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Classifying migraine subtypes and their characteristics by latent class analysis using data of a nation-wide population-based study

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Migraine neither presents with a definitive single symptom nor has a distinct biomarker; thus, its diagnosis is based on combinations of typical symptoms. We aimed to identify natural subgroups of migraine based on symptoms listed in the diagnostic criteria of the third edition of the International Classification of Headache Disorders. Latent class analysis (LCA) was applied to the data of the Korean Sleep-Headache Study, a nationwide population-based survey. We selected a three-class model based on Akaike and Bayesian information criteria and characterized the three identified classes as “mild and low frequency,” “photophobia and phonophobia,” and “severe and high frequency.” In total, 52.0% (65/125) of the participants were classified as “mild and low frequency,” showing the highest frequency of mild headache intensity but the lowest overall headache frequency. Meanwhile, “photophobia and phonophobia” involved 33.6% (42/125) of the participants, who showed the highest frequency of photophobia and phonophobia. Finally, “severe and high frequency” included 14.4% (18/125) of the participants, and they presented the highest frequency of severe headache intensity and highest headache frequency. In conclusion, LCA is useful for analyzing the heterogeneity of migraine symptoms and identifying migraine subtypes. This approach may improve our understanding of the clinical characterization of migraine.

Migraine is a common condition that affects approximately 5–15% of the general population¹. Despite its debilitating effects, there is currently no definitive biomarker or single symptom of migraine; thus, its diagnosis is based on self-reported symptoms. The third edition of the International Classification of Headache Disorders (ICHD-3) requires fulfilling at least two of four typical headache characteristics and at least one typical combination from four accompanying symptoms for a migraine diagnosis². Therefore, individuals with migraine have varying symptom combinations.

Identifying the symptom subtypes of a disorder may help to better characterize typical and atypical populations, improving precision diagnosis and treatment³. In this context, several approaches have been used to identify the heterogeneity of migraine symptomatology^{4–11}. Statistical methodologies, including factor analysis, cluster analysis, discriminant function analysis, factor mixture modeling, latent trait analysis and latent class analysis (LCA), have been used to identify the subtypes of clinical symptoms^{8,10,12}. Among them, LCA is the most commonly used methodology to identify subgroups of migraine according to their symptoms and comorbidity^{11,13}. It is a subset of structural equation modeling used to find subtypes of cases in multivariate categorical data and allows detection of the presence of latent classes (the disease entities), creating patterns of association in the symptoms¹⁴.

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Number of latent classes	2	3	4
AIC	1453	1448	1447
BIC	1524	1556	1592

Table 1. Model selection criteria for latent class analysis. *AIC* Akaike information criterion, *BIC* Bayesian information criterion.

	Total (n = 125)	Class 1 (n = 65)	Class 2 (n = 42)	Class 3 (n = 18)	P-value
Age, years	45.8 ± 15.0	45.8 ± 15.9	45.3 ± 13.6	46.8 ± 15.8	0.934
Sex					0.137
Male	50 (40.0%)	23 (35.9%)	16 (38.1%)	11 (61.1%)	
Female	75 (60.0%)	42 (64.6%)	26 (61.9%)	7 (38.9%)	
Education					0.223
Middle school or lower	16 (12.8%)	11 (16.9%)	5 (11.9%)	0 (0.0%)	
High school	52 (41.6%)	23 (35.4%)	18 (42.9%)	11 (61.1%)	
College or higher	57 (45.6%)	31 (47.7%)	19 (45.2%)	7 (38.9%)	
BMI, kg/m²	22.60 (21.22, 23.64)	22.63 (21.02, 24.08)	22.12 (21.28, 22.95)	22.76 (22.55, 24.99)	0.276
Hypertension	27 (21.6%)	14 (21.5%)	10 (23.8%)	3 (16.7%)	0.827
Diabetes	13 (10.4%)	7 (10.8%)	6 (14.3%)	0 (0.0%)	0.314
Dyslipidemia	11 (8.8%)	3 (4.6%)	7 (16.7%)	1 (5.6%)	0.081

Table 2. Sociodemographic, anthropometric and metabolic characteristics of participants with migraine. Data are presented as the mean ± standard deviation, median (interquartile range), or n (%). *BMI* body mass index. Statistical method for comparison of the three groups: one-way analysis of variance for normally distributed variables; Kruskal–Wallis test for non-normally distributed variables; Chi-square or Fisher’s exact test for categorical variables.

