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Potential triggering factors associated with aneurysmal subarachnoid hemorrhage: A large single-center retrospective study

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Abstract

Controlling blood pressure levels is critical to preventing intracranial aneurysm rupture, and a summary review of induced rupture events allows better health education for patients. We retrospectively reviewed all medical records of consecutive patients with aneurysmal subarachnoid hemorrhage (aSAH) admitted to Beijing Tiantan Hospital from 2015 to 2020. We collected patients' demographic information, aneurysm morphology, blood pressure level on admission, time to onset, and events at the time of aneurysm rupture to analyze the factors precipitating aneurysmal rupture. A total of 764 patients were enrolled for analysis, including 461 (60.3%) female patients and 303 (39.7%) male patients. The mean age of onset in this cohort was 55, and 465 (60.9%) patients had hypertension history. Autumn (245/764 [32.1%]) was the most frequent season for aneurysm rupture, and 07:00–12:59 (277/764 [36.3%]) was the most frequent time frame for aneurysm rupture. The five most prevalent events when aneurysm rupture happened were: (1) daily behaviors that may induce hypertension (181/764 [23.7%]), especially defecation or micturition (116/181 [64.1%]); (2) sporting (162/764 [21.2%]), especially high-intensity sports (108/162 [66.7%]); (3) mood and mental factors (112/764 [14.7%]), especially arguing or quarreling (61/112 [54.5%]); (4) sudden postural changes (93/764 [12.2%]), especially getting up (69/93 [74.2%]); and (5) sleeping (72/764 [9.4%]). Patients should avoid behaviors that may cause fluctuations in blood pressure, including keeping warm during seasonal alternation, keeping their urine and defecation unobstructed, avoiding high intensity physical exercise, maintaining a happy mood, avoiding sudden postural changes, and should not bathe with too cold or too hot water.

KEYWORDS
aneurysm rupture, aneurysmal subarachnoid hemorrhage, event, hypertension

1 | INTRODUCTION

Aneurysmal subarachnoid hemorrhage (aSAH), which accounts for 5% of all strokes, is a life-threatening neurosurgical emergency with a high mortality rate of 22%–50%, and most survivors have a long-term disability or cognitive impairment.[1,2] The mechanism of aneurysm rupture is still unclear. It has been pointed out that aneurysm-related factors such as location, size, and configuration have been identified as the main risk factors contributing to its rupture.[3–5] In addition, hypertension and unhealthy lifestyles such as smoking and excessive alcohol consumption, and genetic-related factors may be potential causes of aneurysm formation or rupture.[6–10] Unruptured intracranial aneurysms (UIAs) are found in up to 3%–5% of the population.[11] Due to the current attention to health management and the development of diagnostic imaging techniques, the detection rate of UIAs has been gradually rising.[12] Although guidelines on unruptured aneurysms and predictive models for rupture risk exist, uncertainty in management practices and wide variation among patients have increased the difficulty for neurosurgeons in making treatment decisions.[4,13,14] Notably, many asymptomatic UIA patients are treated conservatively, what life advice can doctors give during conservative observation? Summarizing triggering factors from a population with ruptured aneurysms may be important for patient health education.

China has the largest population globally and is facing a serious population aging problem, and stroke has become the leading cause of premature death and disease burden.[15] Therefore, if primary stroke prevention strategies are not widely implemented in the population, the burden imposed by stroke may continue to increase. This study aimed to summarize the information about ruptured aneurysm from several perspectives, including patients' demographic information, medical history, aneurysm morphology, blood pressure level on admission, time to onset, and events at the time of aneurysm rupture, to provide reasonable life recommendations and health education for UIA patients.

2 | MATERIALS AND METHODS

2.1 | Study design

We retrospectively reviewed all medical records of consecutive patients with aSAH admitted to Beijing Tiantan Hospital from 2015 to 2020. All patients' data were derived from the Long-term Prognosis of Emergency Aneurysmal Subarachnoid Hemorrhage (LongTEAM) Registry study (Registration No. NCT 04785976). In the present study, all patients had angiographically documented aneurysms with subarachnoid hemorrhage (SAH), which were confirmed by either computed tomography (CT) or lumbar puncture. In this study, the inclusion criteria were (1) age ≥18 years; (2) emergency admission; (3) no previous aneurysm rupture. The study mainly excluded patients whose specific conditions at onset were not recorded in the medical records and still could not be provided through follow-up (shown in Figure 1).

