought to arise through endothelial dysfunction (e.g., reduced nitric oxide production) and structural changes, such as microvascular rarefaction, both of which can increase vascular tone and peripheral resistance.[20,21]

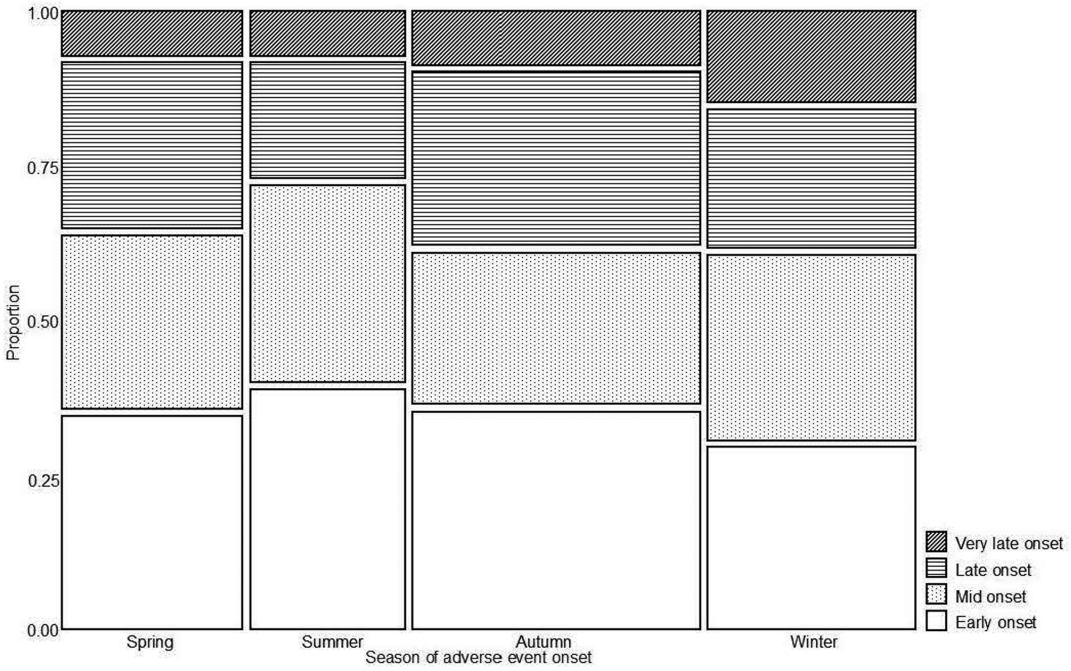

Fig. 3. Mosaic Plot of Stratification by Adverse Event Onset Date

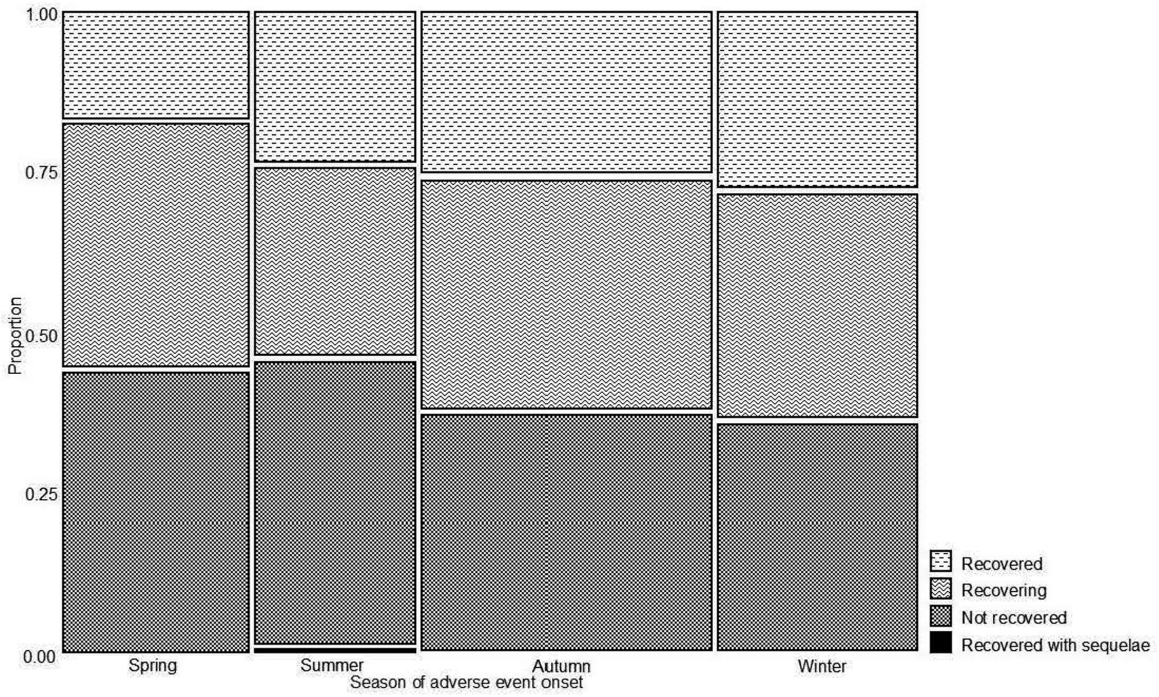

Fig. 4. Mosaic Plot of Outcomes of Bevacizumab-Related Hypertension

Under these conditions, even modest fluctuations in ambient temperature or autonomic activity could more readily translate into blood pressure elevation, potentially contributing to the increased relative reporting frequency observed during September and October. However, since marked diurnal temperature variations are not necessarily specific to autumn and these mechanistic interpretations could not be directly tested in the present study, they should be considered hypothetical.

In addition to meteorological factors, blood pressure is strongly affected by lifestyle-related factors. Reduced physical activity in early autumn,[22] increased salt intake,[23] and psychological stress associated with social events[24] may contribute to high blood pressure.[12] In oncology practice, clinic visits, treatment schedules, concomitant medications, and fluctuations in patients' general conditions may also interact with seasonal factors; therefore, seasonality is unlikely to be determined by

ambient temperature alone.

The discrepancy between the seasonal pattern observed in home blood pressure data (higher in winter and lower in summer)[17] and the BRHT peak observed in this study (September to October) may reflect differences in the underlying population (patients with cancer), exposure (anti-VEGF therapy), and outcome definitions (reportable events captured in an SRS). Accordingly, our results should not be interpreted as a reflection of seasonal blood pressure variation in the general population but rather as a characteristic monthly reporting pattern of hypertension-related events observed under bevacizumab exposure.

