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Subtype shift, relapse rate and risk factors of frequent relapse in cluster headache: A multicenter, prospective, longitudinal observation

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Abstract

Aim: To prospectively determine subtype shift, relapse rate and risk factors of frequent relapse in cluster headache (CH).
Methods: This multicenter cohort study recruited patients with CH at baseline visits between September 2016 and January 2019 and planned to prospectively follow them up for up to five years. The subtype (episodic vs. chronic) was reassessed at baseline visit 2 (2–4 weeks) and serial follow-up visits if unremitted. We assessed the subtype shift of the index bout (i.e. the bout at the baseline visit) in all patients and relapse rates in those with episodic CH who were in an active bout at the time of recruitment. Relapse (i.e. bout recurrence) was prospectively collected via clinic visit or telephone interview at 3 ± 1 months, 1, 2, 3, 4 and 5 years (each ±6 months) after the baseline visit. Risk factors of frequent relapse were analyzed by comparing the incidence rate ratio (IRR) of relapse using Poisson regression analysis (model 1, static variables in all patients; model 2, time-related variables in patients with two or more lifetime bouts) accounted for different follow-up periods using an offset term.
Results: In 295 patients (58 with first-ever bouts) enrolled, CH subtypes were episodic, chronic and unclassified in 252, 11 and 32 at baseline. At baseline V2, CH subtype was re-determined to be chronic in seven (12.1%) of 58 patients with first-onset CH ("primary chronic CH") and nine (3.8%) of 237 with a history of episodic CH ("secondary chronic CH"). When excluding known chronic CHs at baseline, the incidence of chronic CH newly found during a prospective

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observation was 3.8% in patients with first-onset CH and 1.4% in those with a history of episodic CH. In 244 patients with episodic CH in an active bout at the time of recruitment, the relapse rate was 0.29 (95% confidence interval (CI) = 0.27–0.32; $p < 0.001$) per person-year after 5.9 ± 1.37 follow-up visits over a mean duration of 4.2 ± 1.32 years. Models 1 and 2 indicated that age (adjusted IRR = 0.97; 95% CI = 0.95–0.98), longer disease duration (adjusted IRR = 0.97; 95% CI = 0.95–1.00), first-ever bout (adjusted IRR = 0.35; 95% CI = 0.20–0.57), regular (one or more per week) alcohol consumption (adjusted IRR = 0.60; 95% CI = 0.45–0.81), and longer between-bout interval of previous bouts (adjusted IRR = 0.72; 95% CI = 0.60–0.87) were associated with less relapse. Seasonal rhythmicity (adjusted IRR = 1.66; 95% CI = 1.20–2.33) and increasing attack intensity across bouts (adjusted IRR = 1.66; 95% CI = 1.06–2.59) were associated with frequent relapse.

Conclusions: The present study provides data on the subtype shift and relapse rate of CH based on the prospective observation. Although our observation is only limited to a five-year time frame, our findings may suggest that disease activity increases after onset and then regress with age and time, and that seasonal rhythmicity and increasing attack intensity across bouts indicate higher propensity to relapse.

Keywords
cluster headache, long-term outcome, prognosis, relapse

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Introduction

Cluster headache (CH) is a primary headache disorder characterized by intense pain, predominantly in the trigeminal sensory distribution, accompanied by ipsilateral autonomic symptoms (1). The hallmark of CH is the clustering of attacks called cluster periods or "bouts," which recur after a certain pain-free period called remission period or "between-bout period". Bouts and between-bout periods serve as subtype-defining parameters: episodic (bout lasting less than one year and remission periods of three months or more) and chronic (bout lasting at least one year without remission or with remission lasting less than three months) CH (1-3).

Although CH is one of the most painful human conditions (4), the natural course and prognosis of CH have not been well studied. Prognosis of CH can be defined either (1) long-term remission; (2) development of chronic CH; and (3) bout relapse (i.e. recurrence of bout; conversion to active CH phase from remission). The first outcome, long-term remission, has been investigated in a few retrospective studies including ours (5-7), which requires a long-term observation (often five or more years, ideally >15 years) and is less feasible for a prospective setting. The second outcome, development of chronic CH, has been relatively more investigated in previous studies. Chronic CH can develop in a first-onset CH ("primary chronic CH") or result from subtype transition from episodic CH ("secondary chronic CH") (8). Research on the incidence rate of primary chronic CH in first-onset CH are scarce, with the retrospective study conducted in 1998 being the only one, which reported primary chronic CH in four (11.1%) out of 36 patients with first-onset CH (9-5,6,9). However, these studies were conducted before the current diagnostic criteria have been established and limited by retrospective design and unstructured follow-up durations. A recent study reported transition from episodic to chronic CH in 14.4% of participant by patient recall in a cross-sectional design (10-21), there has been a lack of prospective research on bout relapse and relapse rates. Consequently, the risk factors of frequent relapse remain unexplored yet.

In the present study, we aimed to investigate the prognosis of CH with a special interest on the incidence rate of primary chronic CH and subtype shifts and relapse rates of episodic CH in a multicenter prospective setting. We followed up the prognosis of ongoing bout to prospectively determine subtype shift. Then we conducted five-year follow-up to provide the relapse rate of bouts in patients with episodic CH and potential risk factors associated with the frequent relapse.

Methods

Study design

This study was structured as a longitudinal investigation within the framework of the Korean Cluster Headache Registry (KCHR) study. The KCHR is a prospective, longitudinal, multicenter observational study that consecutively enrolled patients with CH from 16 hospitals in Korea. Patients diagnosed with CH between September 2016 and January 2019 were included in this study. Participants were eligible for inclusion if they met the following criteria: (1) patients who fulfilled the diagnostic criteria for CH according to the most recent version of the International Classification of Headache Disorders (ICHD) established by the International Headache Society; (2) adults aged 19 years or older; and (3) individuals who voluntarily agreed to participate in the study and provided written informed consent after fully understanding its purpose

and procedures. Exclusion criteria were as follows: (1) patients who had already provided clinical information for the same study at another institution (to prevent duplicate enrollment of patients visiting multiple hospitals); (2) individuals of non-Korean nationality, as the questionnaires were administered in Korean; and (3) individuals with physical or mental conditions that precluded completion of the study questionnaires. CH diagnosis was made by KCHR investigators, who were neurologists specializing in headache disorders, using the latest criteria of the ICHD at the time of enrollment, specifically ICHD, 3rd edition (ICHD-3) beta or ICHD-3. Chronic CH was diagnosed in accordance with the criteria outlined in the ICHD-3, and episodic CH was characterized by cluster bouts lasting less than one year with a clear remission period of at least three months. Further details regarding the KCHR study have been documented in our previous studies (22-24).

