

The disease burden of migraine patients receiving prophylactic treatments in Korea: A population-based claims database analysis

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Abstract

Background: Despite guideline recommendations, the limited benefits and failure of prophylactic treatment in patients with migraine have been reported. This study aimed to estimate the incremental burden (i.e., healthcare resource use and cost) of disease in patients who received at least one prophylactic treatment compared to those who did not.

Methods: This study analyzed the Health Insurance Review and Assessment Service database, which covers the entire population of Korea from December 2014 to November 2019. We included adult patients with migraine (≥ 18 years) who had ≥ 1 claim with migraine diagnosis (G43) or received ≥ 1 prescription of triptan or ergotamine between December 2015 and November 2018. We defined two groups: (1) migraine patients who received at least one prophylactic treatment (prophylaxis group) and (2) migraine patients who never received prophylactic treatments (non-prophylaxis group). We performed propensity score matching to balance the baseline covariates between the two groups. In a matched cohort, we estimated healthcare resource use and costs in terms of outpatient visits, outpatient visits to neurologists, emergency department (ED) visits, and hospitalizations.

Results: After matching, 633,709 and 633,709 patients were identified in the prophylaxis and non-prophylaxis groups, respectively. The healthcare resource utilization was significantly higher in the prophylaxis group than in the non-prophylaxis group in terms of the number of outpatient visits (2.34 vs 1.70), outpatient visits to neurologists (2.23 vs 1.61), ED visits (1.07 vs 1.05), and hospitalizations (1.12 vs 1.09) (all $P < 0.05$). The estimated annual costs per patient were significantly higher in the prophylaxis group than in the non-prophylaxis group for outpatient (102.37 USD vs. 62.46 USD), neurology outpatient (141.80 USD vs. 120.30 USD), and ED visits (550.51 USD vs. 234.14 USD) and hospitalization (817.01 USD vs. 645.97 USD) (all $P < 0.001$).

Conclusions: Migraine patients who received ≥ 1 prophylactic treatment had a higher burden of disease than migraine patients who received no prophylaxis. This indicates that despite migraine prophylaxis, the migraine-related disease burden remains high, and more efficient migraine prophylaxis strategies are needed.

Background

Migraine is a chronic neurological disease characterized by periodic pulsatile headaches and accompanying symptoms such as photophobia, phonophobia, nausea, and vomiting [1]. Migraine has a prevalence of 14.4% worldwide, and its prevalence in Korea is estimated to be 25.9% in women and 12.8% in men [2, 3]. According to the 2016 Global Burden of Disease study, migraines are the primary cause of years lived with disability worldwide in both men and women aged 15–49 years, demonstrating that the burden is higher in major productivity groups [4]. Migraine not only reduces the quality of life but also causes a great social and economic burden [5].

To address its substantial burden, international guidelines recommend prophylactic treatments to reduce the burden of migraines and number of attacks. However, prophylactic treatments are still underutilized in patients who appear to be clear candidates [6]. Wang et al. reported that despite 87.5% of migraine patients taking acute medications, only 29.2% of the patients took prophylactic medications, and 68.2% of migraine patients who had not received prophylactic treatment needed prophylactic treatment [7]. Moreover, most migraine patients who received prophylactic treatments dropped out because of adverse events and the low efficacy of drugs [8].

Although assessing the migraine disease burden and effect of prophylactic treatment on patients has garnered increasing attention, studies using real-world data are scarce, and studies observing the burden of migraine among patients receiving prophylactic treatments are lacking.

This study aimed to estimate the incremental burden (i.e., healthcare resource utilization and cost) of disease in those receiving migraine prophylactic treatments compared with those not receiving prophylactic treatments using nationwide population-based claims data.

Methods

Data source

This study used the Health Insurance Review and Assessment Service (HIRA) database, which contains national health insurance claims data in Korea from December 1, 2014, to November 30, 2019. The health insurance system in Korea covers approximately 98% of the overall Korean population [9]. The HIRA data that we used included patients' diagnosis, treatment, procedures, surgical history, cost information on all medical services, and prescription drugs that are reimbursed by the health insurance authority.

Study population

The study scheme is shown in Fig. 1. Adult patients (≥ 18 years) were identified as migraine patients if they met any of the following inclusion criteria between December 1, 2015, and November 30, 2018: (1) having a diagnosis of migraine (International Classification of Diseases, Tenth Revision [ICD-10] code G43); and (2) having at least one prescription claim for either triptan or ergotamine. The first identified migraine diagnosis or prescription claim for triptan/ergotamine was the cohort entry date. Patients were not included in the study if they met any of the following exclusion criteria within 1 year prior to the diagnosis date: (1) having a diagnosis of migraine (ICD-10 code G43); (2) having at least one prescription claim for either triptan or ergotamine; and (3) having a diagnosis of epilepsy or seizure (ICD-10 codes G40, G41, G56, or F44.5).

