Healthcare Resource Utilization and Costs Associated with Misdiagnosis of Migraine

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Abstract

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BACKGROUND: Migraine is commonly misdiagnosed and undertreated and can be confused with other conditions that also cause facial pain or headache. The most common misdiagnoses for migraine are headache, sinusitis, and cervical pain. It is possible that misdiagnosis may lead to inappropriate and ineffective treatment, unnecessary consultations, and unnecessary diagnostic evaluations for patients, culminating in untreated migraine and an economic burden for patients. This study evaluated healthcare resource utilization (HRCU) and costs among migraine patients with a prior misdiagnosis of migraine versus migraine patients without a prior misdiagnosis.

OBJECTIVE: To assess the impact of a migraine misdiagnosis on all-cause health care resource utilization and all-cause direct healthcare costs in migraine patients.

METHODS: A retrospective claims analysis was conducted using data from the Merative™ Marketscan® Commercial and Medicare Supplemental Databases. Adults with a migraine diagnosis were identified from June 2018 to June 2019, and further classified into a misdiagnosis

cohort or correct diagnosis cohort based on whether or not they had a prior potential misdiagnosis (PM). PM was defined as a prior diagnosis of headache, sinusitis, or cervical pain within 2 years prior to the migraine diagnosis date. HCRU and direct healthcare costs were compared between the two groups, as well as between a subgroup of multiple misdiagnosis and the correct diagnosis group. Outcomes were reported as incidence rate ratios (IRR), adjusted for age, gender, region, plan type, and comorbidities.

RESULTS: In all, 3,841 migraine patients with a prior PM, and 29,147 migraine patients without a prior PM met the inclusion criteria. Patients with PM had a significantly higher rate of inpatient admissions, emergency department (ED) visits, neurologist visits, outpatient visits, and prescription fills per month (IRR: 1.61, 1.92, 5.92, 1.67, and 1.52, respectively, all $p<0.001$) compared to patients without PM. Patients in the misdiagnosed cohort also had a significantly higher rate of healthcare cost accrual for inpatient admissions, ED visits, neurologist visits, outpatient visits, and prescription fills per month (IRR: 3.22, 2.66, 2.28, 2.06, and 1.36, respectively, all $p<0.001$) compared to patients without PM.

CONCLUSION: Our study suggests that migraine patients with a prior PM have significantly higher rates of HCRU, and cost accrual compared to migraine patients without a prior PM. Our results suggest that an incorrect incident migraine diagnosis significantly increases HCRU and costs for migraine patients.

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1. INTRODUCTION

Migraine is a disabling, complex neurological disorder, classified by distinctive features such as attack duration between 4 to 72 hours, unilateral location, pulsating quality, moderate-severe intensity, and associated features (e.g., photophobia, nausea/vomiting).[1] Migraine is one of the most common neurologic diseases and the second most disabling disease worldwide.[2] In 2019, migraine represented 5.4% of total years of healthy life lost due to disability (YLD) [2] globally. In the United States, migraine affects 15.9% of all adults.[3] Migraine is associated with considerable personal and economic burden. In 2016, the annual cost of migraine including indirect, and direct costs in the United States (US) were estimated to be about $36 billion.[4] A more recent study estimates that indirect costs alone were approximately $19.3 billion, without accounting for presenteeism.[5]

Migraine is a clinical diagnosis, not requiring any specific tests or investigations.[6] However, it is estimated that < 5% of persons with migraine in the United States traverse key steps along the care continuum, including consultation with a health care provider (HCP), diagnosis of migraine and prescription of appropriate treatments.[7] Migraine remains underdiagnosed and undertreated, and can be confused with other conditions that also cause facial pain or headache.[8]

Among persons not receiving an accurate diagnosis, the most common misdiagnoses are sinus headache (49.1%), stress headache (43.8%), and tension-type headache (31.4%).[9] In addition to headache, conditions commonly misdiagnosed for migraine are sinusitis and cervical pain.[10,-13] Commonly cited reasons for misdiagnosis and delayed diagnosis include younger age at onset, lower level of education, consultation with different specialists, inadequate migraine knowledge by providers, and late referral to a headache center.[13-15] It is possible that misdiagnosis may lead to inappropriate and ineffective treatment, unnecessary consultations, and unnecessary diagnostic evaluations for patients, culminating in untreated migraine and an economic burden for patients.

Previous literature has reported that migraine imposes a significant direct and indirect cost burden compared to matched non-migraine patients. Furthermore, other studies have compared chronic migraine to episodic migraine, stable vs. worsened migraine, or with insufficient response to specific treatment options. However, the cost and clinical implications of a misdiagnosis remain to be characterized. To our knowledge this study is the first to characterize

the impact of a migraine misdiagnosis on patients' HCRU and costs. The primary objective of this study was to quantify the impact of a migraine misdiagnosis on all-cause HCRU and all-cause direct healthcare costs in migraine patients.

2. METHODS

2.1. Data Source

We conducted a retrospective cohort study using health insurance claims data from the Merative™ Marketscan® Commercial and Medicare Supplemental Databases. Both databases contain individual-level insurance claims data for inpatient, outpatient, and pharmacy claims information and this is used to capture health care resource utilization and direct healthcare costs. This study used data collected from June 1st, 2016, to June 1st, 2020.