Standard protocol approvals, registrations and patient consent

The study protocol was approved by the institutional review board of each participating hospital, and written informed consent was obtained from all patients prior to their recruitment.

Baseline evaluation

The study design is illustrated in Figure 1. We defined the "index bout" as the active cluster headache period ongoing at the time of enrollment, regardless of whether it was the patient's first or a recurrent bout. At the baseline visit, comprehensive data were gathered on various aspects, including patient demographics and characteristics (age, sex and body mass index), CH characteristics (age at onset, total number of lifetime bouts and disease duration), characteristics of the index bout (first vs recurrent bouts, onset date, episodic vs chronic CH, circadian rhythmicity and seasonal rhythmicity), attributes of attacks (headache side, location, frequency, duration, intensity and associated symptoms) and comorbidities (migraine, anxiety and depression). Anxiety and depression were defined using the Generalized Anxiety Disorder-7 score $\geq$6 and the Patient Health Questionnaire-9 score $\geq$8, respectively (25,26). For patients who had experienced two or more lifetime bouts (excluding first-onset CH), additional data were collected, including average bout duration, average duration of between-bout periods, patterns of relapse (regular vs irregular; i.e. with a fixed interval vs varying interval), history of side shift, temporal changes in the bout duration (no change, increasing, inconsistent or decreasing), temporal changes in the duration of between-bout periods (no change, increasing, inconsistent or decreasing), temporal changes in ipsilateral autonomic symptoms such as conjunctival injection, lacrimation, nasal congestion and rhinorrhea (no change, inconsistent, becoming more prominent or becoming less prominent), temporal changes in circadian rhythmicity, such as a propensity toward attack recurrence in a certain time of the day (no change, inconsistent, becoming more prominent or becoming less prominent) and temporal changes in seasonal rhythmicity, such as a propensity toward bout recurrence in a certain season of the year (no change, inconsistent, becoming more prominent or becoming less prominent).

At the second visit (between 2 and 4 weeks after the first visit), patients were reevaluated on items that required clarification or longer observation from the baseline visit (e.g. circadian rhythmicity). The subtype (episodic vs. chronic) was determined at visit 2. In cases of primary chronic CH (i.e. the chronic CH without a previous history of episodic CH) that lasted more than one year, it was considered as

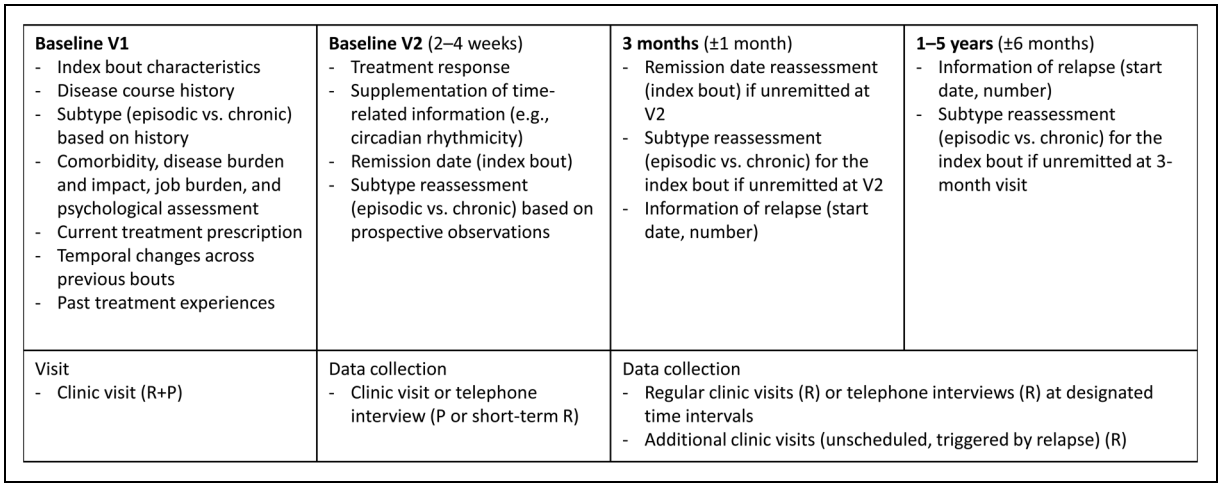


Figure 1. Study design of KCHR. R or P indicates the mode of data collection. R = retrospective; P = prospective.

first onset CH, and the diagnosis of chronic CH was made at the baseline visit and reassured at visit 2. In addition, the treatment response of the index bout was assessed at the second visit, which is further detailed in our previous study (23).

Follow-up scheme

The follow-up scheme is illustrated in Figure 1. We followed up patients at 3 ± 1 months, 1, 2, 3, 4 and 5 years (each ± 6 months) after the baseline visit. Data on the number and timing of relapses were collected through in-person assessments or telephone interviews. Although this study was conducted prospectively, the nature of data collection was either prospective when patients presented to the clinic promptly after a relapse (unscheduled visit), or retrospective, based on short-term recall, when information was obtained during scheduled follow-up visits or telephone interviews. In-person assessments were conducted by investigators during patients' regular clinic visits or unscheduled visits triggered by a new bout. In addition, follow-up completeness was screened at designated intervals, and telephone interviews were conducted by investigators or trained clinical research nurses for patients who missed scheduled visits or visited outside the follow-up scheme. Throughout the follow-up scheme, the remission date of the index bout was prospectively captured, and the subtype (episodic vs. chronic) of the index bout was re-evaluated based on the observed bout duration using the aforementioned criteria. Remission date was defined as the day of the last CH attack of the index bout, regardless of whether it was spontaneous or treatment-induced. We primarily used the ICHD-3 criteria to define an active bout, which requires a cluster headache attack frequency of at least 0.5 per day. However, as patients approach remission, there can be a natural tendency for attack frequency and intensity to decrease. To account for these transitional phases, we relied on the clinical judgment of investigators to determine the end of the bout, based on a comprehensive assessment of the patient's previous bout patterns, average remission duration, recurrence history and treatment response. Relapse, defined as a new active bout (i.e. a new series of CH attack with increasing attack intensity and frequency) that recurred after complete remission of the previous bout, were also assessed at every follow-up. When multiple follow-ups occurred within the same period, the one closest to each annual milestone after the baseline was retained for analysis.