In the TTO analysis, the median TTO was 21.0 days (IQR, 7.0–45.0) and the 95% CI for the WSP β included 1, suggesting an approximately time-constant hazard. Moreover, no significant differences were observed in the distribution of TTO categories across seasons, indicating no seasonal skew in onset timing (early to very late). The Weber effect generally refers to reporting bias characterized by increased reporting shortly after marketing authorization, followed by a subsequent decline;[25] therefore, it should be conceptually distinguished from the seasonal comparison of TTO distributions performed in the present study to avoid misinterpretation.

No widely accepted standard exists for TTO onset timing. BRHT generally occurs most frequently within 1–2 months of treatment initiation; however, in this dataset, the 90th percentile of TTO was 177.0 days. Therefore, to include the majority of cases while minimizing the influence of extreme outliers (maximum, 1,075 days) on the seasonal analysis, a cutoff of 180 days was applied.

Here, we used the monthly relative frequency, defined as the number of BRHT reports divided by the total number of JADER adverse event reports in the same month. Although this approach can partially account for month-to-month variations in the overall volume of JADER reporting, it does not directly standardize the prescribing volume (exposure). A more rigorous assessment of exposure effects would ideally link SRS reports with external exposure data such as claim-based prescription volumes or sales data. Additionally, a crude adjustment based on bevacizumab prescription volume yielded results consistent with the pattern observed for the monthly relative frequency (Supplementary Table S2).