2.2. Sample Selection

All Patients

We used inpatient and outpatient claims information to identify patients with an incident migraine diagnosis, defined as having ≥1 inpatient claim or ≥2 outpatient claims on different days with an International Classification of Disease, 10th Revision, Clinical Modification (ICD-10-CM) code for migraine [Appendix A] at any time during the enrollment period from June 1st, 2018, to June 1st, 2019. For each patient, the first claim of the migraine diagnosis, either inpatient or outpatient, during this period, served as the migraine diagnosis date. Within 24-months prior to the migraine diagnosis date, we determined the presence of a prior PM, defined as an ICD-10-CM code for headache, sinusitis, or cervical pain.[7,8,11,16] Migraine patients having ≥1 PM during this period was included in the misdiagnosis cohort, and migraine patients having no PM during this period were included in the correct diagnosis cohort.

All patients must have met the following inclusion criteria: (1) ≥1 inpatient or ≥2 outpatient medical claims on different dates with a diagnosis of migraine (2) ≥18 years old at migraine diagnosis date, (3) continuous enrollment in medical and prescription benefits 24 months prior to migraine diagnosis date. Patients receiving any migraine-specific medications such as triptans, onabotulinumtoxinA, ergots, or calcitonin gene-related peptide inhibitor (CGRP) within 24 months prior to their migraine diagnosis date were excluded from the study to examine

exclusively new or recently diagnosed migraine patients. For the same reason, patients with any prior migraine diagnosis within 24 months prior to their migraine diagnosis date were also excluded.

Misdiagnosis Cohort

Patients in the misdiagnosis cohort must have met the following inclusion criteria (1) ≥1 inpatient or ≥2 outpatient medical claims on different dates with a diagnosis of headache, sinusitis, or cervical pain [Appendix A] within 24 months prior to the migraine diagnosis date. We excluded patients with a headache, cervical pain, or sinusitis during the 12 months post migraine diagnosis, as we determined a patient with a diagnosis of these conditions before and after their migraine diagnosis to be a true diagnosis of a comorbid headache, cervical pain, or sinusitis and not a PM [Figure 1].

Correct Diagnosis Cohort

Patients in the correct diagnosis cohort must have met the following inclusion criteria: (1) no diagnosis of headache, cervical pain, or migraine within the 24 months prior to their migraine diagnosis date.

Multiple Misdiagnosis Cohort

Misdiagnosis cohort patients were further stratified into a multiple diagnosis group (≥2 PM) for secondary analysis.

2.3. Analysis Period

The analysis period was used to estimate all-cause HCRU, all-cause direct healthcare costs, headache-related HCRU, and headache-related healthcare costs. The analysis period was different for each cohort. In the misdiagnosis group, the analysis period was defined as the date of misdiagnosis to the date of migraine diagnosis. Each patient had a different analysis period length, as they had different lengths from PM to correct migraine diagnosis [Figure 4]. For the correct diagnosis group, as there was no misdiagnosis that occurred, the analysis period was defined as the 24-month period prior to the migraine diagnosis date.

2.4. Study Measures and Outcomes

All patients were assessed for baseline demographic and clinical characteristics at the date 24 months prior to their migraine diagnosis date. Demographic characteristics included age, gender, region, insurance type, and plan type. Clinical characteristics were characterized using the Charlson Comorbidity Index (CCI) [Appendix B].

The primary outcomes of interest were HCRU and costs in the following service categories: inpatient admissions, ED visits, neurologist visits, outpatient visits, and pharmacy claims and its associated costs. The number of inpatient admissions was determined by counting the total number of unique admission dates. The number of ED visits, neurologist visits, and outpatient visits were determined by counting the total number of unique service dates for each category. The number of pharmacy claims was determined by counting the total number of unique National Drug Code (NDC) numbers associated with each service date.

Costs associated with these variables were calculated by summing costs in each of the categories during the analysis period. Costs were derived from the 'PAY' variable which represents the total gross provider cost for a service before applying deductibles and copayments.

IRR, more specifically, the rate per person-months for both HCRU and costs was used as our outcome to account for the different analysis periods between our cohorts. The rate of visits and costs were calculated by dividing the total of visits and total costs, respectively, by the amount of time each patient contributed. For secondary analysis, we compared the multiple misdiagnosis cohort to the correct diagnosis cohort and observed the same outcomes as our primary analysis. In addition, we also characterized headache-related HRCU and costs for both the misdiagnosis and multiple misdiagnosis cohorts but did not perform comparative analysis.

2.5. Statistical Analysis

For baseline demographic and clinical characteristics, means and standard deviations (SD) were used to describe continuous variables, and counts (n) and percentages (%) were used to describe categorical variables.