Previous studies on subtyping of migraine symptoms were mostly performed during genetic analyses among individuals with headache, mostly using data of twins and their relatives^{4–9}. Although these subtended migraine symptoms, involved individuals included both non-migraine headache and those with migraine. Further, although two studies have subtended clinical symptoms exclusively in individuals with migraine, these studies used cohort data of health professionals^{15,16}. Consequently, these studies may not properly reflect the clinical symptoms of those in the general population.

The Korean Sleep–Headache Survey (KSHS) was a nationwide population-based cross-sectional survey about headaches and sleep that provides an opportunity to evaluate and to subtype clinical symptoms of individuals with migraine in a general population. This study aimed to identify the subtypes of migraine symptoms in individuals with migraine through LCA using the data of KSHS.

Results

Participants. In total, 2501 individuals completed the KSHS in 2018. The distribution of sex, age and educational level was not significantly different from those in the overall Korean population (Supplementary Table S1). Overall, 1186 participants reported experiencing a headache during the previous year; of them, 125 participants (4.99%, 95% confidence interval [CI] 4.14–5.85%) were diagnosed with migraine. They were aged 45.8 ± 15.0 years and included 50 males and 75 females.

Model selection and classification of classes. Three models were proposed and assessed as to their likelihood of prediction error. The Akaike information criterion (AIC) value was the lowest in the four-class model, while the Bayesian information criterion (BIC) value was the lowest in the two-class model (Table 1). Considering the discrepancy between the lowest AIC and BIC values within the models, we selected the three-class model because its BIC was lower than that of the four-class model and because it best described the different characteristics of the latent classes clinically. Both the standard errors of estimated prior probabilities of each class of the latent class membership and the class-conditional response probabilities of the indicators were within acceptable range (Supplementary Tables S2 and S3).

Demographic characteristics of the three classes. The model allowed sorting into Classes 1, 2 and 3, which identified 65, 42 and 18 individuals, respectively (Table 2). There were no significant differences in age, sex, residential area, education, income, body mass index and proportion of obesity among the three classes. The prevalence of comorbidities (hypertension, diabetes and dyslipidemia) was also similar.

	Total (n = 125)	Class 1 (n = 65)	Class 2 (n = 42)	Class 3 (n = 18)	P-value
Headache intensity					0.012 ^{†c}
Mild	21 (16.8%)	13 (20.0%)	8 (19.1%)	0 (0.0%)	
Moderate	78 (62.4%)	35 (53.9%)	31 (73.8%)	12 (66.7%)	
Severe	26 (20.8%)	17 (26.2%)	3 (7.1%)	6 (33.3%)	
Unilateral location	87 (69.6%)	60 (92.3%)	19 (45.2%)	8 (44.4%)	< 0.001 ^{†ab}
Pulsating quality	98 (78.4%)	48 (73.9%)	33 (78.6%)	17 (94.4%)	0.171
Aggravation by routine physical activity	59 (47.2%)	8 (12.3%)	33 (78.6%)	18 (100.0%)	< 0.001 ^{†ab}
Nausea	112 (89.6%)	63 (96.9%)	31 (73.8%)	18 (100.0%)	< 0.001 ^{†a}
Vomiting	56 (44.8%)	34 (52.3%)	20 (47.6%)	2 (11.1%)	0.007 ^{†bc}
Photophobia	45 (36.0%)	1 (1.5%)	42 (100.0%)	2 (11.1%)	< 0.001 ^{†ac}
Phonophobia	66 (52.8%)	22 (33.9%)	42 (100.0%)	2 (11.1%)	< 0.001 ^{†ac}

Table 3. Characteristics of headache under the diagnostic criteria of migraine in the third edition of the International Classification of Headache Disorders. Data are presented as n (%). [†]Significant P-value. ^aSignificant difference between Class 1 and Class 2 in multiple comparisons. ^bSignificant difference between Class 1 and Class 3 in multiple comparisons. ^cSignificant difference between Class 2 and Class 3 in multiple comparisons.