We then defined migraine patients with prophylactic treatments (i.e., prophylaxis group) and patients without prophylactic treatments (i.e., non-prophylaxis group). The prophylaxis group was defined as patients who received at least one prophylactic treatment. The non-prophylaxis group was defined as patients who did not receive any prophylactic treatment. We included the most frequently used

prophylactic medications that were selected in Korean clinical practice based on the clinical practice guidelines and the opinions of Korean neurologists [10–12]. A list of prophylactic medications with anatomical therapeutic chemical codes (ATC codes) is provided in Table 1. In addition, only the claims that prescribed prophylactic treatments with a migraine diagnosis code (ICD-10 code G43) were included in the analysis.

To identify the prophylaxis group, the index date was defined as the date of claim of the first observed prophylactic treatments with migraine diagnosis (ICD-10 code G43). To identify the non-prophylaxis group, the index date was defined as the same date as the matched prophylaxis patient. Detailed information on the matching process is described in the statistical analyses section. The follow-up period for both groups was 1 year from the index date.

Table 1
Medication codes for migraine prophylactic medications

General name	ATC code*
Divalproex sodium	N03AG01
Valproate	N03AG01
Metoprolol	C07AB02
Propranolol	C07AA05
Atenolol	C07AB03
Nebivolol	C07AB12
Amitriptyline	N06AA09
Topiramate	N03AX11
Venlafaxine	N06AX16
Nadolol	C07AA12
Flunarizine	N07CA03
Cinnarizine	N07CA02
Nortriptyline	N06AA10
Levetiracetam	N03AX14
Zonisamide	N03AX15
Verapamil	C08DA01
Nimodipine	C08CA06
Gabapentin	N03AX12
* ATC code, Anatomical Therapeutic Chemical code	

Migraine-related healthcare resource utilization

In this study, we assessed the frequency of healthcare resource use in migraine patients receiving prophylaxis during a 1-year follow-up period. Healthcare resource utilization included outpatient visits, outpatient visits to neurologists, emergency department (ED) visits, and hospitalizations. Healthcare resource utilization was limited to migraine-related visits. To define migraine-related visits, a migraine diagnosis code (ICD-10 code G43) was required for each healthcare resource utilization. ED visits were defined using procedure codes V1100, V1200, V1210, V1220, V1300, V1310, V1320, and V1400.

Migraine-related healthcare costs

We evaluated migraine-related healthcare costs during the 1-year follow-up period. Migraine-related healthcare costs included the cost of each type of visit (e.g., outpatient visits, outpatient visits to neurologists, ED visits, and hospitalizations). Migraine-related healthcare costs were derived from claims attributed to outpatient visits, outpatient visits to neurologists, ED visits, and hospitalizations with a migraine diagnosis (ICD-10 code G43). We estimated the mean annual cost per patient (cumulative costs of events/number of patients visiting each healthcare resource). The costs of outpatient visits consisted of medical expenses and medication costs. Medical expenses were defined as total costs, excluding medication costs. All costs are expressed in 2019 US dollars (1 USD = 1156.40 Korean won).

Statistical analyses

We analyzed the study population from December 1, 2014, to November 30, 2019, and described baseline characteristics such as age, sex, insurance type on the index date, Charlson Comorbidity Index (CCI) score, comorbidities, and co-medications during the year before the index date.

To estimate the incremental burden associated with migraine prophylaxis, propensity score matching was conducted between the prophylaxis and non-prophylaxis groups (controls). Propensity score matching was used to minimize potential confounding effects arising from differences in baseline covariates. The propensity score was calculated using logistic regression by including the following variables: sex, age, insurance type, CCI index, comorbidities, and co-medications). Comorbidities in the propensity score model were based on previous studies [13, 14] and included the following: depression (ICD-10 codes F32 and F33), anxiety (ICD-10 code F41), reactions to severe stress and adjustment disorders (ICD-10 code F43), sleep disorder (ICD-10 code F51), sinusitis (ICD-10 code J01), upper respiratory infections (ICD-10 code J06), bronchitis (ICD-10 code J20), dorsopathies (ICD-10 code M53), dorsalgia (ICD-10 code M54), and dyspepsia (ICD-10 code K30). The co-medications in the propensity score model included triptans and ergotamine to balance the frequency of migraine attacks within 1 year prior to the index date. We used one-to-one greedy matching, in which cases were matched sequentially with controls with the closest propensity score. The balance of baseline covariates between the two groups was assessed using standardized differences in the matched samples, and standardized differences of less than 10% were considered acceptable.