We used generalized linear regression models (GLM) to control for the effects of confounders such as age, gender, region, insurance type, plan type, and comorbidities. To account for different analysis period lengths for each patient, we included a time-offset variable in our

models. All patients in the correct diagnosis cohort had a time-offset of 24 months, while the misdiagnosis cohort's time-offset depended on the time contributed from PM to correct migraine diagnosis. In each patient, the length of PM was rounded up to the nearest month. For example, patients with 5 days of PM would be represented as 1 month in the time-offset variable. This was to account for over-inflated visit or cost rates from patients with short PM periods. A patient with 1-day of PM and 1 inpatient visit would have an inpatient visit rate of 1 visit per person-month, instead of 30 visits per person-month, which would have been the result without our assumption.

We created separate models for inpatient visits, ED visits, neurologist visits, outpatient visits, and pharmacy claims and their associated costs. A negative binomial regression model was used for count data including inpatient visits, ED visits, neurologist visits, outpatient visits and pharmacy claims. Modeling cost data was problematic due to a long right-tail distribution with a heavy right skew due to most patients having zero costs. We used a two-part model to take into account the large proportion of zero cost-subjects for inpatient costs, ED costs, and neurologist costs. Outpatient costs and pharmacy costs were analyzed with a GLM, gamma family, log link. [Appendix D].

Due to our cohort definition, all patients in the misdiagnosis cohort had one additional visit from their PM visit. To account for the fact that the misdiagnosis cohort had one additional visit, we excluded the one misdiagnosis visit and associated costs from the analysis. Other visits and costs that occurred on the same date of the misdiagnosis were not excluded.

We used a two-sided alpha level of 0.05 throughout. All statistical analyses were performed in SAS studio 3.81 (SAS Institute Inc., Cary, NC, USA) and R studio version 3.6.3 (RStudio, PBC, Boston, MA, USA).

This study met the criteria for non-human subjects and did not warrant further review by the University of Washington Human Subjects Division Institutional Review Board (IRB).

3. RESULTS

Study Cohort and Baseline Characteristics

From the MarketScan commercial claims and Medicare supplemental databases 316,917 patients were identified as having an incident diagnosis of migraine. As seen in figure 2, a total of 3,841 patients were identified in the misdiagnosis cohort, and 29,147 patients were identified in the correct diagnosis cohort after applying all the exclusion criteria.

As reported in Table 1, patients in both cohorts were primarily female, with commercial insurance, and subscribed to an EPO/PPO plan or CDHP/HDHP plan. The average age was similar in both cohorts. The highest proportion of patients in both cohorts were from the south region. Baseline characteristics were similar across both cohorts, with the exception of CCI score. The misdiagnosis cohort had a greater proportion of a presence of any comorbidity (CCI score greater than equal to 1, 43.79% compared to 33.87%, respectively). There was a direct association between the proportion of patients misdiagnosed and the length of the misdiagnosis period, with an upward trend, quarter over quarter [Figure 4].

Diagnosis Characteristics

Among providers of interest, primary care providers (PCP) rendered the greatest proportion of misdiagnosis (n = 1691, 44.0%) [Figure 5]. Misdiagnosis occurred at a lower frequency for emergency medicine (n = 258, 6.7%), neurologists (n = 162, 4.2%), and otolaryngology (n = 506, 2.0%). In the misdiagnosed cohort, neurologists most frequently eventually provided the correct diagnosis, whereas in the correct diagnosis cohort, the neurologists diagnosis was not as frequent (23.0% vs. 8.7% respectively). Among diagnosis settings, misdiagnosis occurred most frequently in an outpatient PCP setting (n = 1691, 44%) [Table 2]. As seen with diagnosing providers, we found that in patients with PM, there was a higher proportion of outpatient neurologist as the setting of correct migraine diagnosis compared to patients without PM (22.33% compared to 8.07%, respectively) [Figure 6].

Healthcare Resource Utilization

Patients with PM had a higher rate of HRCU per month compared to those without PM. After adjusting for covariates, the rate inpatient admissions, ED visits, OP visits, and prescription fills were all higher in patients with PM compared to patients without PM. Patients without PM

utilized 1.07 outpatient visits per person-months, which increased by 1.61 times (95% CI 1.62 – 1.72; $p < 0.001$) more often in patients with PM. [Table 3].

Direct Healthcare Costs

Similarly, we found that all-cause direct healthcare costs were higher for patients with PM compared to patients without PM. After adjusting for covariates, the rate of cost accrual for inpatient admissions, ED visits, OP visits, and prescription fills were all higher in patients with PM when compared to patients without PM. We found that the rate at which patients without PM accrued outpatient visit costs per month were $481 per person months, which increased by 2.12 times (95% CI, 1.90 – 2.37; $p<0.001$) for outpatient visit costs in patients with PM.

Multiple Misdiagnosis Subgroup

In the adjusted secondary analysis of the multiple misdiagnosis subgroup (≥2 PM) compared to the correct diagnosis cohort, patients in the multiple misdiagnosis subgroup used healthcare resources more frequently across all service categories [Table 5].

Similarly, in our adjusted analysis of all-cause direct healthcare costs, we found that patients in the multiple misdiagnosis subgroup accrued healthcare costs at a higher rate compared to patients in the correct diagnosis cohorts for all service categories [Table 6].