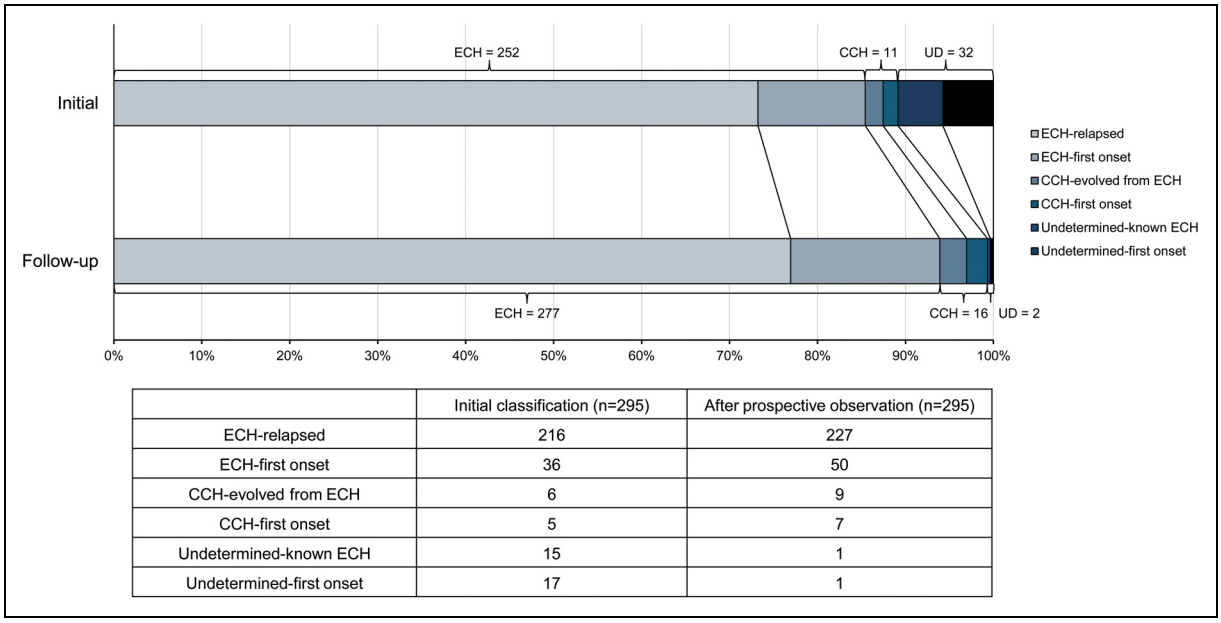
Statistical analysis

Data are presented as the mean $\pm$ SD or as numbers with percentages. The sample size was not calculated *a priori* because our primary objective was to observe the relapse rate by consecutively enrolling all eligible patients during the recruitment period. Post-hoc power calculations were performed to ensure that the observed relapse rate differed significantly from the relapse rates reported in the literature. Baseline data were categorized into variables common to all patients and time-related variables specific to patients with two or more lifetime bouts, excluding those with first-onset CH. For prospective data on bout recurrence, we calculated the relapse rate in patients with episodic CH whose index bouts were active at baseline. All the participants were included until their last visit. The incidence rate of relapse (i.e. relapse rate) and 95% confidence interval (CI) were determined by dividing the sum of all observed relapses by person-years. The crude incidence rate ratio (IRR) of relapse was estimated and compared using the univariable Poisson regression analysis using an offset term accounting for different follow-up periods. To evaluate the independent effect of each variable on the risk of frequent relapse, two multivariable Poisson regression models were used to estimate the IRR of relapse based on (1) the static characteristics of the disease in all patients with CH and (2) time-related characteristics and temporal changes of bouts in patients with two or more lifetime bouts. Data analysis was conducted using the R, version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria). $p < 0.05$ (two-sided) was considered statistically significant.

Results

Patient characteristics and subtype shift of the index bout

In total, 295 patients were enrolled at baseline in the KCHR. In total, 262 (88.8%) patients were enrolled during active bouts. The index bout was the first-ever bout in 58 (19.7%) patients. Details of classification shifts are shown in Figure 2. At the time of recruitment, 252 (85.4%) and 11 (3.7%) had episodic and chronic CH, respectively. In the remaining 32 (10.8%) patients, CH subtype was undetermined. After a prospective observation of the index bout, the diagnosis was finally made as episodic CH in 277 (93.9%) patients and chronic CH in 16 (5.4%) patients; two (0.7%) remained unclassified due to insufficient follow-up duration. Among 58 patients with first-ever bout, seven (12.1%) were determined to have chronic CH. After excluding five patients with a long-standing history of chronic CH already at baseline to avoid overestimation of the chronification rate and preserve the natural course of newly-onset CH, the rate of primary chronic CH was 3.8% (2/53) during a prospective observation of the first bout. Among those with known episodic CH, three (1.4%) newly developed secondary chronic CH during a prospective observation of the index bout. Patient demographics and characteristics of the index bouts are presented according to the final diagnosis in Table 1.



	Initial classification (n=295)	After prospective observation (n=295)
ECH-relapsed	216	227
ECH-first onset	36	50
CCH-evolved from ECH	6	9
CCH-first onset	5	7
Undetermined-known ECH	15	1
Undetermined-first onset	17	1

Figure 2. Diagnostic shift of the index bout. At the baseline visit, 252 (216 with clear history of recurrent bouts and 36 with first-ever bout) patients were classified into episodic CH per our definition and 11 (six with previous history of ECH and five with first-ever bout) had CCH. Thirty-two (15 with previous history of ECH and 17 with first-over bout) were unclassified at baseline visit. CH subtype (episodic vs. chronic) was reassessed over follow-up visits if unremitted at the previous visit. After prospective observation of the index bout, ECH and CCH were diagnosed in 277 and 16 patients, respectively, and two remained unclassified. Among 58 patients with first-ever bout, seven (12.1%) were finally classified into CCH. When excluding five patients with a long-standing history of chronic CH already at baseline, two (3.8%) developed chronic CH during a prospective observation of the first bout. Among those with known episodic CH, three (1.4%) newly developed chronic CH during a prospective observation. CCH = chronic cluster headache; ECH = episodic cluster headache.

Characteristics and temporal changes of lifetime bouts

Table 2 presents the characteristics and temporal changes in the lifetime bouts of 237 patients (comprising 227 with episodic CH, nine with secondary chronic CH and one unclassified) who had experienced two or more bouts at baseline. Seasonal rhythmicity was reported by approximately half (49.4%) of patients. Among the 237 patients, 195 (82.6%) responded to the survey regarding temporal changes in lifetime bouts. Notable changes such as increases, decreases and variations were reported from bout to bout in 37.5%, 40.0%, 47.3%, 45.6%, 50.0%, 49.0%, 21.3% and 21.1% for the attack intensity and frequency, bout duration and interval, seasonal and circadian rhythmicity, autonomic symptoms, and attack side, respectively. Detailed responses are provided in Table 2.