Study variables are summarized as counts with percentages for categorical variables and as mean and standard deviations for continuous variables. Chi-squared tests were used for categorical variables, and Student's t-test was used for continuous variables. All statistical analyses were performed using SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, North Carolina, USA). We considered a result to be statistically significant when the *p*-value was less than 0.05.

Results

Sample selection

Between December 1, 2015, and November 30, 2018, a total of 1,636,105 patients with a diagnosis of migraine or prescription for triptan or ergotamine were defined as migraine patients. Of the 638,441 migraine patients who received prophylactic treatments and 997,664 migraine patients who did not receive prophylactic treatment were identified. After matching, 633,709 patients in the prophylaxis group and 633,709 patients in the non-prophylaxis group were selected (Fig. 2).

Baseline characteristics

The baseline characteristics of the unmatched cohorts are shown in Table 2. Before matching, the prophylaxis group had a higher age, CCI index, and higher prevalence of medical comorbidities than those of the non-prophylaxis group. The prophylaxis group had higher triptan and ergotamine use than the non-prophylaxis group. The absolute standardized differences were greater than 0.1 for single episode major depressive disorder, anxiety, and dorsalgia before matching (Table 2). The baseline characteristics of the matched cohorts are shown in Table 3. The mean age was 49.04 years, and 69.74% of patients were female in the matched cohort. Triptan and ergotamine use were similar in the matched cohort. After matching, all absolute standardized differences were less than 0.1.

Table 2
Baseline characteristics of prophylaxis and non-prophylaxis groups in unmatched cohort

Unmatched cohort				
	Prophylaxis group (N = 638441)	Non-prophylaxis group (N = 997664)	<i>P</i> -value*	Absolute standardized difference
Age in years, mean (SD)	49.00 (16.90)	48.25 (17.47)	< 0.001	0.04
Sex, No. (%)				
Male	192587 (30.17)	333657 (33.44)	< 0.001	-0.07
Female	445854 (69.83)	664007 (66.56)		
Insurance type, No (%)				
National Health Insurance program	611578 (95.79)	957794 (96.00)	< 0.001	-0.01
Medical aid	26654 (4.17)	39261 (3.94)		
Charlson Comorbidity Index, mean (SD)	1.47 (1.72)	1.30 (1.68)	< 0.001	0.1
Comorbidities, No (%)				
Major depressive disorder, single episode	77058 (12.07)	85091 (8.53)	< 0.001	0.12
Major depressive disorder, recurrent	6268 (0.98)	7252 (0.73)	< 0.001	0.03
Other anxiety disorders	135537 (21.23)	153141 (15.35)	< 0.001	0.15
Reaction to severe stress and adjustment disorders	11232 (1.76)	13364 (1.34)	< 0.001	0.03
Sleep disorders not due to a substance or known physiological condition	41749 (6.54)	52976 (5.31)	< 0.001	0.05
Acute sinusitis	111703 (17.50)	157676 (15.80)	< 0.001	0.05
Acute upper respiratory infections of multiple and unspecified sites	180798 (28.32)	262532 (26.31)	< 0.001	0.05

Unmatched cohort				
Acute bronchitis	365723 (57.28)	531149 (53.24)	< 0.001	0.08
Other and unspecified dorsopathies, not elsewhere classified	31926 (5.00)	41017 (4.11)	< 0.001	0.04
Dorsalgia	279153 (43.72)	383924 (38.48)	< 0.001	0.11
Dyspepsia	268219 (42.01)	378967 (37.99)	< 0.001	0.08
Number of uses of triptan, mean (SD)	0.37 (5.08)	0.47 (5.43)	< 0.001	-0.02
Number of uses of ergotamine, mean (SD)	0.52 (8.97)	0.96 (11.47)	< 0.001	-0.04
SD, standard deviation				
* Chi-squared test and Student's t-test were used to compare prophylaxis and non-prophylaxis groups.				

Table 3
Baseline characteristics of prophylaxis and non-prophylaxis groups in matched cohort

Matched cohort				
	Prophylaxis group (N = 633709)	Non-prophylaxis group (N = 633709)	<i>P</i> -value*	Absolute standardized difference
Age in years, mean (SD)	49.04 (16.91)	49.04 (16.96)	0.97	-0.00006
Sex, No. (%)				
Male	191749 (30.26)	191749 (30.26)	1.00	0.000
Female	441960 (69.74)	441960 (69.74)		
Insurance type, No (%)				
National Health Insurance program	607088 (95.80)	607692 (95.89)	0.009	-0.005
Medical aid	26412 (4.17)	25842 (4.08)		
Charlson Comorbidity Index, mean (SD)	1.47 (1.72)	1.46 (1.72)	0.08	0.003
Comorbidities, No (%)				
Major depressive disorder, single episode	75245 (11.87)	74501 (11.76)	0.04	0.003
Major depressive disorder, recurrent	6143 (0.97)	5608 (0.88)	< 0.001	0.009
Other anxiety disorders	132771 (20.95)	134017 (21.15)	0.007	-0.005
Reaction to severe stress and adjustment disorders	10966 (1.73)	10766 (1.70)	0.17	0.002
Sleep disorders not due to a substance or known physiological condition	41126 (6.49)	41115 (6.49)	0.97	0.0001
Acute sinusitis	110284 (17.40)	109915 (17.34)	0.39	0.002
Acute upper respiratory infections of multiple and unspecified sites	178928 (28.24)	178950 (28.24)	0.97	-0.0001