Headache characteristics under the ICHD-3 migraine diagnostic criteria. The headache characteristics according to the ICHD-3 diagnostic criteria of migraine among the three classes are summarized in Table 3. The results of multiple comparisons are shown in Supplementary Table S4. There were significant differences in the distribution of headache intensity, unilateral pain, aggravation by routine physical activity, nausea, vomiting, photophobia and phonophobia among the three classes but not in pulsating quality. Unilateral pain and mild headache intensity were the most frequent symptoms, and aggravation by routine physical activity was the least frequent in Class 1, while photophobia and phonophobia were the most frequent in Class 2. Class 3 showed the highest frequency of nausea, aggravation of routine physical activity and severe headache intensity.

The multiple comparisons revealed that the frequency of unilateral pain, aggravation by routine physical activity, nausea, photophobia and phonophobia was significantly different between Class 1 and Class 2. Meanwhile, the frequency of unilateral pain, aggravation by routine physical activity and vomiting differed significantly between Class 1 and Class 3. Headache intensity, photophobia and phonophobia were significantly different between Class 2 and Class 3.

Clinical features of migraine outside the ICHD-3 diagnostic criteria. Headache frequency per month, headache duration (in minutes), osmophobia, impact of headache, visual aura, anxiety and fatigue were significantly different among the three classes (Table 4). Multiple comparisons showed that the frequency of osmophobia, visual aura, anxiety and fatigue was significantly different between Class 1 and Class 2 (Supplementary Table S4).

Characterization of the three classes. The three classes were named to reflect the unique characteristics of each class. Class 1 was characterized by mild and low frequency migraine and was the most common, with 52.0% (65/125) of the participants belonging to this classification. We named Class 1 as “mild and low frequency.” Class 2 as the next most common class was characterized by intermediate headache frequency and headache intensity. Nevertheless, this class showed the highest frequency of photophobia and phonophobia and was thus named “photophobia and phonophobia.” This class involved 33.6% (42/125) participants. Class 3 was the least common and was characterized by the highest headache intensity and headache frequency. We named this as “severe and high frequency.” This class included 14.4% (18/125) of the participants.

Discussion

Migraine diagnosis is challenging because it does not present with a definitive single symptom or have a distinct biomarker. LCA in this study enabled us to classify each of the 125 participants with migraine into three classes. Each class showed distinct characteristics that can be briefly described as “mild and low frequency,” “photophobia and phonophobia” and “severe and high frequency”.

Several studies have attempted to subclassify migraine. Schürks et al. evaluated women with migraine and found three classes related to central nervous system (CNS) sensitization, attack frequency and pain location and aura and visual phenomena¹⁵. The “CNS sensitization” and “attack frequency and pain location” classes may correspond to our “severe and high frequency” and “mild and low frequency” classes, respectively. Both the “CNS sensitization” and “severe and high frequency” classes showed high headache frequency and aggravation by routine physical activity. Meanwhile, the “attack frequency and pain location” and “mild and low frequency” classes presented with frequent unilateral pain and mild headache intensity. However, photophobia and phonophobia were significantly related in our study, but not in Schürks et al.’s study. This discrepancy may be due to differences in study population, ethnicity, sex and analysis methods. Studies on twins and their relatives included