This study has obtained approval from the Institutional Review Board of Beijing Tiantan Hospital (KY 2021-008-01). Informed consent for clinical analysis was obtained from all individual participants or their authorized representatives. All the analysis was performed according to the Declaration of Helsinki and the local ethics policies.

2.2 | Parameters

We collected patients' data at the time of initial aSAH, including patients' demographic information, medical history, aneurysm morphology, blood pressure level on admission, time to onset, and events at the time of aneurysm rupture. Patients were divided into four-season groups according to the time of admission: spring, summer, autumn, and winter. We divided events into nine categories: daily behaviors that may induce hypertension (DBIH), sporting, mood and mental factors, sudden postural changes, sleeping, sudden changes in body surface temperature, eating, staying up late, and alcohol consumption. Events that cannot be classified in the above categories were classified as other reasons. Supplemental Table 1 shows the detailed definition of the above information.

2.3 | Statistical analysis

Statistical analysis was performed using SPSS Statistics 26.0 (IBM Corp.) and GraphPad PRISM 8.3.0. (GraphPad Software Inc.). The circular statistical analysis was performed using R-package circular of R software (Version 4.1.2).

$P < 0.05$ was considered significant. Descriptive variables were summarized as the mean ± standard deviation (SD) or median with interquartile range (IQR) for continuous variables and frequencies (percentage) for categorical variables. Variables were tested by using chi-square test for categorical variables, Student's *t*-test, Mann–Whitney test, and ANOVA test for continuous variables, as appropriate. For data with circular distribution (diurnal and seasonal patterns), the Rayleigh test and Rao's spacing test were used to explore whether they lay in the von-Mises distribution. If there was a deviation from uniformity, the Watson–Wheeler test would be performed to test the significance of the medians.

3 | RESULTS

A total of 764 aSAH patients were enrolled in this study, including 461 (60.3%) female patients and 303 (39.7%) male patients. The mean age in this cohort was 55, and 465 (60.9%) patients had a hypertension history. The patient's systolic blood pressure (SBP) and diastolic blood pressure (DBP) on admission were 148.6 ± 22.8 mmHg and 87.9 ± 13.1 mmHg, respectively. The mean maximum diameter of the aneurysm was 6.7 mm. The three most prevalent locations of ruptured aneurysm were internal carotid artery (ICA) (256/764 [33.5%]), anterior communicating artery (AcoA) (250/764 [32.7%]), and middle cerebral artery (MCA) (137/764 [17.9%]). Compared with men, women were older (56.9±10.4 vs. 52.3±11.3, $p < 0.001$), a lower