	Matched cohort			
Acute bronchitis	362187 (57.15)	363553 (57.37)	0.01	-0.004
Other and unspecified dorsopathies, not elsewhere classified	31349 (4.95)	30542 (4.82)	< 0.001	0.006
Dorsalgia	275789 (43.52)	275928 (43.54)	0.8	-0.0004
Dyspepsia	265291 (41.86)	265901 (41.96)	0.27	-0.002
Number of uses of triptan, mean (SD)	0.37 (5.09)	0.35 (4.50)	0.02	0.004
Number of uses of ergotamine, mean (SD)	0.52 (8.99)	0.63 (9.22)	< 0.001	-0.012
SD, standard deviation				
* Chi-squared test and Student's t-test were used to compare prophylaxis and non-prophylaxis groups.				

Migraine-related healthcare resource utilization

Migraine-related visits were assessed during the 1-year follow-up period (Table 4). Migraine-related healthcare resource utilization was significantly higher in the prophylaxis group than in the non-prophylaxis group. The mean number of migraine-related outpatient visits per patient was 2.34 (SD = 3.00) in the prophylaxis group and 1.70 (SD = 2.13) in the non-prophylaxis group ($P < 0.001$). The mean number of migraine-related outpatient visits to neurologists per patient was 2.23 (SD = 2.26) in the prophylaxis group and 1.61 (SD = 1.20) in the non-prophylaxis group ($P < 0.001$). Although the difference was small, the mean numbers of migraine-related hospitalizations (1.12 vs. 1.09; $P < 0.001$) and ED visits (1.07 vs. 1.05; $P < 0.001$) were also significantly higher in the prophylaxis group than in the non-prophylaxis group.

Table 4
Migraine-related healthcare resource utilization in the prophylaxis and non-prophylaxis groups

	Prophylaxis group (N = 633709)	Non-prophylaxis group (N = 633709)	P-value*
Outpatient visits, mean (SD)	2.34 (3.00)	1.70 (2.13)	< 0.001
Neurologist visits, mean (SD)	2.23 (2.26)	1.61 (1.20)	< 0.001
ED visits, mean (SD)	1.07 (0.37)	1.05 (0.39)	0.0025
Hospitalizations, mean (SD)	1.12 (1.39)	1.09 (0.55)	0.01
SD, Standard Deviation			
* Student's t-test were used to compare prophylaxis and non-prophylaxis groups.			

Migraine-related healthcare costs

Table 5 shows mean migraine-related healthcare costs per patient for outpatient visits, outpatient visits to neurologists, ED visits, and hospitalizations during the 1-year follow-up period. In the prophylaxis group, mean outpatient costs per patient were 102.37 USD, with medical expenses accounting for 68.73 USD and medication costs accounting for 33.65 USD. In the non-prophylaxis group, mean outpatient costs per patient were 62.46 USD, with medical expenses accounting for 43.81 USD and medication costs accounting for 18.65 USD. The mean costs for outpatient visits to neurologists per patient were significantly higher in the prophylaxis group than in the non-prophylaxis group (141.80 USD vs. 120.30 USD; $P < 0.001$). The mean costs of ED visits (550.51 USD vs. 234.14 USD) and hospitalizations (817.01 USD vs. 645.97 USD) were also significantly higher for the prophylaxis group than for the non-prophylaxis group. Throughout the 1-year follow-up period, all migraine-related healthcare costs per patient in the prophylaxis group were greater than those in the non-prophylaxis group.

Table 5
Migraine-related healthcare costs of the prophylaxis and non-prophylaxis groups