Relapse rate of episodic CH

To calculate the relapse rate of episodic CH, we focused on 244 patients whose index bouts were finally classified as episodic CH and who were in an active bout at the time of recruitment (Figure 3). The average frequency of follow-ups was 5.9 ± 1.37 (range = 1–7) times per patient, over a mean period of 4.2 ± 1.32 years. One hundred eight (44.2%) completed five-year follow-up due to loss to follow-up and voluntary withdrawal. The first relapse occurred, on average, at 618.2 ± 435.48 days (approximately 20.6 ± 14.52 months) after the remission of the index bout, ranging from 16 to 1729 days, affecting 142 (58.1%) patients. The calculated relapse rate was 0.29 (95% CI = 0.27–0.32) per person-year. Notably, patients with recurrent CH (i.e. two or more lifetime bouts) showed a higher relapse rate of 0.33 (95% CI = 0.30–0.37) per person-year than those with first-onset CH, who had a relapse rate of 0.11 per person-year (95% CI = 0.07–0.15). These rates correspond to annual relapse risks of 29% overall, 33% in patients with recurrent CH, and 11% in those with first-onset CH. The between-bout interval calculated per patient was 2.6 ± 1.56 (range = 0.16–6.08) years. Figure 4 illustrates the timeline of relapses observed across the entire cohort.

Risk factors of frequent relapse

Table 3 shows the IRR of relapse according to the characteristics of the index bouts in all patients. The multivariable model revealed that advanced age (adjusted IRR = 0.97; 95% CI = 0.95–0.98; $p < 0.001$), longer disease duration

Table 1. Patient demographics and characteristics of the baseline bout.

	All CH (n = 295)*	Episodic CH (n = 277)	Chronic CH (n = 16)
Age (years)	37.6 ± 10.6	37.6 ± 10.5	39.4 ± 11.1
Male sex	248 (84.1%)	232 (83.8%)	14 (87.5%)
Body mass index	23.9 ± 3.1	23.8 ± 3.1	25.3 ± 3.2
Onset age	29.0 ± 11.6	28.7 ± 11.6	34.2 ± 10.2
Total lifetime bouts (n)	9.0 ± 13.2	8.7 ± 12.5	11.6 ± 19.0
Disease duration (years)	8.6 ± 7.9	8.8 ± 7.9	5.2 ± 7.5
Lifetime bouts			
One (first-onset)	58 (19.7%)	50 (18.1%)	7 (43.8%)
Two or more (recurred)	237 (80.3%)	227 (81.9%)	9 (56.2%)
Attack side (%)			
Left	121 (41.0%)	114 (41.2%)	5 (31.2%)
Right	163 (55.3%)	152 (54.9%)	11 (68.8%)
Alternating or bilateral	11 (3.7%)	11 (4.0%)	0 (0.0%)
Attack frequency per day	2.0 ± 1.7	2.0 ± 1.7	2.5 ± 2.2
Attack duration (min)**	104.1 ± 104.3	101.4 ± 102.1	146.2 ± 134.6
Attack intensity (NRS)	9.0 ± 1.2	9.0 ± 1.2	8.8 ± 1.2
Circadian rhythmicity	143 (48.8%)	135 (49.1%)	8 (50.0%)
Seasonal rhythmicity	121 (45.3%)	118 (47.0%)	3 (20.0%)
Smoking			
Never	111 (37.6%)	106 (38.3%)	5 (31.2%)
Ex	53 (18.0%)	48 (17.3%)	4 (25.0%)
Current	131 (44.4%)	123 (44.4%)	7 (43.8%)
Regular alcohol drinking	147 (52.7%)	140 (53.4%)	6 (37.5%)
Comorbid migraine	45 (15.3%)	40 (14.4%)	5 (31.2%)
Anxiety	146 (60.8%)	135 (60.8%)	9 (56.2%)
Depression	102 (42.3%)	90 (40.4%)	11 (68.8%)

Data are presented as the mean ± SD or number (percentage).
CH = cluster headache; NRS = numeric rating scale.
*Two patients remained unclassified due to insufficient follow-up duration.
**Untreated attack duration.

(adjusted IRR = 0.97; 95% CI = 0.95–1.00; $p = 0.022$), having the first bout (compared with a recurred bout) (adjusted IRR = 0.35; 95% CI = 0.20–0.57; $p < 0.001$) and regular alcohol consumption (at least one drink per week) (adjusted IRR = 0.60; 95% CI = 0.45–0.81; $p < 0.001$) were protective factors against relapse. Younger age at onset was associated with a higher relapse rate (univariable IRR = 0.98; 95% CI = 0.97–0.99; $p < 0.001$) in the univariable analysis. However, it was excluded in the multivariable model owing to a high correlation with other variables (e.g. age).

The IRRs for factors associated with the characteristics and temporal changes in lifetime bouts are presented in Table 4. Seasonal rhythmicity (adjusted IRR = 1.66; 95% CI = 1.20–2.33; $p = 0.003$) and a shorter interval between previous bouts (adjusted IRR = 0.72; 95% CI = 0.60–0.87; $p < 0.001$), based on patients' history, were identified as risk factors for frequent relapse during prospective follow-up. Patients whose attack intensity had increased from previous bouts to the index bout experienced bout relapses more frequently (adjusted IRR = 1.66; 95% CI = 1.06–2.59; $p = 0.027$). No other temporal changes were found to be associated with the relapse rates.

Discussion

To our knowledge, this is the first report on the relapse rates and risk factors of frequent relapse in prospectively recorded bouts. The study findings were as follows: chronic CH was diagnosed after a prospective observation of the index bout of first-onset CH (primary chronic CH: 3.8%) and a history of episodic CH (secondary chronic CH: 1.4%); the average relapse rate of episodic CH was 0.29 (95% CI = 0.27–0.32) per person-year; disease activity of CH declined with time, as advanced age and longer disease duration independently correlated with a lower relapse rate; first-onset CH and regular alcohol consumption are associated with less relapse, whereas seasonal rhythmicity and increasing attack intensities at baseline are associated with frequent relapse.

In the present study, chronic CH comprised 3.7% (11/295) of the total cohort at baseline, which shows a typically low prevalence of chronic CH in Asian CH compared to that in European or North American cohorts (27). After the longitudinal observation of the index bout, the proportion of chronic CH increased to 5.4% in the overall cohort, including 12.1% for first-onset CH (primary

Table 2. Characteristics and temporal changes of lifetime bouts in patients with two or more lifetime bouts.