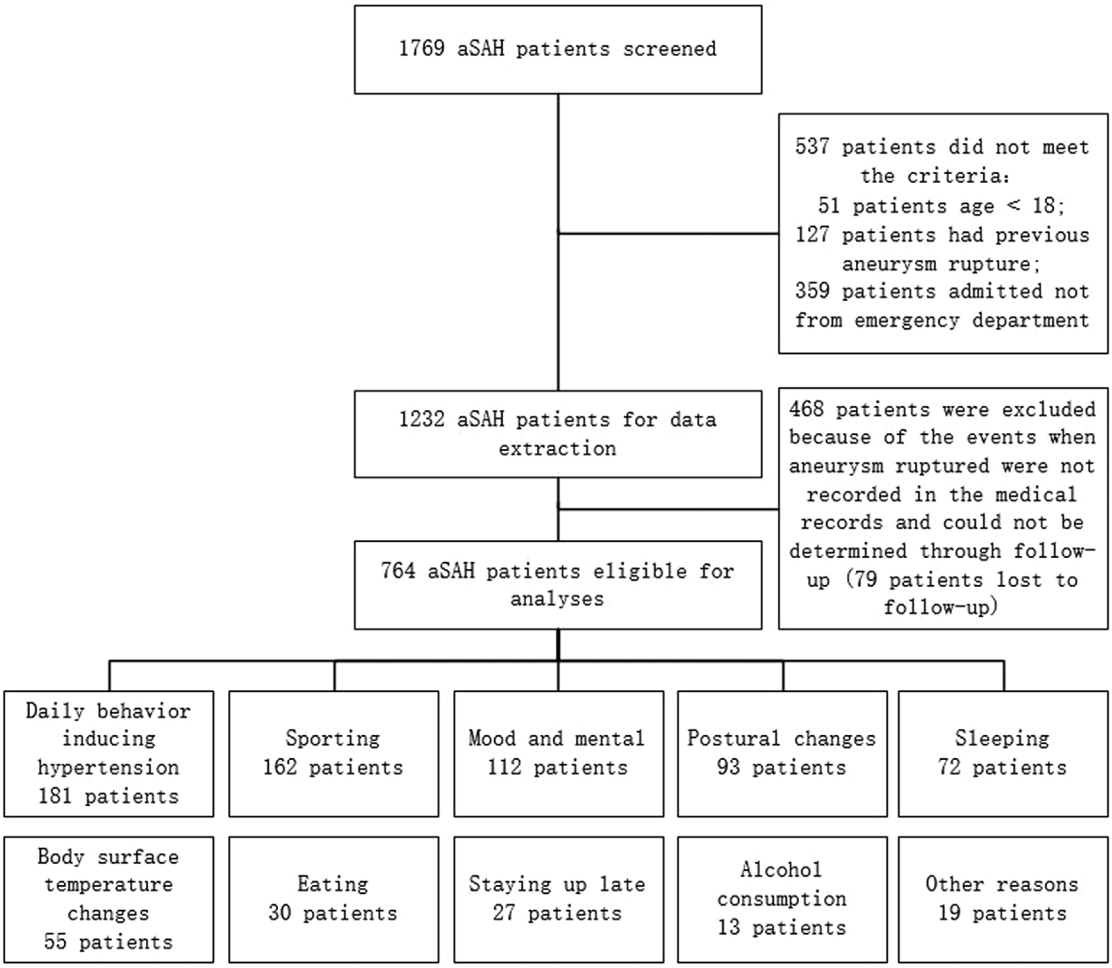

FIGURE 1 Flowchart of study patients

proportion of current smoking (40/461 [8.7%] vs. 197/303 [65.0%], $p < 0.001$), a lower proportion of current drinking (19/461 [4.1%] vs. 166/303 [54.8], $p < 0.001$), a smaller mean maximum aneurysm diameter (5.9±3.3 vs. 7.1±4.8, $p < 0.001$). There were also differences in the location of ruptured aneurysms between genders, with women having more ruptured aneurysms originating from the ICA (194/461 [42.1%]), while men more from the AcoA (135/303 [44.6%]) (shown in Table 1).

3.1 | Time of onset

Autumn (245/764 [32.1%]) was the most frequent season for aneurysm rupture, followed by summer (191/764 [25.0%]), spring (172/764 [22.5%]), and winter (156/764 [20.4%]). No significant difference in the median season of onset between men and women (Autumn vs. Autumn, $p = 0.617$). 07:00–12:59 (277/764 [36.3%]) was the most frequent time frame for aneurysm rupture, followed by 13:00–18:59 (199/764 [26.0%]), 19:00–00:59 (199/764 [26.0%]), and 01:00–06:59 (89/764 [11.6%]). The median time of onset showed a statistical difference between men and women (07:00–12:59 vs. 13:00–18:59, $p = 0.003$) (shown in Table 1).

3.2 | Association between blood pressure on admission and season of onset

No significant different between heart-rate and DBP in the four season groups. The comparison in season groups showed that SBP on admission was statistically different ($p = 0.044$), autumn showed a higher SBP on admission (153.0 ± 22.6 mmHg) (shown in Table 2).

3.3 | Events at the time of aneurysm rupture

The five most prevalent events when aneurysm rupture happened were (1) daily behaviors that may induce hypertension (DBIH) (181/764 [23.7%]), of which 102 (56.4%) patients had hypertension history; (2) sporting (162/764 [21.2%]), of which 108 (66.7%) patients had hypertension history; (3) mood and mental factors (112/764 [14.7%]), of which 61 (54.5%) patients had hypertension history; (4) sudden postural changes (93/764 [12.2%]), of which 64 (68.8%) patients had hypertension history; (5) sleeping (72/764 [9.4%]), of which 44 (61.1%) patients had hypertension history (shown in Figure 2).