Headache-Related Healthcare Resource Utilization and Costs

We further examined headache-related HCRU and costs for the misdiagnosis group and the multiple misdiagnosis group. There was no headache-related HCRU in the correct diagnosis cohort due to our cohort definition. Although no comparative analysis was performed, the multiple misdiagnosis group had a higher rate of headache-related neurologist visits compared to the misdiagnosis cohort (0.04 visits per person-months vs. 0.02 visits per person-months). A similar trend was seen with headache cost data. We found that the multiple misdiagnosis group accrued costs at a higher rate in neurologist visits ($84 per person-months compared to $59 per person-months). Although the mean rate of inpatient admissions was similar in both groups (0.14 admissions per person months and 0.14 admissions per person-months), the multiple misdiagnosis group accrued costs at a higher rate for inpatient admissions compared to the misdiagnosis group ($222 per person-months compared to $127 per person-months) [Table 7].

4. DISCUSSION

This study characterized all-cause HRCU and direct healthcare costs in migraine patients with a prior PM compared to migraine patients without a prior PM. This is the first study to examine the cost and clinical implications of a migraine misdiagnosis. This study quantifies implications of misdiagnosis and may inform clinicians regarding the importance of an initial correct diagnosis for incident migraine patients to reduce cost burden, unnecessary investigations, and inadequate care for patients. We found that there was a greater proportion of neurologists that diagnosed migraine for patients with PM than patients without PM. In addition, we found that migraine patients with PM utilized healthcare resources at a significantly higher rate and accrued costs at a faster rate compared to migraine patients without PM, which highlights the increased economic burden for a migraine misdiagnosis. In our subgroup analysis of multiple PM patients, we also found a greater rate of HCRU, and cost accrual compared to patients without PM. We speculate that patients with PM are frequently utilizing health care resources as they don't have the right diagnosis and need more reassessments until they find the correct diagnosis. As migraine is a disease with multiple presentations such as facial pressure, or postnasal drip, an incorrect diagnosis may lead to a specialist visit to the ENT for example, followed by a return to a PCP to be assessed for neck pain, ultimately leading to an increased utilization of the system.

Similar to the results of our study, Blumenfeld et al. demonstrated that healthcare resource utilization decreased with correct management of migraine.[16] This study found there was a significant decrease in health care resource utilization after a neurologist led headache management program. Our study further adds to the conclusion that insufficient management for migraine patients leads to increased health care resource utilization and costs. In addition, our study confirms results of other observational studies of delayed and misdiagnosis of migraine. Similar to other studies[11, 15, 18-19] we found that most patients are initially diagnosed by a non-specialist, or a PCP in their initial visit. This visit may lead to a correct diagnosis, but it's also where a misdiagnosis predominantly occurs. Viana et al. found that of patients that visited a PCP for their migraine, only 28% were correctly diagnosed.[11] Rai et al. found similar results where, of patients that consulted a non-neurologist only 8.3% made a correct diagnosis.[15] These discrepancies can be attributed to a varied knowledge of migraine and migraine diagnosis guidelines by PCPs.[18-20] Different diagnostic settings have different characteristics, where PCPs

may be subject to greater time constraints in diagnosis, and ED may be more concerned about secondary causes of migraine and its risks.

However, this retrospective claim analysis should be interpreted in the context of some limitations. The biggest limitation of this study is in our cohort definition of PM. The patients in the misdiagnosis cohort are not a confirmed misdiagnosis, but rather a potential misdiagnosis. These patients may truly have comorbid conditions that weren't captured in the claims data. A confirmed misdiagnosis by a clinician or patient would provide a more accurate picture of the impact of misdiagnosis, and a direction for future research. To address this limitation, we looked forward one year after the migraine diagnosis date and excluded any patients that had a diagnosis of headache, sinusitis, or cervical pain. We determined that if patients had a diagnosis of these conditions before and after their migraine diagnosis, this would likely not be a misdiagnosis but a true comorbidity. However, we acknowledge that diagnosis codes often get carried forward within claims databases as the provider may not take it off during the next visit. This may have resulted in reducing our misdiagnosis cohort size by excluding too many patients. Another limitation is how we defined the reference group (correct diagnosis group). Individuals without a misdiagnosis in this period may have had quiescent migraine and not needed as much care to begin with and those with a misdiagnosis may inherently have more symptoms. We attempted to address this by capturing only incident migraine patients through our inclusion and exclusion criteria. One of the methods we used to examine only incident migraine patients was by excluding patients with any prior use of migraine medications. However, we acknowledge that medication use can precede diagnosis in some cases, and by excluding these patients, this may not be truly representative of incident migraine patients. Next, this study used a short timeframe of analysis due to the inherent limitations of the database used. Our study looked back 2-years prior to the diagnosis of migraine to determine if there were any misdiagnosis. However, there may have been misdiagnoses that occurred prior to this period that we failed to capture, or a correct diagnosis of migraine that occurred prior to this period as well. Finally, diagnosis of migraine, headache, sinusitis, and cervical pain were determined using ICD-10-CM diagnosis codes, which are subject to data entry error in addition to variability from provider preference and incentive.