	Total (n = 237)	ECH (n = 227)	Secondary CCH (n = 9)
Total lifetime bouts (n)	10.9 ± 14.0	10.4 ± 13.2	19.8 ± 22.5
Disease duration (years)	10.6 ± 7.5	10.7 ± 7.4	7.8 ± 9.2
Average duration of bouts (weeks)	5.9 ± 6.2	5.7 ± 5.5	11.6 ± 15.2
Average interval of bouts (years)	1.6 ± 2.4	1.7 ± 2.5	1.0 ± 1.2
Seasonal rhythmicity	115 (49.4%)	113 (50.7%)	2 (22.2%)
Temporal changes in attack intensity			
No change	122 (62.6%)	120 (64.2%)	2 (28.6%)
Increasing	43 (22.1%)	41 (21.9%)	1 (14.3%)
Decreasing	30 (15.4%)	26 (13.9%)	4 (57.1%)
Inconsistent	0 (0%)	0 (0%)	0 (0%)
Temporal changes in attack frequency			
No change	117 (60.0%)	113 (60.4%)	4 (57.1%)
Increasing	55 (28.2%)	53 (28.3%)	1 (14.3%)
Decreasing	23 (11.8%)	21 (11.2%)	2 (28.6%)
Inconsistent	0 (0%)	0 (0%)	0 (0%)
Temporal changes in bout duration			
No change	102 (52.6%)	99 (53.5%)	3 (37.5%)
Increasing	54 (27.8%)	51 (27.6%)	2 (25.0%)
Decreasing	22 (11.3%)	20 (10.8%)	2 (25.0%)
Inconsistent	16 (8.2%)	15 (8.1%)	1 (12.5%)
Temporal changes in bout interval			
No change	104 (54.5%)	100 (54.6%)	4 (57.1%)
Increasing	28 (14.7%)	27 (14.8%)	1 (14.3%)
Decreasing	31 (16.2%)	29 (15.8%)	1 (14.3%)
Inconsistent	28 (14.7%)	27 (14.8%)	1 (14.3%)
Temporal changes in seasonal rhythmicity			
No change	97 (50.0%)	95 (51.1%)	2 (28.6%)
Increasing	19 (9.8%)	18 (9.7%)	1 (14.3%)
Decreasing	39 (20.1%)	36 (19.4%)	2 (28.6%)
Inconsistent	39 (20.1%)	37 (19.9%)	2 (28.6%)
Temporal changes in circadian rhythmicity			
No change	99 (51.0%)	96 (51.6%)	3 (42.9%)
Increasing	17 (8.8%)	17 (9.1%)	0 (0.0%)
Decreasing	31 (16.0%)	28 (15.1%)	2 (28.6%)
Inconsistent	47 (24.2%)	45 (24.2%)	2 (28.6%)
Temporal changes in autonomic symptoms			
No change	113 (58.9%)	110 (59.8%)	3 (42.9%)
Increasing	24 (12.5%)	23 (12.5%)	1 (14.3%)
Decreasing	5 (2.6%)	5 (2.7%)	0 (0.0%)
Inconsistent	12 (6.2%)	12 (6.5%)	0 (0.0%)
Never experienced	38 (19.8%)	34 (18.5%)	3 (42.9%)
Side shift of attacks	41 (21.1%)	37 (20.0%)	3 (37.5%)

Data are presented as the mean ± SD or number (percentage).

*Patients who experienced two or more lifetime bouts at baseline were eligible for this survey.

ECH = episodic cluster headache; CCH = chronic cluster headache.

chronic CH) and 3.8% for previously episodic CH (secondary chronic CH). When excluding known chronic CHs at baseline, the incidence of primary and secondary chronic CH newly found during a prospective observation was 3.8% and 1.4%, respectively. Consistent with our findings, a study conducted by Sjöstrand et al.(9) reported that the first bout became chronic in four (6.7%) of 60 patients, and the secondary chronification occurred in one (3.1%) of 32 patients with episodic CH during follow-up. Together with our findings, these data collectively suggest a higher rate of chronic CH in first-onset CH (termed primary chronic CH) than in episodic CH (termed secondary chronic CH). As our study was not designed to compare the incidence rate between primary and secondary chronic CHs, we cannot draw a firm conclusion at this stage. Future studies should explore these