TABLE 1 Demographics of the study patients

Characteristic	Total	Men	Women	*p*
No. of patients	764	303	461	
Age, y, mean ± SD	55.0 ± 11.0	52.3 ± 11.3	56.9 ± 10.4	<0.001
Hypertension, *n* (%)	465 (60.9)	183 (60.4)	282 (61.2)	0.830
HR, mean ± SD	77.1 ± 11.2	75.2 ± 11.1	78.2 ± 11.1	0.100
SBP, mean ± SD	148.6 ± 22.8	147.8 ± 21.6	149.1 ± 23.6	0.737
DBP, mean ± SD	87.9 ± 13.1	90.2 ± 13.8	86.4 ± 12.6	0.083
Hyperlipidemia, *n* (%)	91 (11.9)	34 (11.2)	57 (12.4)	0.835
Diabetes mellitus, *n* (%)	73 (9.6)	25 (8.3)	48 (10.4)	0.320
Current smoking, *n* (%)	237 (31.0)	197 (65.0)	40 (8.7)	<0.001
Current drinking, *n* (%)	185 (24.2)	166 (54.8)	19 (4.1)	<0.001
Maximum diameter of aneurysm[a], mean ± SD	6.7 ± 5.8	7.1 ± 4.8	5.9 ± 3.3	<0.001
Location of aneurysm				<0.001
ICA, *n* (%)	256 (33.5)	62 (20.5)	194 (42.1)	
AcoA, *n* (%)	250 (32.7)	135 (44.6)	115 (24.9)	
MCA, *n* (%)	137 (17.9)	61 (20.1)	76 (16.5)	
Other, *n* (%)	121 (15.8)	45 (14.9)	76 (16.5)	
Median time of onset	7:00–12:59	7:00–12:59	13:00–18:59	0.003
Median season of onset	Autumn	Autumn	Autumn	0.617

Abbreviations: SD, standard deviation; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; ICA, internal carotid artery; AcoA, anterior communicating artery; MCA, middle cerebral artery.
[a]Unit of measurement: mm.

TABLE 2 Season of onset and blood pressure

	Spring	Summer	Autumn	Winter	*p*
HR, mean ± SD	75.0 ± 8.4	79.7 ± 12.6	74.8 ± 10.1	79.6 ± 10.5	0.057
SBP[a], mean ± SD	147.1 ± 18.9	141.5 ± 18.5	153.0 ± 22.6	150.5 ± 30.2	0.044
DBP[a], mean ± SD	83.4 ± 7.7	86.1 ± 11.0	89.6 ± 12.6	87.5 ± 19.5	0.387

Abbreviations: HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.
[a]Unit of measurement: mmHg.

In the DBIH group, the three most prevalent events were defecation or micturition (116/181 [64.1%]), cooking (25/181 [13.8%]), and lifting or carrying heavy things (15/181 [8.3%]). In the sporting group, the three most prevalent events were high-intensity sports (108/162 [66.7%]), low-intensity sports (28/162 [17.3%]), and housework (23/162 [14.2%]). In the mood and mental factors group, the three most prevalent events were arguing or quarreling (61/112 [54.5%]), playing cards or video games (23/112 [20.5%]), and driving (10/112 [8.9%]). In the sudden postural changes group, the three most prevalent events were getting up (69/93 [74.2%]), squatting or sitting then suddenly being upright (8/93 [8.6%]), and bending then suddenly being upright (7/93 [7.5%]). In the sudden changes in body surface temperature group, the three most prevalent events were taking a shower (35/55 [63.6%]), washing face or brushing teeth (12/55 [21.8%]), and washing hair with cold water (2/55 [3.6%]) (shown in Figure 3).

3.4 | Association between events and seasons of onset

In spring, the three most prevalent events were defecation or micturition (25/172 [14.5%]), high-intensity sports (22/172 [12.8%]), and sleeping (18/172 [10.5%]). In summer, the three most prevalent events were high-intensity sports (23/191 [12.0%]), sleeping (23/191 [12.0%]), and arguing or quarreling (22/191 [11.5%]). In autumn, the three most prevalent events were defecation or micturition (44/245 [18.0%]), high-intensity sports (35/245 [14.3%]), and getting up (20/245 [8.2%]). In winter, the three most prevalent events were defecation or micturition (31/156 [19.9%]), getting up (21/156 [13.5%]), and high-intensity sports (18/156 [11.5%]) (shown in Figure 4).