(Unit: USD)							
	Prophylaxis group (N = 633709)			Non-prophylaxis group (N = 633709)			<i>P</i> -value*
	Mean (%)	Median	SD	Mean (%)	Median	SD	
Outpatient visits (per patient)							
Total visits							
Total outpatient cost	102.37	38.74	239.23	62.46	25.07	137.62	< 0.001
Medical expense	68.73(67.13)	25.58	142.51	43.81 (70.14)	16.53	104.65	< 0.001
Medication cost	33.65 (32.87)	6.22	171.96	18.65 (29.86)	3.88	72.84	< 0.001
Neurologist visits							
Total cost	141.80	64.34	339.38	120.30	49.78	215.46	< 0.001
Medical expense	85.57 (60.35)	33.75	137.67	82.37 (68.47)	24.71	175.90	0.01
Medication cost	56.23 (39.65)	10.70	294.32	37.93 (31.53)	5.61	113.25	< 0.001
ED visits (per patient)							
Total ED cost	550.51	269.35	1055.11	234.14	175.54	435.65	< 0.001
Medical expense	549.81 (99.87)	268.78	1055.08	233.71 (99.81)	175.35	435.58	< 0.001
Medication cost	0.70 (0.13)	0	4.83	0.44 (0.19)	0	2.89	< 0.001
Hospitalizations (per patient)							
Hospitalization cost	817.01	482.56	1342.32	645.97	347.19	1,212.88	< 0.001
SD, standard deviation							
* Chi-squared test and Student's t-test were used to compare prophylaxis and non-prophylaxis groups.							

Discussion

This is the first study to estimate the incremental disease burden incurred by the migraine prophylaxis group compared with that of the non-prophylaxis group in Korea, based on national health insurance claims data. To compare the two groups, propensity score matching was conducted to balance the baseline characteristics and minimize selection bias.

In this retrospective study using the Korea national health insurance claims data, 1,636,105 migraine patients were identified, of whom 638,441 patients (39%) received at least one migraine prophylactic treatment. In two previous studies, 33.8% and 38.8% of migraine patients were estimated to require prophylactic treatment, which is consistent with our findings [6, 15].

In this study, the mean annual number of migraine-related outpatient visits per patient was 2.34 and 1.70, respectively. Similar trends were observed in the number of outpatient visits among migraine patients in Finland. The number of outpatient visits was 2.4 per patient-year in migraine patients receiving prophylactic treatments and 1.3 per patient-year in migraine patients only receiving acute treatment [13]. A cross-sectional analysis of survey data from France, Germany, Italy, Spain, and the United Kingdom estimated healthcare resource utilization from visits to the healthcare system 6 months before survey participation [16]. In this study, they reported the mean number of outpatient visits to neurologists was 0.19, and the mean number of ED visits was 0.46 in migraine patients. The estimated numbers of visits were lower than those reported in our study (2.23 outpatient visits to neurologists and 1.07 ED visits per patient-year). This may reflect differences in access to healthcare. Most European countries offer gatekeeping systems in which patients first see a general practitioner before a specialized physician; however, in Korea, patients can see a specialized physician directly without having to see a general practitioner [17, 18].

Yu et al. reported that the mean annual outpatient cost per patient was 46.5 USD among migraine patients in China [3]. In the current study, the mean annual outpatient costs were 102.37 USD in the prophylaxis group and 62.46 USD in the non-prophylaxis group. Migraine patients receiving prophylactic treatment were not included in the Chinese study. Thus, it was difficult to make an accurate comparison; however, in the non-prophylaxis group, the mean annual outpatient costs were similar to those in the study from China.

The current study did not observe the effect of migraine prophylactic treatments but instead evaluated the present status of disease burden in patients receiving migraine prophylactic treatments. These study findings indicate that migraine-related healthcare resource utilization and healthcare costs were significantly higher in migraine patients who received at least one migraine prophylactic treatment than in those who never received migraine prophylactic treatment. Although international guidelines recommend prophylactic treatment to reduce the burden of migraine and number of migraine attacks, prophylactic treatments for migraine remained underutilized in patients who appear to be clear candidates [6]. Moreover, most migraine patients who receive prophylactic treatments dropped out because of adverse events and the low efficacy of drugs [8]. Therefore, these findings suggest that despite the use of

migraine prophylactic treatments, there are still unmet medical needs in the migraine patients who received prophylactic treatment. These results are consistent with those of previous studies investigating the effect of migraine prophylactic treatment and estimating the burden of unmet medical needs in migraine patients [8, 19]. As a result, these findings reveal that more effective strategies and treatments to prevent migraine attacks are needed to reduce the burden of migraine patients receiving prophylactic treatment.

The current study has several limitations. First, we used propensity score matching to minimize potential confounding effects on incremental disease burden. Although we accounted for measured confounders in the matching process, unmeasured confounders, such as monthly migraine days and clinical data representing the severity of migraine, which were not included in the claims data, were not considered and may have affected the analysis. However, we considered the use of triptan and ergotamine in the matching process to balance the severity of migraine between the two groups. Second, in the current study, since we identified the migraine patients who received at least one migraine prophylactic treatment as the prophylaxis group, treatment discontinuation that may be due to adverse effects or lack of efficacy may have occurred during the follow-up period and the compliance of the treatment was not considered. A previous study reported that prophylactic treatments were associated with a high rate of discontinuation due to adverse effects or lack of efficacy [13, 20]. Third, since the migraine prophylactic medications used in this study are migraine non-specific medications, some prophylactic medications could have been prescribed for other indications [21]. Thus, it may cause overestimation of certain treatments and costs. To minimize this probability, we selected the most frequently used prophylactic treatments in Korean clinical practice based on clinical expert opinions of Korean neurologists. In addition, we only included claims with a migraine diagnosis code (ICD-10 code G43) in the analysis.