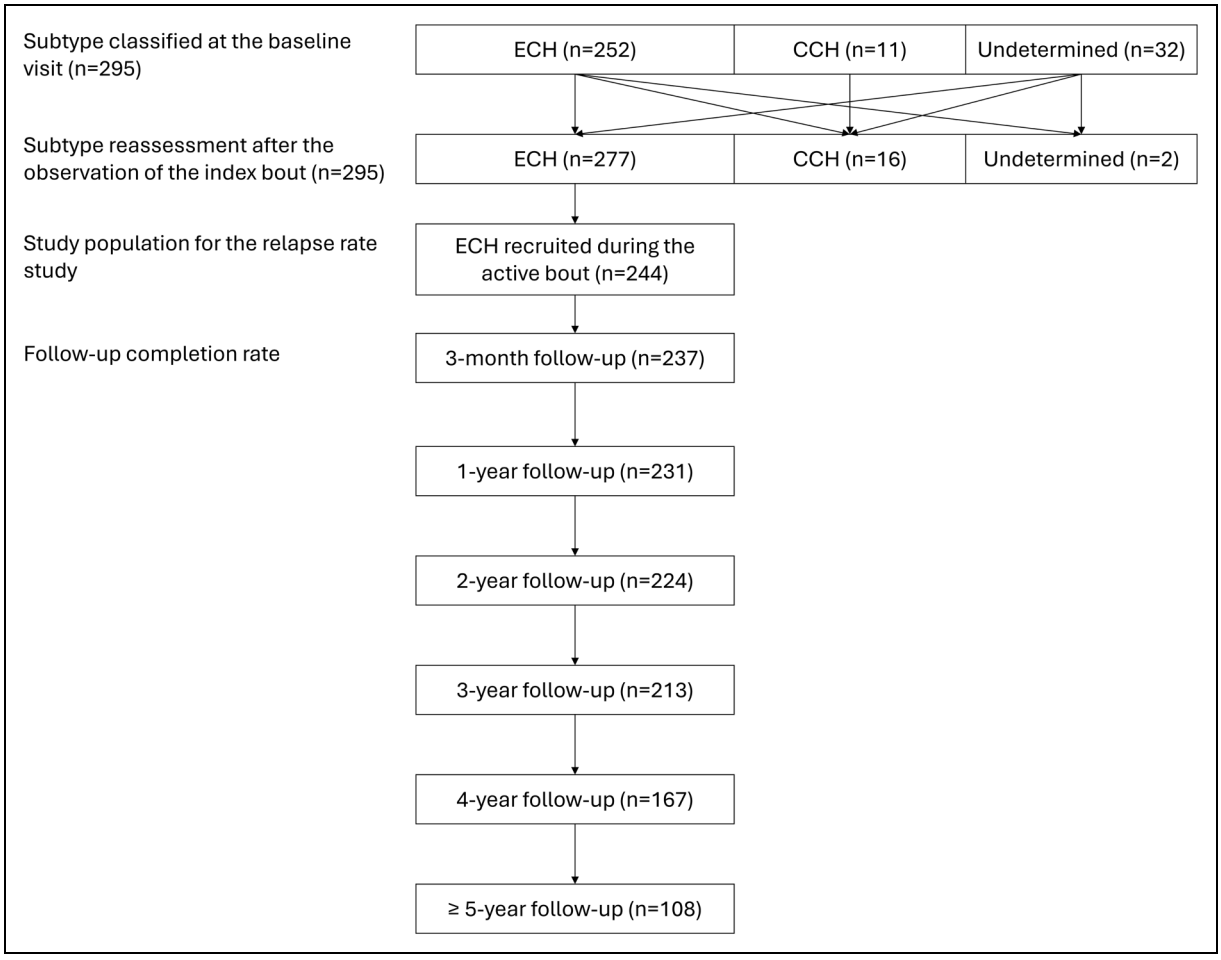


Figure 3. Flowchart. Among 295 patients enrolled, 277 patients were finally classified into ECH after serial reassessment over prospective visits. Relapse rate was determined in 244 patients with ECH who were recruited during the active bout. Follow-up completion rates were 97.1% at three months, 94.7% at one year, 91.8% at two years, 87.3% at three years and 68.4% at four years after enrollment, and 44.3% completed at least five years of follow-up. CCH = chronic cluster headache; ECH = episodic cluster headache.

distinctions, focusing on genetic and clinical risk factors, as existing genetic investigations of chronic CH have not considered subtype classification (primary vs. secondary) (28,28,29,30).

The present study was the first to provide prospective data on the relapse rate of episodic CH. Unlike previous reports, which relied on retrospective assessments based on patients' self-reports, this study was the first that used a prospective design to enhance the accuracy of relapse rate estimation. The natural course of CH is known to vary between individuals and even within patients, necessitating longer follow-up durations for prospective studies. Consequently, investigations into the long-term disease course of CH have predominantly relied on retrospective cohorts (5-7,9,31,9,31,32), allowing for the longest follow-up and identification of long-term remission. However, this study design has limitations, including potential recall bias and the inability to assess annual relapse rates and risk factors of early or frequent recurrence.

To ensure the accuracy of relapse rate estimation, we meticulously classified index bouts. Chronic CH, while imposing a greater burden than episodic CH, can lead to underestimation of the relapse rate if included, as it can present a single prolonged bout persisting over years, rather than multiple discrete recurrences. We obtained a relapse rate of 0.29 per person-year for overall CH, which corresponds to an approximate 29% annual relapse risk for an individual patient, meaning that about one in three patients may experience a relapse each year. Patients with recurrent CH had an estimated 33% annual relapse risk, whereas those with first-onset CH had a considerably lower risk of approximately 11% per year. Notably, this recurrence rate is considerably lower than that reported in previous case series or cohorts, including our own, where the average bout frequency ranged from one to two per year (14,15,16-17,19-20). This discrepancy between our findings and those of previous reports may indicate the influence of patients' subjective recall and prospective