This study has some limitations common to SRS-based research. First, spontaneous reporting data are subject to under-reporting, stimulated reporting (e.g., media coverage or safety alerts), duplicate reporting, and confounding by concomitant medications and underlying diseases. Second, because the denominator (i.e., the number of exposed patients) is unknown, incidence rates cannot be estimated; thus, the results reflect relative reporting patterns rather than the true risk. Third, missing information on the first administration date and/or adverse event onset date restricted the population eligible for TTO analysis and may have introduced selection bias.

Because the JADER database lacks geographic information for individual adverse event cases, the monthly mean temperatures in Tokyo were presented as a representative indicator of seasonal trends in Japan. However, regional differences in temperature can be substantial, with northern and southern areas potentially experiencing markedly different temperatures even in the same month. Therefore, this study was not intended to demonstrate a direct causal relationship between temperature in a specific region and the occurrence of adverse events; rather, the temperature data provide general background on the seasonal variation observed in the reporting pattern.

Additionally, the monthly relative frequencies used in this study were not standardized by either the number of patients exposed to bevacizumab or the total number of bevacizumab-related adverse event reports. Consequently, these frequencies do not represent the true incidence of BRHT but reflect monthly reporting patterns. Given this lack of standardization, the findings should be interpreted as potential reporting trends rather than definitive risk estimates.

Taken together, these limitations mean that the present study cannot establish causality. However, it provides a pharmacovigilance signal suggesting that hypertension-related events reported after bevacizumab exposure may occur more frequently in early autumn (particularly September and October), which could be clinically informative.

Accordingly, during bevacizumab therapy, clinicians should consider not only the general tendency for blood pressure to rise in winter but also the potential for elevations to become more apparent in early autumn, when temperature variability and lifestyle-related factors may overlap. Strengthening patient education and monitoring, such as encouraging home blood pressure measurements and implementing timely antihypertensive interventions, may help support the safer continuation of bevacizumab treatment.

Conclusion Analysis of SRS data from the JADER database showed a higher tendency for BRHT reporting in autumn than in winter, particularly in September and October. These findings may help healthcare professionals enhance blood pressure monitoring and implement proactive preventive interventions in early autumn, facilitating the safe continuation of bevacizumab therapy.

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Ethical approval Ethical approval was not sought for this study because the study was a database-related observational study without directly involving any research subjects. All results were obtained from data openly available online from the PMDA website. All data from the JADER database were fully anonymized by the relevant regulatory authority before we accessed them.

Conflict of interest The authors declare no conflict of interest.

REFERENCES

1) Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. *Nat. Med.*, **9**, 669–676 (2003).
2) Ferrara N, Davis-Smyth T. The biology of vascular endothelial growth factor. *Endocr. Rev.*, **18**, 4–25 (1997).
3) Presta LG, Chen H, O'Connor SJ, Chisholm V, Meng YG, Krummen L, Winkler M, Ferrara N. Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. *Cancer Res.*, **57**, 4593–4599 (1997).
4) Willett CG, Boucher Y, di Tomaso E, Duda DG, Munn LL, Tong RT, Chung DC, Sahani DV, Kalva SP, Kozin SV, Mino M, Cohen KS, Scadden DT, Hartford AC, Fischman AJ, Clark JW, Ryan DP, Zhu AX,