Future work is warranted to fully understand the implications of a misdiagnosis in migraine patients. In our study we assessed the implications of a misdiagnosis from the time the patient was misdiagnosed to a correct migraine diagnosis. The next step would be to analyze the implications in the period after the correct migraine diagnosis. The long-term implications of misdiagnosis is another question that remains unanswered that was not addressed in this study due to the limitations of the time length of the data available. It's important to consider that this study only focused on the direct costs associated with a misdiagnosis of migraine. Characterization of the indirect costs such as productivity loss or workdays loss associated with a misdiagnosis would fully capture the personal loss to the patient due to a misdiagnosis.

5. CONCLUSION

The results of this analysis highlight the economic burden associated with a misdiagnosis of migraine. Patients with a prior misdiagnosis had a higher rate of health care resource utilization, and direct health care cost accrual across all service categories.

6. FIGURES

Figure 1: *Schematic of Study Design (Misdiagnosis Cohort)*

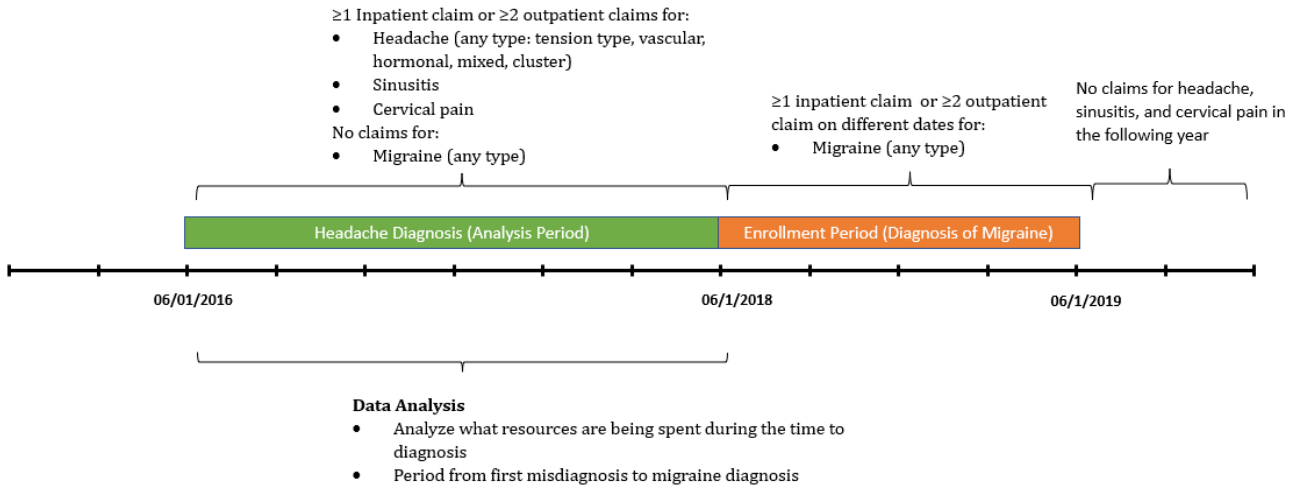


Figure 2: *Schematic of Study Design (Correct Diagnosis Cohort)*

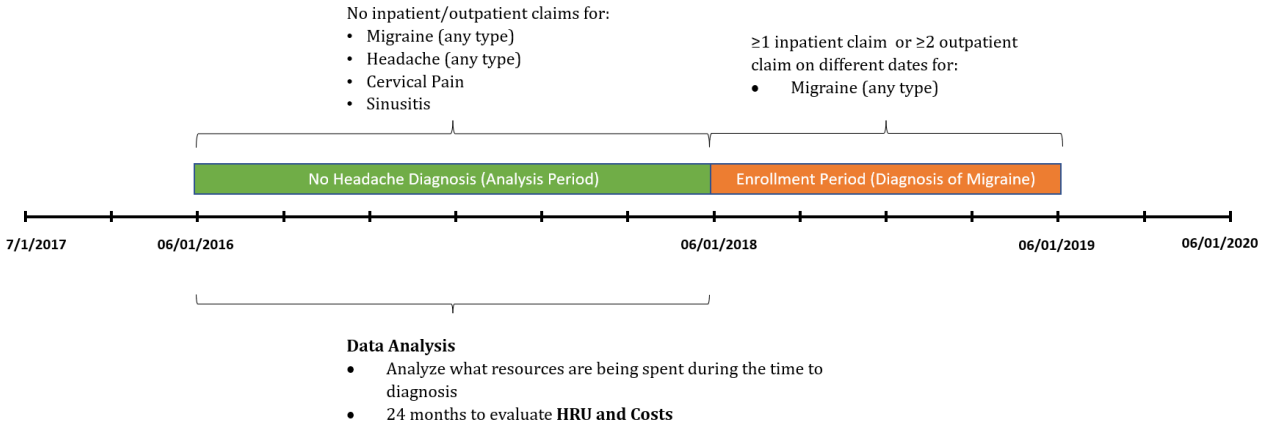


Figure 3: *Study Identification Flowchart*

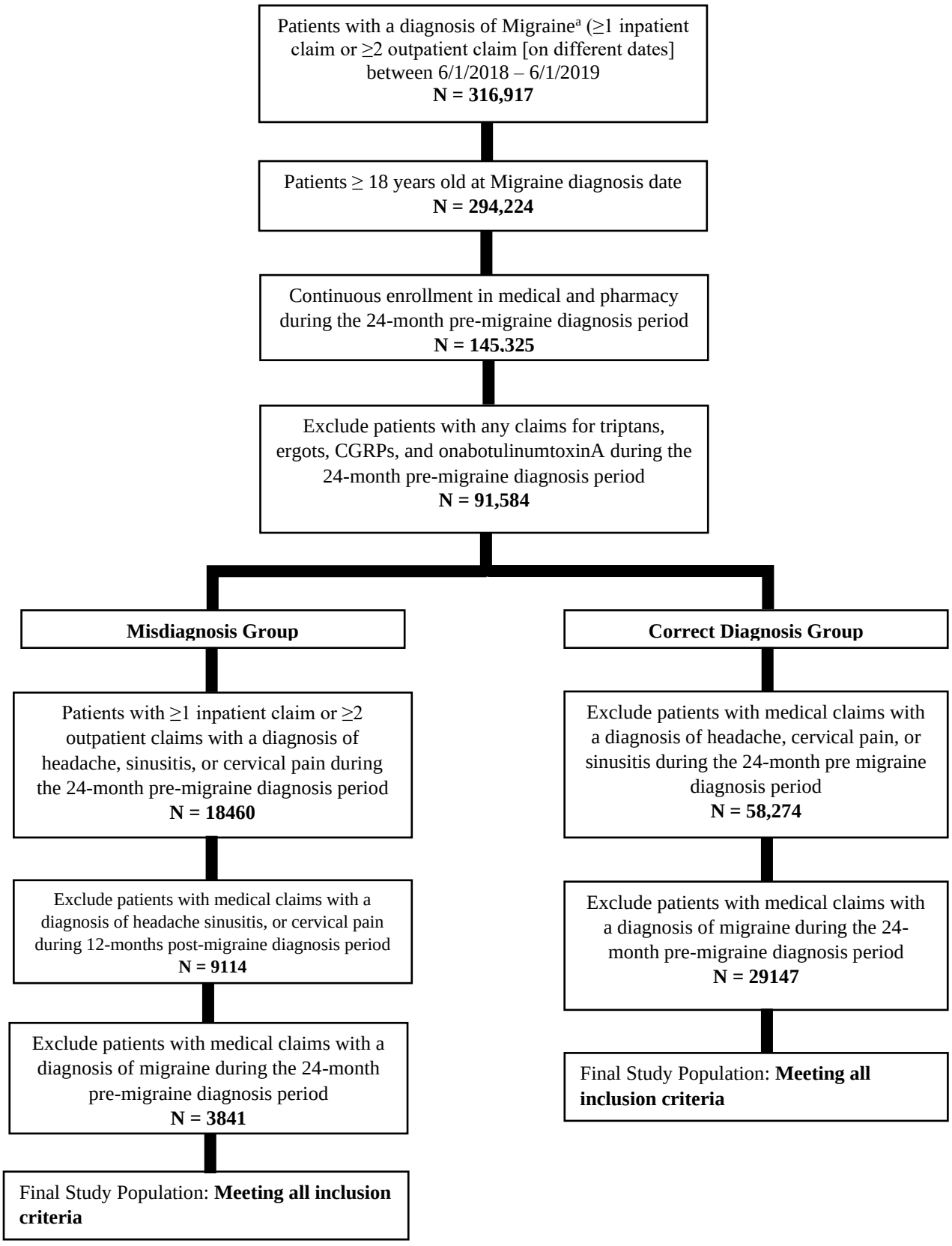


Figure 4: *Misdiagnosis Time by Quarter*

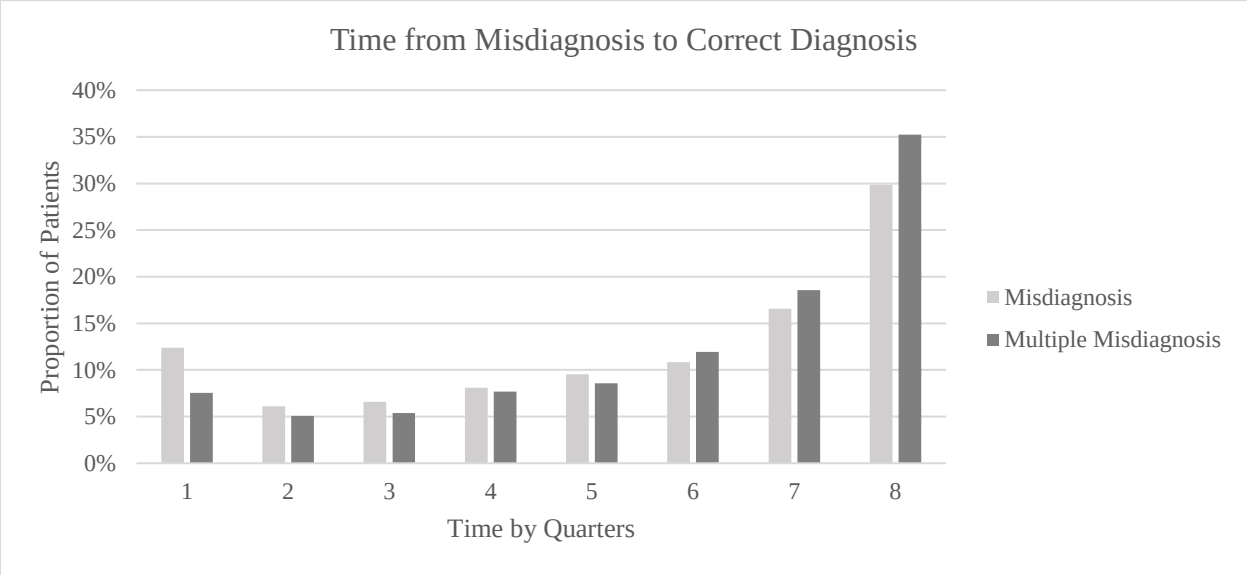


Figure 5: *Migraine Diagnosing Provider*

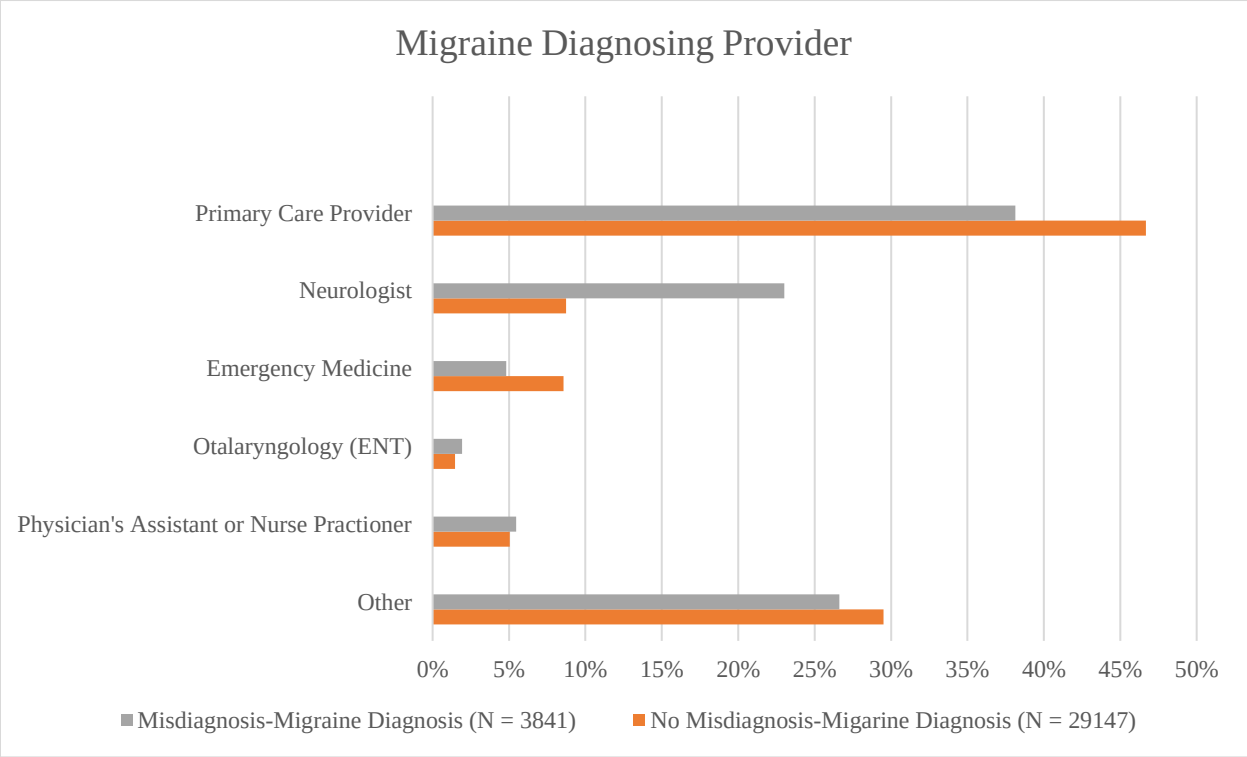
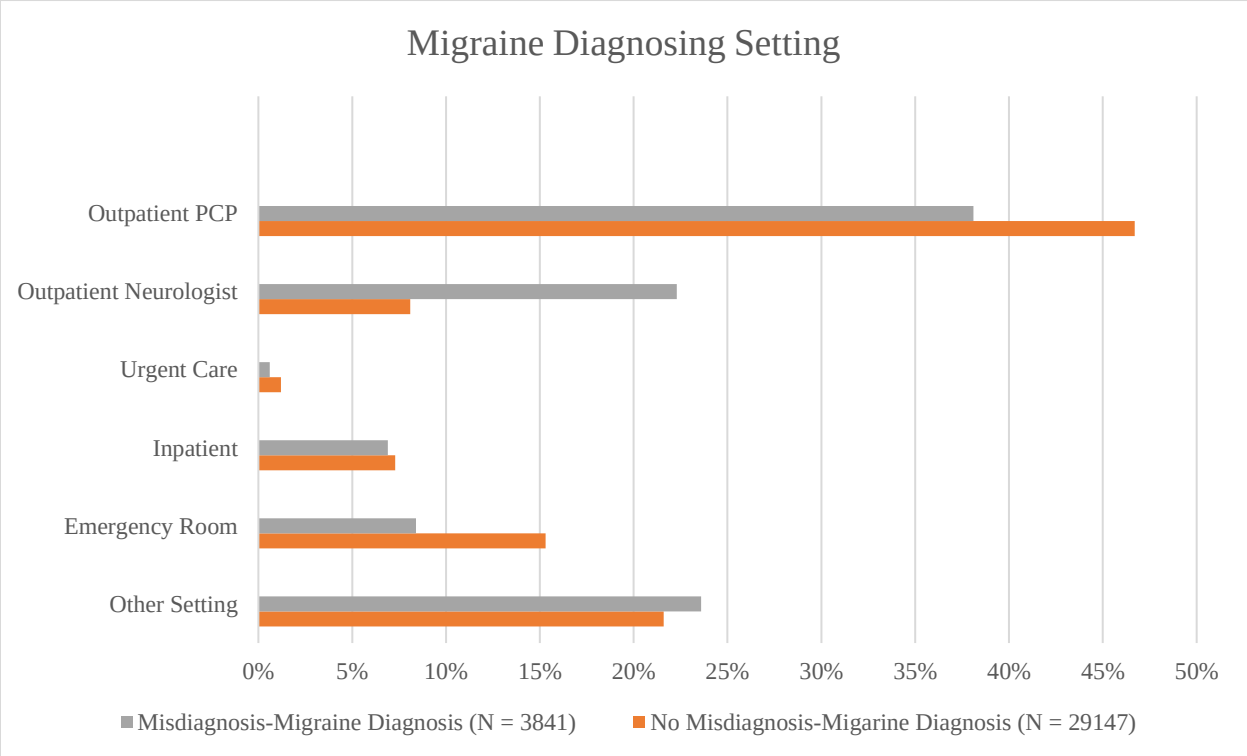