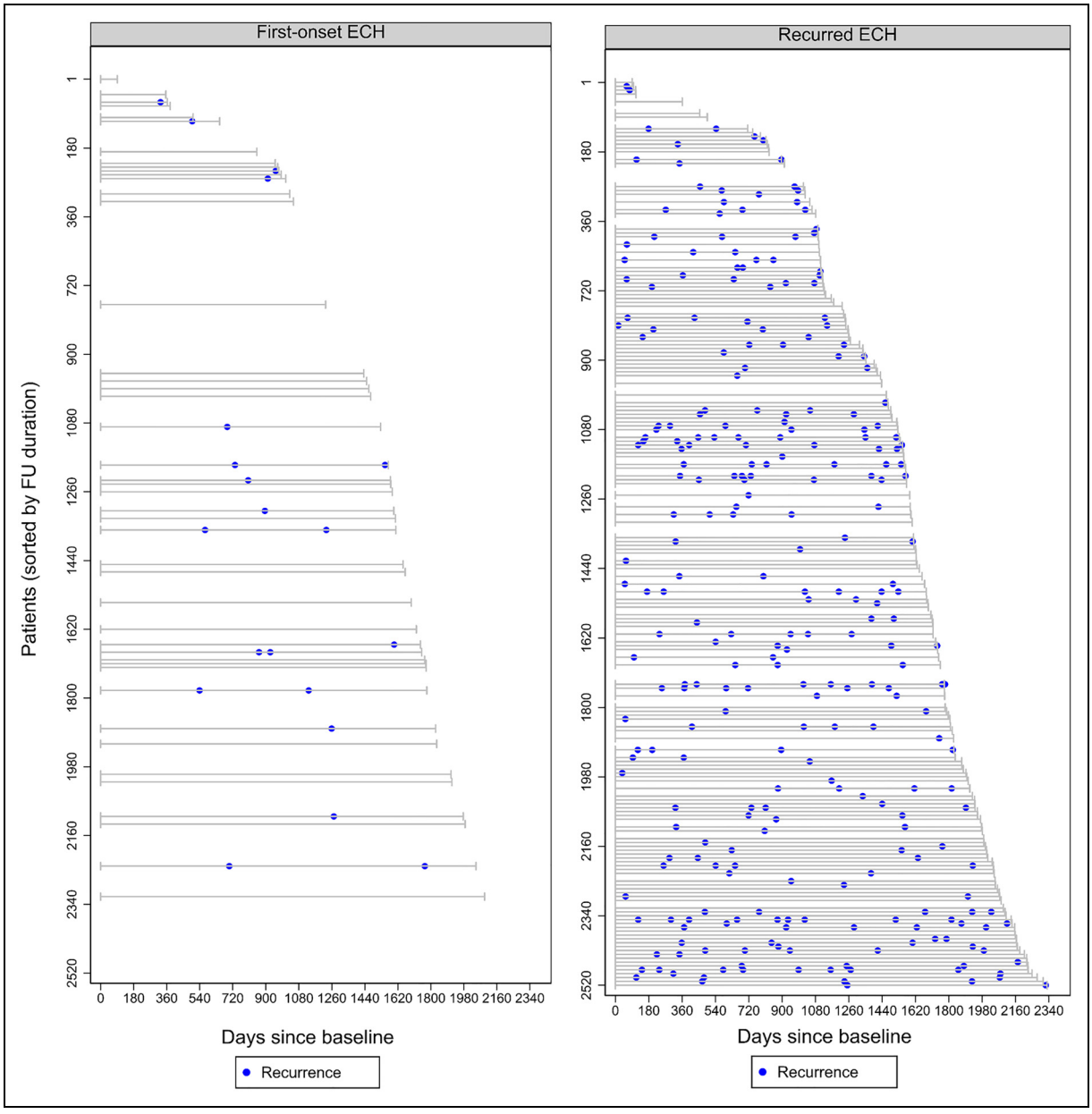


Figure 4. Timeline of bout relapses. Patients with ECH who had an active bout at the enrollment were included in this analysis. Patients were stratified into first-onset ECH (left) and recurrent ECH (right). Each gray line represents each patient, sorted by their follow-up (FU) duration (*Y*-axis). The length of gray line indicates follow-up duration of individual patients, with a starting point (day 0) at the date of enrollment. Blue dots represent the relapses of bout. ECH = episodic cluster headache.

observation rather than the effects of preventive treatment because no preventive treatment has been proven to prevent bout recurrence, and most of our patients did not undergo long-standing preventive treatment in between-bout periods. Interestingly, no significant discrepancy was noted between recalled between-bout intervals and observed ones (20.4 vs. 20.6 months), suggesting that the nature of the questions posed can influence the magnitude of subjective recall.

Once determined to have episodic CH, patients with first-onset CH generally showed a favorable prognosis, exhibiting a relapse rate of approximately one-third that of recurrent CH over the same period. This observation suggests that the disease activity of CH is lower at disease onset, gradually increasing during the disease course. Regarding aging, we found that advanced age is associated with less frequent recurrence. In addition, we found that regarding age at onset, younger age at onset was also associated with frequent relapses,

Table 3. Predictors of relapse: static factors in all patients.

	Univariable		Multivariable	
	IRR (95% CI)	*p*-value	IRR (95% CI)	*p*-value
Age (years)	0.97 (0.96–0.98)	<0.001	0.97 (0.95—0.98)	<0.001
Sex				
Male	(Ref.)		(Ref.)	
Female	1.41 (1.05–1.86)	0.018	1.24 (0.83–1.84)	0.284
Age at onset (years)	0.98 (0.97–0.99)	<0.001	NA*	
Total lifetime bouts (n)	1.01 (1.00–1.02)	0.001	1.01 (1.00–1.01)	0.219
Disease duration (years)	1.00 (0.99–1.02)	0.802	0.97 (0.95–1.00)	0.022
Index bout				
Recurred	(Ref.)		(Ref.)	
First-onset	0.33 (0.20–0.51)	<0.001	0.35 (0.20–0.57)	<0.001
Attack side				
Left	(Ref.)		(Ref.)	
Right	1.00 (0.79–1.26)	0.990	1.17 (0.88–1.56)	0.294
Alternating or bilateral	0.95 (0.48–1.68)	0.877	0.95 (0.36–2.24)	0.917
Attack frequency per day	0.99 (0.92–1.06)	0.796	1.02 (0.94–1.10)	0.581
Attack duration (minutes)	1.00 (1.00–1.00)	0.584	1.00 (1.00–1.00)	0.173
Attack intensity (NRS) (0–10)	1.07 (0.97–1.19)	0.181	1.07 (0.95–1.21)	0.3
Circadian rhythmicity				
No	(Ref.)		(Ref.)	
Yes	1.19 (0.95–1.50)	0.132	1.20 (0.92–1.58)	0.175
Body mass index	0.99 (0.95–1.03)	0.564	1.00 (0.95–1.05)	0.956
Smoking class				
Never-smoker			(Ref.)	
Current smoker	0.72 (0.56–0.92)	0.009	1.13 (0.79–1.61)	0.501
Ex-smoker	0.85 (0.61–1.17)	0.341	1.48 (0.95–2.29)	0.078
Alcohol consumption				
Less than one per week	(Ref.)		(Ref.)	
At least one per week	0.67 (0.52–0.85)	0.001	0.60 (0.45–0.81)	<0.001
Comorbid migraine				
No	(Ref.)		(Ref.)	
Yes	1.12 (0.81–1.51)	0.494	1.05 (0.70–1.53)	0.810
Anxiety				
No	(Ref.)		(Ref.)	
Yes	1.11 (0.86–1.44)	0.413	1.00 (0.72–1.40)	0.993
Depression				
No	(Ref.)		(Ref.)	
Yes	1.16 (0.91–1.49)	0.222	1.10 (0.79–1.53)	0.583

CI = confidence interval; IRR = incidence rate ratio; NA = not available; NRS = numeric rating scale.
*Excluded in the multivariable model owing to a high correlation with other variable (age).

suggesting higher disease activity when CH develops early in life. In addition, longer disease duration was associated with lower relapse rates, suggesting a decrease in disease activity over time. This insight may address a common question from patients in clinical settings: "Whether the recurrence of bouts will eventually remit over time?" Taken together, these findings, in conjunction with those related to first-onset CH, indicate that the disease activity of episodic CH tends to gradually increase after onset and then regress over time.

Our study also identified seasonal rhythmicity as a risk factors of frequent relapses. Seasonal rhythmicity is a known characteristic of CH, but its biological mechanism remains unclear. The suprachiasmatic nuclei, which are hypothalamic nuclei responsible for circadian rhythms and encoding seasonal rhythms, along with seasonal changes in relevant hormones, have been suggested to play a role in the seasonal predilection of bouts in CH (33). Our findings suggest that seasonal rhythmicity may serve as a marker of disease activity in CH, supporting the hypothesis of aberrant interaction between the hypothalamus and the trigeminal system. Among the lifestyle factors, we did not observe an increased risk of relapse associated with smoking. By contrast, interestingly, regular alcohol intake was associated with a lower relapse rate. This finding may be explained by confounding by indication or reverse causality, whereby patients with higher

Table 4. Predictors of relapse: time-related factors in patients with two or more lifetime bouts at baseline.