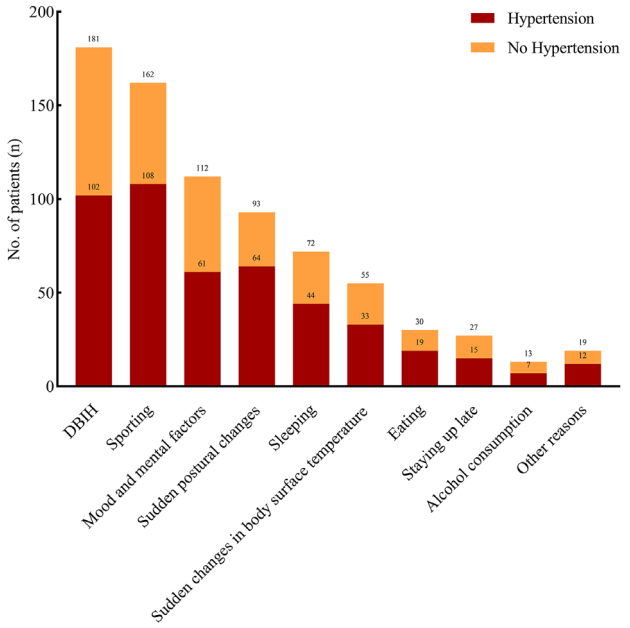

FIGURE 2 Potential triggering events associated with aneurysm rupture

3.5 | Association between events and time of onset

At 07:00–12:59, the three most prevalent events were defecation or micturition (66/277 [23.8%]), getting up (51/277 [18.4%]), and high-intensity sports (33/277 [11.9%]). At 13:00–18:59, the three most prevalent events were high-intensity sports (38/199 [19.1%]), arguing or quarreling (20/199 [10.1%]), and lifting or carrying heavy things (11/199 [5.5%]). At 19:00–00:59, the three most prevalent events were high-intensity sports (23/199 [11.6%]), arguing or quarreling (17/199 [8.5%]), and defecation or micturition (17/199 [8.5%]). At 01:00–06:59, the three most prevalent events were sleeping (37/89 [41.6%]), defecation or micturition (22/89 [24.7%]), and getting up (12/89 [13.5%]) (shown in Figure 5).

4 | DISCUSSION

This study comprehensively summarized the potential triggering factors of aneurysm rupture. Moreover, this is the first study to differentiate events at the time of or preceding the onset of aneurysm rupture, which is of great significance for health education for patients with unruptured aneurysms. One study in 2007 demonstrated that aneurysmal rupture occurred most frequently when patients were talking, chatting, watching television, or at home without any strenuous physical activity, and hypertension was the most common pre-existing medical problem.[16] Another study in 2020 indicated that aSAH most commonly occurred during nonstrenuous physical activity.[17] However, highlighting events by patients' actions may lead to more intuitive recommendations for patients. In addition, people are now paying more attention to the management of their health, and the rapid development of the internet has accelerated the dissemination of health management information. Do these factors change the characteristics of aSAH patients?

From various perspectives, our study reviewed and summarized morbidity characteristics in aSAH patients admitted to Beijing Tiantan Hospital between 2015 and 2020. Our study showed a higher aSAH incidence, advanced age, and smaller mean maximum diameter of the aneurysm in female patients, consistent with previous studies.[18–20] Autumn is the most frequent season for aneurysm rupture and no significant variations in men and women. Previous studies have also investigated the effect of season on the incidence of aSAH. One study indicated that aSAH often occurred with a peak in the spring and autumn.[21] Two studies showed that aSAH often occurred in the winter.[22,23] Another study demonstrated that a 1-day decrease in temperature and colder daily temperatures were associated with an increased risk of incident aSAH, acting independently of season.[24] There is controversy about the season of onset because temperature, humidity, and altitude are not the same at different times in different regions. Therefore, the season of onset can only represent the characteristics of some areas and cannot compare the seasonal features of onset in the other areas. The patients in our study were from northern China, and the temperature varied greatly with the season. The transition from summer to autumn may lead to a sudden decrease in temperature, inducing more incidence of aSAH. For example, according to the average daily minimum temperature in Beijing in 2021, the average daily minimum temperature in September and October were 17°C, and 8°C, had the maximum change in a year. The relationship between blood pressure and temperature has also been reported in one previous study in China, indicating that each 10°C lower ambient temperature was associated with 6.9/2.9 mmHg higher SBP/DBP.[25] Interestingly, we found a peak

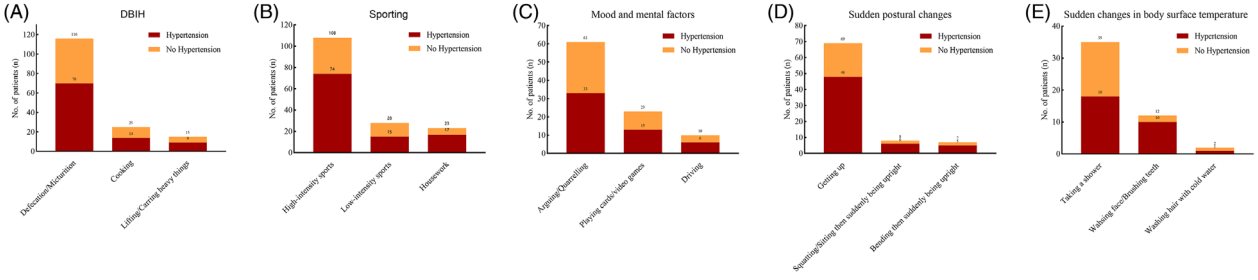

FIGURE 3 Specific events in the DBIH, sporting, mood and mental factors, sudden postural changes, and sudden changes in body temperature groups