	Total (n = 125)	Class 1 (n = 65)	Class 2 (n = 42)	Class 3 (n = 18)	P-value
Monthly headache frequency					
n	0.83 (0.33, 3.00)	0.50 (0.33, 2.00)	1.00 (0.42, 4.00)	1.50 (0.52, 7.00)	0.030 [†]
By category					
< 2	75 (60.0%)	44 (67.7%)	22 (52.4%)	9 (50.0%)	
≥ 2, < 8	33 (26.4%)	18 (27.7%)	11 (26.2%)	4 (22.2%)	
≥ 8, < 15	12 (9.6%)	1 (1.5%)	6 (14.3%)	5 (27.8%)	
≥ 15	5 (4.0%)	2 (3.1%)	3 (7.1%)	0 (0.0%)	
Headache duration (min)	300.0 (240.0, 480.0)	300.0 (240.0, 600.0)	300.0 (240.0, 465.0)	240.0 (240.0, 300.0)	0.030 ^{†b}
Osmophobia	48 (38.4%)	13 (20.00%)	28 (66.67%)	7 (38.89%)	< 0.001 ^{†a}
Aura (VARS score ≥ 3)	22 (17.6%)	6 (9.23%)	14 (33.33%)	2 (11.11%)	0.004 ^{†a}
HIT-6 score	53.0 ± 8.9	51.3 ± 8.2	55.8 ± 10.0	52.3 ± 7.9	0.038 ^{†a}
MIDAS score	1.00 (0.00, 3.00)	0.00 (0.00, 2.00)	1.00 (0.00, 4.00)	2.50 (0.25, 8.25)	0.069
Anxiety (GAD-7 score ≥ 8)	14 (11.2%)	3 (4.6%)	9 (21.4%)	2 (11.1%)	0.018 ^{†a}
Depression (PHQ-9 score ≥ 10)	24 (19.2%)	9 (13.9%)	9 (21.4%)	6 (33.3%)	0.161
Cutaneous allodynia (ASC-12 score ≥ 3)	20 (16.0%)	10 (15.9%)	8 (19.1%)	2 (11.1%)	0.730
Fatigue (FSS score ≥ 4)	44 (35.2%)	16 (24.6%)	20 (47.6%)	8 (44.4%)	0.035 ^{†a}
FSS score	3.67 (2.89, 4.33)	3.44 (2.78, 3.89)	3.89 (3.56, 4.44)	3.89 (3.00, 4.17)	0.021 ^{†a}
Excessive daytime sleepiness (ESS score ≥ 11)	27 (21.8%)	14 (21.5%)	12 (29.8%)	1 (5.6%)	0.127
ESS score	8.00 (5.00, 10.00)	8.00 (5.00, 10.00)	8.00 (5.00, 11.00)	5.00 (4.25, 8.00)	0.167

Table 4. Clinical features not included in the diagnostic criteria of migraine in the third edition of the International Classification of Headache Disorders. Data are presented as the mean ± standard deviation, median (interquartile range), or n (%). VARS Visual Analogue Rating Scale, HIT-6 Headache Impact Test-6, MIDAS Migraine Disability Assessment, GAD-7 General Anxiety Disorder-7, PHQ-9 Patient Health Questionnaire-9, ASC-12 The 12-item Allodynia Symptom Checklist, FSS Fatigue Severity Scale, ESS Epworth Sleepiness Scale. [†]Significant P-value. ^aSignificant difference between Class 1 and Class 2 in multiple comparisons. ^bSignificant difference between Class 1 and Class 3 in multiple comparisons. ^cSignificant difference between Class 2 and Class 3 in multiple comparisons.

individuals with migraine and non-migraine headache and selected a three- or four-class model. These studies found subtypes of high, intermediate, low and minimal frequency of migraine symptoms^{4,5,7,8,13}.

Our study found several noteworthy findings on the subtypes and symptoms of migraine. First, Class 2 (photophobia and phonophobia) showed the highest rate of osmophobia (i.e., intolerance of or hypersensitivity to smells), which is a common symptom of migraine and has high specificity for migraine diagnosis^{17,18}. Photophobia, phonophobia and osmophobia are sensory hypersensitivity symptoms¹⁹. Our findings support that there is a migraine subtype that presents with a high frequency of sensory hypersensitivity symptoms. Second, considering that the intensity and frequency of headache are key parameters for determining migraine severity²⁰, we found that each symptom is closely related to severity. Unilateral pain was most common in Class 1 (mild and infrequent) and least common in Class 3 (severe and frequent). In contrast, aggravation by routine physical activity was the most frequent in Class 3 and the least frequent in Class 1.

Photophobia and severe headache intensity were prevalent in 36.0% and 20.8% of our participants, respectively. These rates are lower than those in Western countries but are similar to those in Asian countries. Approximately 68% to 84.5% of patients with migraine in Western countries have photophobia^{21,22}, whereas the rates range from 53.9 to 67.4% in Asian countries^{23,24}. Similarly, the prevalence of severe headache intensity is lower in Asian countries (19.5–38.0%) than in Western countries (60–85%)^{23,25–27}.