Despite these limitations, this study has several strengths. First, this study showed that a sufficient reduction in the burden of migraine was not observed in patients receiving prophylaxis, although the guidelines recommend preventive therapies to reduce the burden of migraine. It is necessary to examine whether prophylactic treatments are used properly, and more effective treatment strategies are needed. Second, this result is meaningful because evidence regarding disease burden in patients with migraine who received prophylactic treatments is very scarce [13]. In addition, the results of this study are representative and reliable because we used a nationwide claims database that represents approximately 98% of the overall Korean population [9].

Conclusions

This study assessed the incremental disease burden related to migraine prophylaxis on healthcare resource utilization and healthcare costs among migraine patients who received prophylaxis compared with those who did not in Korea using representative population-based data. This study is significant because it showed that a sufficient reduction in the burden of migraine was not observed in patients with prophylaxis, although guidelines recommended preventive therapies to reduce the burden of migraine. The findings of this study indicate that there are still unmet needs in migraine patients with prophylactic

treatments and highlight the need for appropriate prevention strategies for migraine to reduce the burden of disease.

Abbreviations

HIRA: Health Insurance Review and Assessment Service; ED: Emergency Department; ICD-10: International Classification of Diseases, Tenth Revision; ATC: Anatomical Therapeutic Chemical; CCI: Charlson Comorbidity Index; SD: Standard Deviation

Declarations

Ethics approval and consent to participate

This study was conducted according to the guidelines of the Declaration of Helsinki, and approved by Pusan National University Institutional Review Board (PNU IRB/2020_76_HR). The need for Informed Consent was waived by the PNU IRB because datasets are completely anonymous.

Consent for publication

Not applicable.

Availability of data and materials

The study data were extracted and analyzed from the Korea Health Insurance Review & Assessment Service (HIRA) claims database, and additional data may be obtained from a third party (with appropriate authorization approval) but are not publicly available.

Competing interests

The authors declare that they have no competing interests.

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The authors did not receive funding for the design of the study and collection, analysis, and interpretation of results and in writing the manuscript.

Authors' contributions

All authors contributed to the study conception and design, data collection, data analysis, and interpretation of results. The first draft of the manuscript was written by SP and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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References

1. Arnold M (2018) Headache classification committee of the international headache society (IHS) the international classification of headache disorders. *Cephalalgia* 38:1–211.
2. Song TJ, Cho SJ, Kim WJ, Yang KI, Yun CH, Chu MK (2019) Sex Differences in Prevalence, Symptoms, Impact, and Psychiatric Comorbidities in Migraine and Probable Migraine: A Population-Based Study. *Headache: The Journal of Head and Face Pain* 59:215 – 23.
3. Yu S, Zhang Y, Yao Y, Cao H (2020) Migraine treatment and healthcare costs: retrospective analysis of the China Health Insurance Research Association (CHIRA) database. *The journal of headache and pain* 21:1–7.
4. Stovner LJ, Nichols E, Steiner TJ, Abd-Allah F, Abdelalim A, Al-Raddadi RM, et al (2018) Global, regional, and national burden of migraine and tension-type headache, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology* 17:954–76.
5. Feigin VL, Abajobir AA, Abate KH, Abd-Allah F, Abdulle AM, Abera SF, et al (2017) Global, regional, and national burden of neurological disorders during 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet Neurology* 16:877–97.
6. Katsarava Z, Mania M, Lampl C, Herberhold J, Steiner TJ (2018) Poor medical care for people with migraine in Europe—evidence from the Eurolight study. *The journal of headache and pain* 19:1–9.
7. Wang SJ, Chung CS, Chankrachang S, Ravishankar K, Merican JS, Salazar G, et al (2008) Migraine disability awareness campaign in Asia: migraine assessment for prophylaxis. *Headache: The Journal of Head and Face Pain* 48:1356–65.
8. Delussi M, Vecchio E, Libro G, Quitadamo S, De Tommaso M (2020) Failure of preventive treatments in migraine: an observational retrospective study in a tertiary headache center. *BMC neurology* 20:1–12.
9. Kim L, Kim J-A, Kim S (2014) A guide for the utilization of health insurance review and assessment service national patient samples. *Epidemiology and health*. doi: 10.4178/epih/e2014008.
10. Loder E, Burch R, Rizzoli P (2012) The 2012 AHS/AAN guidelines for prevention of episodic migraine: a summary and comparison with other recent clinical practice guidelines. *Headache: The Journal of Head and Face Pain* 52:930–45.
11. Society AH (2019) The American Headache Society position statement on integrating new migraine treatments into clinical practice. *Headache: The Journal of Head and Face Pain* 59:1–18.
12. Society KH (2019) Treatment guideline of pharmacological preventive therapy for episodic migraine. Medical Publisher Co., Korea.