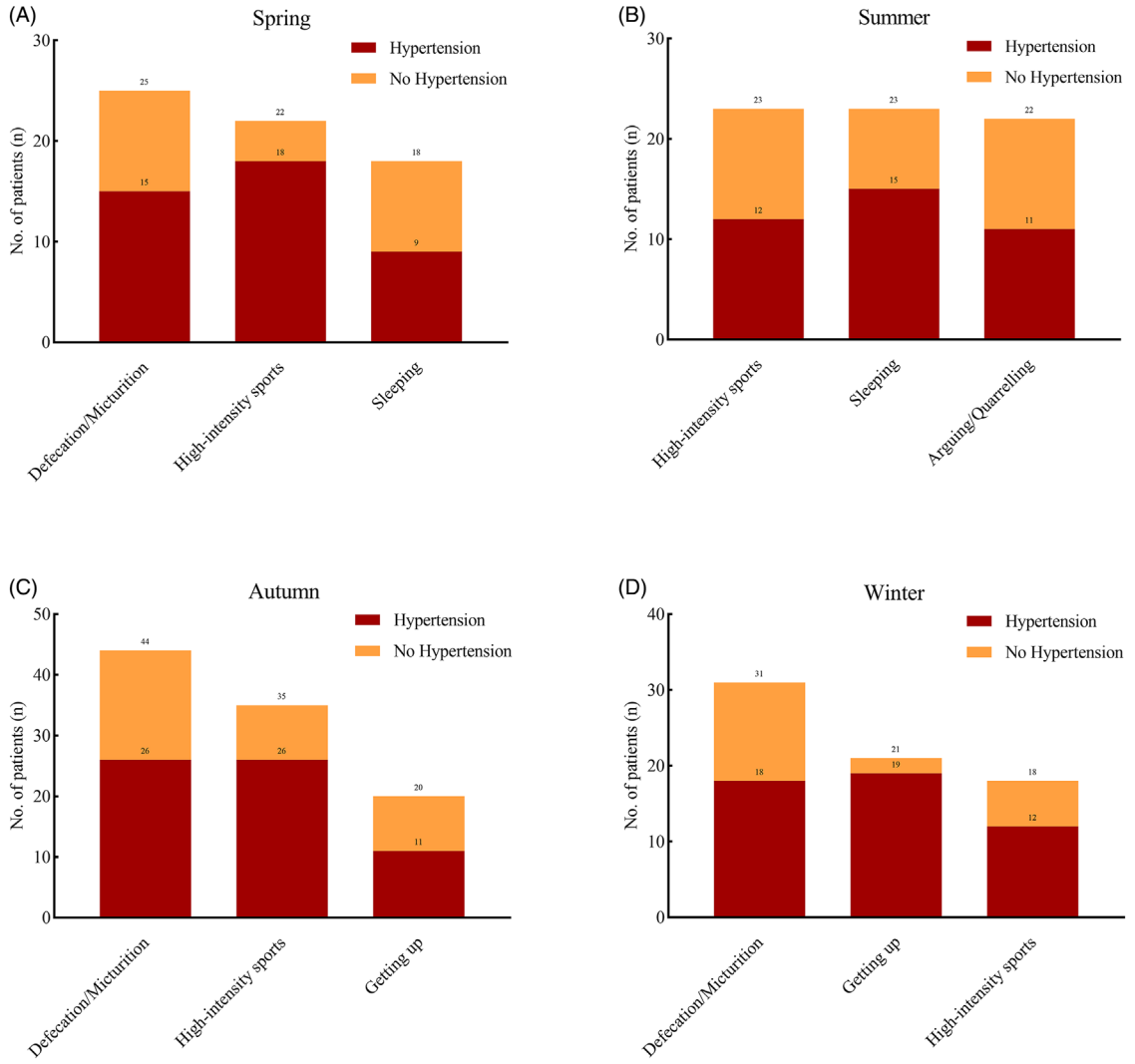

FIGURE 4 Specific events in the spring, summer, autumn, and winter groups

SBP/DBP on admission in autumn. We suppose the sudden change in temperature affects the regulatory mechanism of blood vessels, inducing high blood pressure, which may be a potential trigger for the high incidence of aSAH in autumn.