	Univariable		Multivariable	
	IRR (95% CI)	*p*-value	IRR (95% CI)	*p*-value
Seasonal rhythmicity				
No	(Ref.)		(Ref.)	
Yes	1.79 (1.40–2.30)	<0.001	1.66 (1.20–2.33)	0.003
Average duration of past bouts (weeks)	1.00 (0.97–1.02)	0.730	1.00 (0.98–1.03)	0.709
Average interval of past bouts (years)	0.71 (0.62–0.81)	<0.001	0.72 (0.60–0.87)	<0.001
Temporal changes in attack intensity				
No change	(Ref.)		(Ref.)	
Increasing	1.64 (1.23–2.18)	<0.001	1.66 (1.06–2.59)	0.027
Decreasing	1.51 (1.03–2.15)	0.029	1.30 (0.80–2.08)	0.278
Inconsistent	NA		NA	
Temporal changes in attack frequency				
No change	(Ref.)		(Ref.)	
Increasing	1.34 (1.01–1.76)	0.043	1.14 (0.71–1.83)	0.593
Decreasing	1.38 (0.94–1.99)	0.092	1.35 (0.73–2.47)	0.333
Inconsistent	NA		NA	
Temporal changes in bout duration				
No change	(Ref.)		(Ref.)	
Increasing	1.34 (1.00–1.81)	0.052	1.07 (0.70–1.62)	0.746
Decreasing	1.80 (1.24–2.55)	0.001	1.21 (0.69–2.09)	0.500
Inconsistent	1.05 (0.57–1.77)	0.867	1.01 (0.52–1.83)	0.970
Temporal changes in bout interval				
No change	(Ref.)		(Ref.)	
Increasing	0.69 (0.44–1.03)	0.085	0.61 (0.35–1.02)	0.065
Decreasing	1.45 (1.04–1.99)	0.024	1.31 (0.86–1.97)	0.205
Inconsistent	0.90 (0.59–1.32)	0.599	1.24 (0.77–1.93)	0.364
Temporal changes in seasonal rhythmicity				
No change	(Ref.)		(Ref.)	
Increasing	1.19 (0.79–1.75)	0.382	1.38 (0.79–2.32)	0.243
Decreasing	0.95 (0.68–1.31)	0.775	0.87 (0.56–1.32)	0.512
Inconsistent	0.73 (0.48–1.05)	0.105	0.94 (0.53–1.62)	0.825
Temporal changes in circadian rhythmicity				
No change	(Ref.)		(Ref.)	
Decreasing	1.21 (0.86–1.68)	0.250	1.19 (0.78–1.79)	0.414
Increasing	1.27 (0.83–1.89)	0.254	0.73 (0.40–1.30)	0.292
Inconsistent	0.73 (0.51–1.03)	0.083	1.02 (0.64–1.58)	0.936
Temporal changes in autonomic symptoms				
No change	(Ref.)		(Ref.)	
Increasing	1.08 (0.74–1.54)	0.663	0.84 (0.55–1.26)	0.408
Decreasing	1.66 (0.90–2.81)	0.078	0.86 (0.41–1.68)	0.669
Inconsistent	0.55 (0.35–0.84)	0.008	0.72 (0.43–1.15)	0.190
Never experienced	0.56 (0.27–1.03)	0.092	0.64 (0.29–1.28)	0.237
Side shift of attacks				
No	(Ref.)		(Ref.)	
Yes	1.32 (0.98–1.75)	0.063	1.34 (0.95–1.87)	0.089

CI = confidence interval; IRR = incidence rate ratio; NA = not available.

disease activity or alcohol sensitivity likely avoided alcohol consumption, resulting in a relatively less active or sensitive subgroup among regular drinkers.

Patient-reported temporal changes in attack intensity were found to be associated with relapse rates, with those perceiving increasing attack intensity exhibiting a higher likelihood of frequent relapse during a prospective observation. This emphasizes the potential value of patients' self-perceived temporal changes in disease course as a risk factor of future outcomes and should be the focus of future studies. Temporal changes in other markers, such as attack frequency, bout duration, seasonal and circadian rhythmicity, autonomic symptoms or attack side, currently showed no independent association with the observed relapse rate. Despite these

findings, the small sample sizes in each response stratum should be considered cautiously before drawing definitive conclusions.

The strengths of the present study include its prospective design, multicenter participant recruitment, detailed collection of baseline- and temporal-related parameters, and structured patient follow-up protocols. Nevertheless, our study has some limitations. The planned five-year follow-up, established before the study commencement, was determined based on considerations of patient retention rates. However, a longer follow-up duration would be required for a comprehensive exploration of the long-term remission of CH. In addition, less than half of patients completed the five-year follow-up due to lost follow-up and voluntary withdrawal. The effects of long-term preventive treatment could not be assessed in our study, as treatment-related data were only collected at the baseline visit. However, across participating centers, the standard clinical practice was not to offer long-term prophylactic treatment to patients with episodic CH once remission of the bout was achieved. Therefore, although we cannot formally analyze or exclude the effect of long-term preventive treatment, it is unlikely to have significantly influenced our main findings. The data regarding screening failure, illicit drug use (although extremely rare in Korea) and sleep disorders (34) are also lacking. Additionally, the study's exclusive focus on a single ethnicity (i.e. Korean) might limit the generalizability of our findings.

Conclusions

In conclusion, the relapse rate of episodic CH was observed to be approximately 0.3 per person-year, a value lower than retrospective recall estimates. In particular, the disease activity of CH was observed to evolve over time. Advanced age, longer disease duration, first-ever bout, regular (at least one drink per week) alcohol consumption and longer between-bout interval of previous bouts were associated with a lower relapse rate, whereas seasonal rhythmicity and increasing attack intensity during previous bouts were identified as risk factors of frequent relapse. Our prospective findings offer insights into the disease course of CH that can aid physicians in counseling patient and anticipating the disease trajectory of CH.

Clinical implications

- The incidence of chronic CH newly found during a prospective observation was 3.8% in patients with first-onset CH (primary chronic CH) and 1.4% in those with a history of episodic CH (secondary chronic CH).
- The average relapse rate of episodic CH was 0.29 (95% CI = 0.27–0.32) per person-year.
- In patients with episodic CH, age, longer disease duration and first-onset CH are associated with less relapse, whereas seasonal rhythmicity and increasing attack intensities across bouts are associated with frequent relapse.

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Data availability

The data sets analyzed in the current study are not publicly available due to privacy restrictions under Institutional Review Board (IRB) regulations but may be available from the corresponding author upon reasonable request with appropriate IRB approval.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Ethical statement

The study protocol was approved by the institutional review board of each participating hospital, and written informed consent was obtained from all patients prior to their recruitment.

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