13. Korolainen MA, Kurki S, Lassenius MI, Toppila I, Costa-Scharplatz M, Purmonen T, et al (2019) Burden of migraine in Finland: health care resource use, sick-leaves and comorbidities in occupational health care. *The journal of headache and pain* 20:1–16.
14. Polson M, Williams TD, Speicher LC, Mwamburi M, Staats PS, Tenaglia AT (2020) Concomitant medical conditions and total cost of care in patients with migraine: a real-world claims analysis. *Am J Manag Care* 26:S3-S7.
15. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF (2007) Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology* 68:343–9.
16. Vo P, Fang J, Bilitou A, Laflamme AK, Gupta S. Patients' perspective on the burden of migraine in Europe: a cross-sectional analysis of survey data in France, Germany, Italy, Spain, and the United Kingdom. *The journal of headache and pain* 19:1–11.
17. Hofmann SM, Muehlenweg AM (2016) Gatekeeping in German primary health care-impacts on coordination of care, quality indicators and ambulatory costs. *Universitaet Duisburg-Essen, Competent in Competition and Health, Germany*.
18. Kroneman MW, Maarse H, Van Der Zee J (2006) Direct access in primary care and patient satisfaction: a European study. *Health Policy* 76:72–9.
19. Piccinni C, Cevoli S, Ronconi G, Dondi L, Calabria S, Pedrini A, et al (2019) A real-world study on unmet medical needs in triptan-treated migraine: prevalence, preventive therapies and triptan use modification from a large Italian population along two years. *The journal of headache and pain* 20:1–9.
20. Meyers JL, Davis KL, Lenz RA, Sakai F, Xue F (2019) Treatment patterns and characteristics of patients with migraine in Japan: a retrospective analysis of health insurance claims data. *Cephalalgia* 39:1518–34.
21. Silberstein SD (2015) Preventive migraine treatment. *Continuum: Lifelong Learning in Neurology* 21:973.