The most frequent time frame for aneurysm rupture is from 7:00 to 12:00, especially for male patients. Aneurysm ruptures often occur in the early morning and early evening, previous studies have reported the same phenomenon.[16,26–28] The potential reason for this phenomenon may be the fluctuation of systemic blood pressure. It is well known that the systemic blood pressure starts to increase at 05:00–06:00 and reaches the climax at 09:00, then declines gradually at 18:00 toward a minimum at 02:00–03:00.[29,30]

Classifying events which experienced by patients when an aneurysm ruptures by patients' actions facilitates better health education for UIA patients. Hypertension is the most common risk factor for SAH.[31,32] We noticed that among all aSAH patients, 465 (60.9%) patients had a history of hypertension, the median history of hypertension was 8 (IQR [4–14]) years. The proportion of patients with hypertension was more than half in all events. Defecation or micturition, classified in the DBIH group, is the most frequent event at the time of or preceding the onset, probably because such Valsalva maneuver may accompany sudden increased arterial blood pressure and intracranial pressure, and the risk of rupture increases once the aneurysm wall is unable to adapt to this sudden pressure change.[33] Other events, such as sports, particularly high-intensity sports, arguing, and getting up, can also be explained by sudden increases in arterial blood pressure and intracranial pressure. Notably, sudden body surface temperature changes may cause frequent switching of vessels in a state of contraction and relaxation. The impact of frequent fluctuations in blood pressure on the vessel wall may induce the rupture of aneurysms, which may be responsible for aneurysm rupture in many patients while bathing. There are also some more interesting phenomena, such as more patients with ruptured aneurysms due to quarrels in the summer, more patients with ruptured aneurysms due to getting up in the winter, and fewer patients with ruptured aneurysms due to exercise in the winter, which a single reason may not explain, such as considering that hot summer temperatures lead to people becoming irritable, cold winter temperatures lead to less outdoor activity, and getting up from a warm bed