Blaszkowsky LS, Chen HX, Shellito PC, Lauwers GY, Jain RK. Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer. *Nat. Med.*, **10**, 145–147 (2004).
5) U.S. FOOD & DRUG ADMINISTRATION. "Avastin® approved letter." <https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2004/125085ltr.pdf> cited 28 December, 2025.
6) Abu-Hejleh T, Mezhir JJ, Goodheart MJ, Halfdanarson TR. Incidence and management of gastrointestinal perforation from bevacizumab in advanced cancers. *Curr. Oncol. Rep.*, **14**, 277–284 (2012).
7) Hamnvik OP, Choueiri TK, Turchin A, McKay RR, Goyal L, Davis M, Kaymakcalan MD, Williams JS. Clinical risk factors for the development of hypertension in patients treated with inhibitors of the VEGF signaling pathway. *Cancer*, **121**, 311–319 (2015).
8) Dahlberg SE, Sandler AB, Brahmer JR, Schiller JH, Johnson DH. Clinical course of advanced non-small-cell lung cancer patients experiencing hypertension during treatment with bevacizumab in combination with carboplatin and paclitaxel on ECOG 4599. *J. Clin. Oncol.*, **28**, 949–954 (2010).
9) Marik PE, Varon J. Hypertensive crises: challenges and management. *Chest*, **131**, 1949–1962 (2007).
10) Mourad JJ, des Guetz G, Debbabi H, Levy BI. Blood pressure rise following angiogenesis inhibition by bevacizumab. A crucial role for microcirculation. *Ann. Oncol.*, **19**, 927–934 (2008).
11) Japan Heart Foundation. "Practical Knowledge about Blood Pressure" < https://www.jhf.or.jp/topics/2014/003745/> cited 28 December, 2025.
12) Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, Ramirez A, Schlaich M, Stergiou GS, Tomaszewski M, Wainford RD, Williams B, Schutte AE. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. *Hypertension*, **75**, 1334–1357 (2020).
13) Pharmaceuticals and Medical Devices Agency. "Adverse Drug Reaction Database" <https://www.info.pmda.go.jp/fukusayoudb/CsvDownload.jsp> cited 28 December, 2025.
14) Chugai Pharmaceutical Co. Ltd. "Avastin® [package insert]" <https://chugai-pharm.jp/view-pdf/?file=/content/dam/chugai/product/ava/div/pi/doc/ava_pi.pdf> cited 28 December, 2025.
15) Japan Meteorological Agency. "Monthly values since the start of observations" < https://www.data.jma.go.jp/stats/etrn/view/monthly_s3.php?%20prec_no=44&block_no=47662> cited 28 December, 2025.
16) Ministry of Health. Labour and Welfare. "10th NDB Open Data: G. Injections – Number of claims by month of medical service" < https://www.mhlw.go.jp/content/12400000/001493142.xlsx> cited 28 December, 2025.
17) Iwahori T, Miura K, Obayashi K, Ohkubo T, Nakajima H, Shiga T, Ueshima H. Seasonal variation in home blood pressure: findings from nationwide web-based monitoring in Japan. *BMJ Open*, **8**, e017351 (2018).
18) Japan Meteorological Agency. "Daily maximum and minimum temperature data" < https://www.data.jma.go.jp/risk/obsdl/index.php> cited 28 December, 2025.
19) Greaney JL, Kenney WL, Alexander LM. Sympathetic regulation during thermal stress in human aging and disease. *Auton. Neurosci.*, **196**, 81–90 (2016).
20) Pandey AK, Singhi EK, Arroyo JP, Ikizler TA, Gould ER, Brown J, Beckman JA, Harrison DG, Moslehi J. Mechanisms of VEGF (vascular endothelial growth factor) inhibitor-associated hypertension and vascular disease. *Hypertension*, **71**, e1–e8 (2018).
21) Versmissen J, Mirabito Colafella KM, Koolen SLW, Danser AHJ. Vascular cardio-oncology: vascular endothelial growth factor inhibitors and hypertension. *Cardiovasc. Res.*, **115**, 904–914 (2019).
22) Garriga A, Sempere-Rubio N, Molina-Prados MJ, Faubel R. Impact of seasonality on physical activity: A systematic review. *Int. J. Environ. Res. Public Health*, **19**, 2 (2021).
23) Shinozaki N, Murakami K, Masayasu S, Sasaki S. Ecological momentary assessment of meal context and food types contributing to salt intake at meals. *Int. J. Behav. Nutr. Phys. Act.*, **22**, 85 (2025).
24) Suzuki K, Endo A, Akutsu T, Hoshi H, Suekane A, Yamamoto R, Yamakawa K, Watanabe S, Hirakawa A, Otomo Y, Morishita K. Seasonal and cultural effects on calendar day variations in trauma incidence in Japan. *Sci. Rep.*, **15**, 44106 (2025).
25) McAdams MA, Governale LA, Swartz L, Hammad TA, Dal Pan GJ. Identifying patterns of adverse event reporting for four members of the angiotensin II receptor blockers class of drugs: revisiting the Weber effect. *Pharmacoepidemiol. Drug Saf.*, **17**, 882–889 (2008).