LCA has been used in genetic research to capture underlying phenotypic and genetic variance in diseases with complex etiologies^{7–9,13}. The three symptom subtypes of migraine identified in our study based on LCA may provide clues in understanding the pathophysiological and genetic mechanisms of migraine. The presence of a subtype with a high frequency of photophobia and phonophobia suggests a shared, rather than an independent, pathophysiological mechanism in sensory hypersensitivity symptoms. In a similar context, the co-occurrence of a high headache frequency and severe headache intensity suggests that high headache frequency and severe headache intensity have overlapping pathophysiological mechanisms. In genetic studies, the identification of different subtype symptom profiles suggests the presence of different genetic loci in each phenotype.

This study had some limitations. First, the symptoms of migraine were evaluated based on the participant's report. These symptoms can vary between attacks in the same person²⁸. A headache diary could have been a more accurate method for symptom evaluation; however, it is difficult to use in epidemiological studies. Second, although we used data from a large-scale epidemiological study, the sample size of this study was relatively small for LCA. The minimum sample size for LCA is not fixed, although better performance is expected with larger sample sizes²⁹. To overcome this issue, we used high-quality indicators with strong theoretical bases as variables, which allowed us to use a small sample and made classification and interpretation easy^{30,31}. To avoid local maxima

in the expectation–maximization algorithm, the latent class model was estimated 20 times using various initial parameter values; convergence failure was not present (Supplementary Tables S2 and S3).

However, the present study also had several strengths. First, our study used data from a nationwide population-based study that included a sample proportional to the population distribution of Korea. As such, the risk of selection bias was minimized. Second, we used a validated questionnaire for the diagnosis of migraine. Depression, anxiety, visual aura, fatigue, disability and impact of headache were also evaluated using validated Korean versions of the Patient Health Questionnaire-9 (PHQ-9), General Anxiety Disorder-7 (GAD-7), self-administered Visual Analogue Rating Scale (VARS), Fatigue Severity Scale (FSS), Migraine Disability Assessment (MIDAS) and Headache Impact Test-6 (HIT-6). This enabled an accurate evaluation of migraine and its clinical features. Third, we selected items of LCA based on the ICHD-3 diagnostic criteria of migraine, which comprised key characteristics of migraine. This allowed us to properly analyze and to compare findings. Other approaches of migraine subtyping including genetic, biochemical and neuroimaging studies are needed to verify our findings.

In this study, LCA identified three classes of migraine that showed distinct characteristics. These classes were “mild and low frequency,” “photophobia and phonophobia,” and “severe and high frequency,” in order of prevalence. LCA can be useful to analyze the heterogeneity of migraine symptoms and to identify migraine subtypes.

Methods

Survey. The method of sampling and survey of KSHS in 2018 has been previously described in detail³². Briefly, the survey used a two-stage clustered random sampling method proportional to population distribution of all Korean territories, except for Jeju-do, based on data from the 2017 population and housing census conducted by the National Statistical Office of Korea³³. The target sample size was 2500 adults aged ≥ 19 years, and the estimated sampling error was $\leq 1.9\%$. The survey was conducted between October 2018 and November 2018 using face-to-face questionnaire interviews by trained interviewers. All interviewers were employees of Gallup Korea and had experiences in social survey. The questionnaire items included demographic characteristics, headache profiles, headache diagnosis, use of medical services, medical consultation, disability from headache, impact of headache, anxiety, depression and fatigue. This study was the secondary analysis of the KSHS.

Diagnosis of migraine. Migraine was diagnosed based on the diagnostic criteria for migraine without aura in ICHD-3 (code 1.1)². The diagnostic validity of the questionnaire has been previously reported³². Participants with a positive response to the question “Did you experience headache during the previous year?” and fulfilling the ICHD-3 criteria of migraine were diagnosed with migraine.

The presence of a visual aura was assessed using the self-administered VARS, for which the Korean version has been validated, with a score of ≥ 3 defined as having a visual aura^{34,35}. Participants who fulfilled the ICHD-3 diagnostic criteria of migraine without aura but reported visual aura were diagnosed with migraine with aura (code 1.2)².

Assessment of physical and mental impact of headache. Migraine disability and the impact of headache were evaluated using the MIDAS and HIT-6 tools, respectively^{36,37}. The Korean versions of the MIDAS and HIT-6 were previously validated^{38,39}.