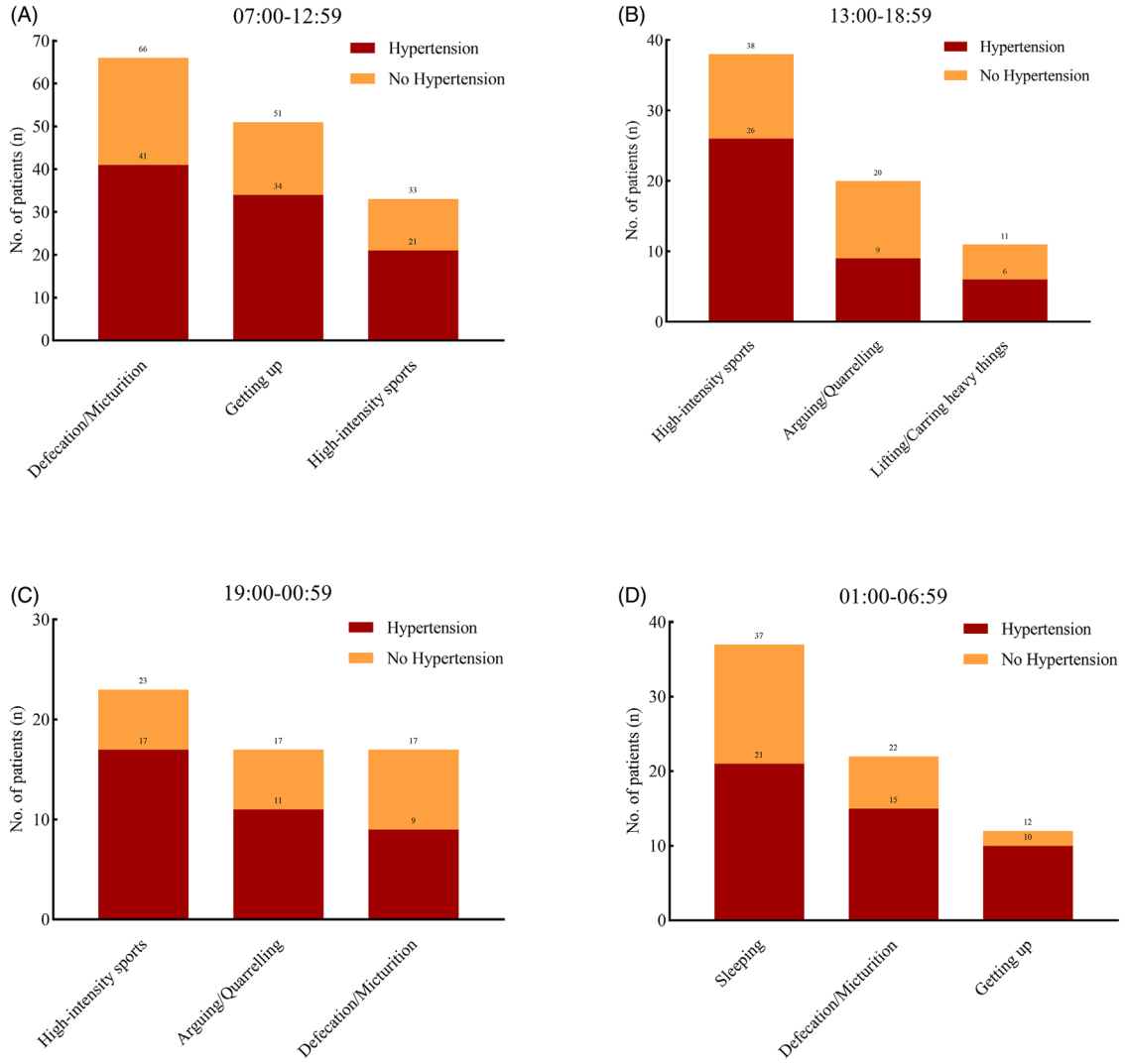

FIGURE 5 Specific events in the four-time periods

will cause sudden changes in body surface temperature. In addition, we observed among male patients, more than half had a history of current smoking or current drinking history. Cigarette smoking and alcohol drinking can stimulate arterial vasoconstriction to induce the formation of hypertension and are also involved in vascular inflammatory responses, which may be a potential cause of aneurysm rupture.[34–36] Thus, patients are encouraged to develop good living habits, further reducing the potential resulting risk of aneurysm rupture.

Health education for people with unruptured aneurysms is very meaningful. However, it has been found from our study that this health education is far from enough. On the one hand, doctors should convey accurate information to patients and attract the attention of patients. On the other hand, patients are also required to improve their ability to restrain themselves and avoid these dangerous events as much as possible. Some recommendations for the UIA patients can be summarized from our study, the most important of which is controlling hypertension and developing good living habits.

Attention should be paid to the treatment of hypertension, and each patient is encouraged to consult a professional doctor for treatment and monitoring of his/her blood pressure. Besides, we recommend that patients (1) Keep warm during seasonal alternation; (2) keep the intestinal tract and urethra unobstructed, prevent the occurrence of constipation; (3) moderate exercise, avoid high intensity physical exercise as far as possible; (4) maintain a happy mood; (5) avoid sudden postural changes (6) should not bathe with too cold or too hot water and pay attention to keep warm after the bath.

The present study has several limitations. First, our findings were not based on conclusions drawn from the follow-up of patients with UIA but rather a summary of the pathogenetic regularity of patients with aSAH. Therefore, some factors that truly contribute to aneurysm rupture might be overlooked. Second, the blood pressure level of hypertensive patients before rupture and treatment information was missing, and the blood pressure level before rupture of patients without a history of hypertension was unknown. These limitations of retrospective studies may potentially bias the results. Third, researchers subjectively define patients' events, and a single action cannot explain some events. Fourth, the patients in our study were from northern China. There may be regional attributes to some events,

so it is unclear whether the conclusions drawn from the study are generalizable.

5 | CONCLUSIONS

Our study summarized the rupture-related potential factors of patients with aneurysms in northern China. The study results showed that aneurysm ruptures frequently occurred in middle-aged people, and women were at high risk. Autumn was the most frequent season for aneurysm rupture, and 07:00–12:59 was the most frequent time frame. Controlling hypertension is always important, including keeping warm during seasonal alternation, keeping their urine and defecation unobstructed, avoiding high intensity physical exercise, maintaining a happy mood, avoiding sudden postural changes, and should not bathe with too cold or too hot water, and pay attention to keep warm after the bath.

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CONFLICT OF INTEREST

The authors have no personal, financial, or institutional interest in any of the materials or methods used in this study or the findings specified in this paper.

AUTHOR CONTRIBUTIONS

Conception and design: Xiaolin Chen, Yuanli Zhao. Acquisition of data: Runting Li. Analysis and interpretation of data: All authors. Drafting the article: Runting Li. Reviewed submitted version of manuscript: Xiaolin Chen, Yuanli Zhao. Statistical analysis: Runting Li. Administrative/technical/material support: Xiaolin Chen, Yuanli Zhao. Study supervision: Xiaolin Chen, Yuanli Zhao.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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