Figures

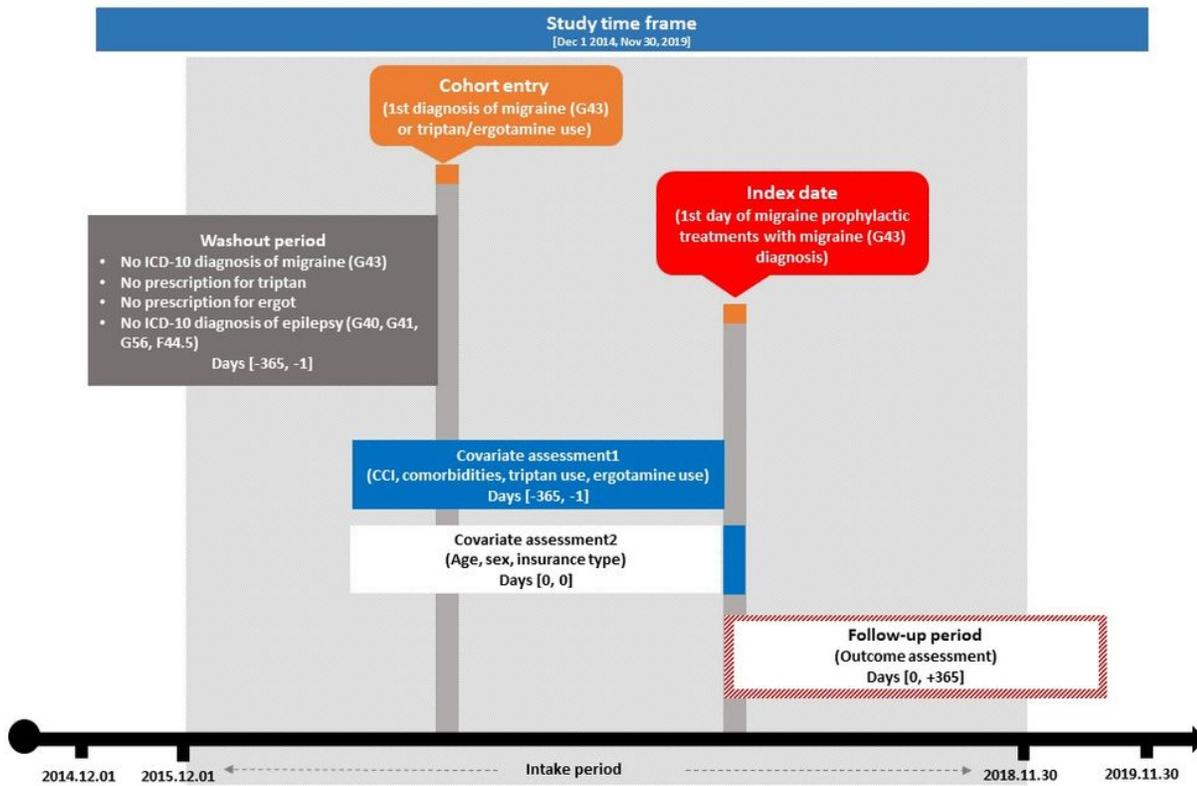


Figure 1

Study scheme

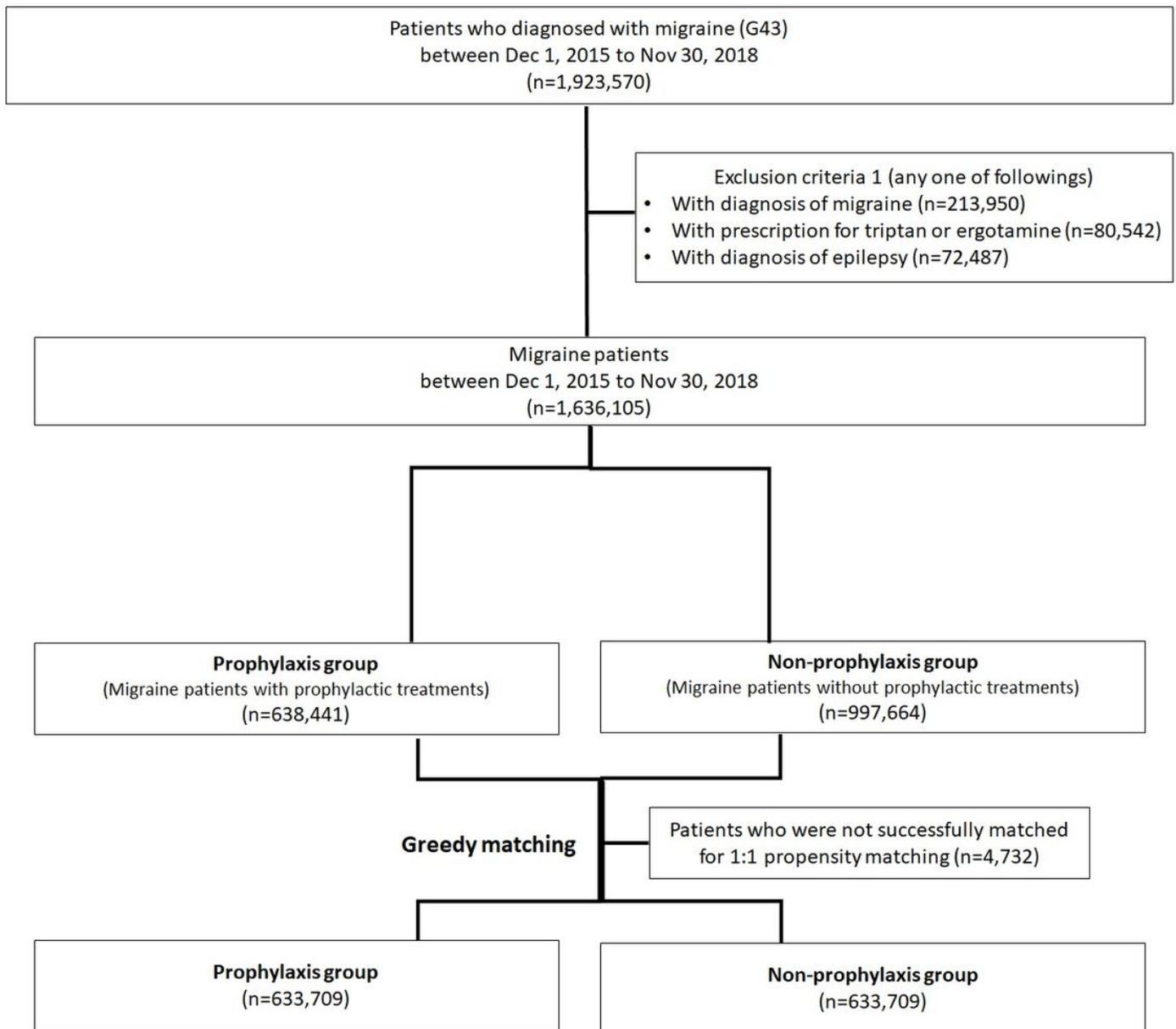


Figure 2

Flow chart of study sample selection