The level of anxiety was assessed using the GAD-7 tool⁴⁰. Participants with a GAD-7 score of ≥ 8 were classified as having anxiety⁴¹. Depression was evaluated using the PHQ-9, with a PHQ-9 score of ≥ 10 defined as depression⁴². The Korean versions of the GAD-7 and PHQ-9 were previously validated^{43,44}.

Cutaneous allodynia, fatigue, and excessive daytime sleepiness. Cutaneous allodynia was evaluated using the Allodynia Symptom Checklist-12 (ASC-12), with an ASC-12 score of ≥ 3 being indicative of cutaneous allodynia⁴⁵. Fatigue was defined as an FSS score of ≥ 4 ⁴⁶. Excessive daytime sleepiness was defined as an ESS score of ≥ 11 ⁴⁷.

Model selection of LCA. LCA was used to differentiate the natural subgroups of migraine. It is a type of finite mixture model, a statistical technique for the analysis of multivariate categorical data, used for examining relationships among observed variables. It stratifies the cross-classifications and probabilistic groups and characterizes them into unobserved (latent), unordered categorical variable classes^{48,49}. In this way, observations with similar sets of responses on the manifest variables tend to cluster within the same latent classes⁴⁹. In this study, LCA was performed using the “poLCA” package by R, which is a frequently used package for LCA⁴⁹.

Given that all participants with migraine satisfied criteria A (total attack number), B (typical duration) and E (exclusion of other diagnosis), we used items in criteria C and D of migraine without aura (code 1.1)² as variables for LCA. Headache intensity (mild, moderate and severe), unilateral location, pulsating quality, aggravation by routine physical activity, nausea, vomiting, photophobia and phonophobia were used as categorical variables in the gathered data. The headache frequency per month was categorized into a four-class variable (< 2 , ≥ 2 but < 8 , ≥ 8 but < 15 and ≥ 15). We evaluated the prior probabilities of latent class membership and class-conditional probabilities to check the quality of the indicators³⁰. To avoid local maxima in the expectation–maximization algorithm, the latent class model was estimated 20 times using various initial parameter values.

The model with the best fit was selected primarily based on AIC and BIC, with their lowest values predicting the best fit model⁴⁸. For comparison among classes, a one-way analysis of variance was used for normally distributed variables, while a Kruskal–Wallis test was used for non-normally distributed variables. A chi-square or Fisher’s exact test was used to compare categorical variables, as appropriate. Among observed variables in LCA and those with significant P values, normally distributed variables were compared using an independent t-test, whereas Dunn’s procedure was used for non-normally distributed variables⁵⁰. Multiple comparison was

conducted with the Bonferroni method, with P values represented as adjusted P values. All statistical analyses were performed using R version 3.6.0 (R Core Team, 2019)⁵¹. A two-sided P-value of <0.05 was considered significant. There was no missing data except for monthly headache frequency in one participant with migraine which was adjusted as mean value.

Ethical approval. This study was approved by the Institutional Review Board of Severance Hospital, Yonsei University (Approval No. 2018-1269-001). Written informed consent was obtained from all participants before the survey. Prior to obtaining written informed consent, all participants were given an explanation on the objective of the study and the data to be collected by interviewers. All procedures involving human participants were in accordance with the ethical standards of the institutional and/or national research committee as well as the tenets of the 1964 Declaration of Helsinki and its later amendments, or comparable ethical standards.

Data availability

The data used in this study are available from the corresponding author on reasonable request.

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Author contributions

W.W.L. conceptualized and designed the study, analyzed the data and drafted the manuscript. I.K.M. analyzed the data. K.I.Y., D.Y.K. and C.H.Y. collected the data. M.K.C. conceptualized and designed the study, collected the data and drafted the manuscript. All authors have read and approved the final manuscript.

Competing interests

M.K.C. was a site investigator for a multicenter trial sponsored by Otsuka Korea, Novartis, International AG and Eli Lilly and Co. He also worked as an advisory member for Teva and has received lecture honoraria from Allergan Korea, Handok-Teva and Yuyu Pharmaceutical Company in the past 24 months. Further, he received grants from the Yonsei University College of Medicine (2018-32-0037) and National Research Foundation of Korea (2019R1F1A1053841). The other authors have no potential conflicts of interest to disclose.

Additional information

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