Figure 6: *Migraine Diagnosis Setting*



7. TABLES

Table 1: Baseline Clinical and Demographic Characteristics

Clinical and Demographic Characteristics	All Patients (N = 32988)	Correct Diagnosis (N = 29147)	Misdiagnosis (N = 3841)	Multiple Misdiagnosis Subgroup (N = 1482)
	n (%)	n (%)	n (%)	n (%)
Age (years)±, mean (SD)	40.53 (14.00)	40.57 (14.01)	40.14 (13.95)	41.07 (14.14)
Sex±				
Male	7346 (22.%)	6635 (22.8%)	711 (18.51%)	290 (19.6%)
Female	25642 (77.7%)	22512 (77.2%)	3130 (81.548%)	1192 (80.4%)
Insurance Type				
Commercial	32357 (98.1%)	28611 (98.2%)	3746 (97.53%)	1441 (97.2%)
Medicare	631 (1.9%)	536 (1.8%)	95 (2.547%)	41 (2.8%)
Plan Type±				
Comprehensive	1682 (5.1%)	1491 (5.1%)	191 (5.04.97%)	62 (4.2%)
EPO/PPO	17370 (52.7%)	15303 (52.5%)	2067 (53.81%)	809 (54.6%)
HMO	4097 (12.4%)	3667 (12.6%)	430 (11.219%)	144 (9.7%)
POS	1486 (4.5%)	1303 (4.5%)	183 (4.876%)	75 (5.1%)
CDHP/HDHP	7282 (22.1%)	6440 (22.1%)	842 (21.92%)	348 (23.5%)
POS with capitation	408 (1.2%)	357 (1.2%)	51 (1.32%)	15 (1.0%)
Unknown	663 (2.0%)	586 (2.0%)	77 (2.00%)	8 (2.0%)
Region±				
Northeast	5428 (16.5%)	4828 (16.6%)	600 (15.62%)	218 (14.7%)
North Central	7032 (21.3%)	6220 (21.3%)	812 (21.14%)	328 (22.1%)
South	14245 (43.2%)	12432 (42.7%)	1813 (47.20%)	699 (47.2%)
West	4553 (13.8%)	4017 (13.8%)	536 (13.95%)	210 (14.2%)
Unknown	1730 (5.2%)	1650 (5.7%)	80 (2.108%)	27 (1.8%)
CCI±				
0	21436 (65.0%)	19277 (66.1%)	2159 (56.21%)	787 (53.1%)
1	7312 (22.2%)	6308 (21.6%)	1004 (26.13%)	391 (26.4%)
2	2162 (6.6%)	1856 (6.4%)	306 (8.07.96%)	129 (8.7%)
3+	2078 (6.3%)	1706 (5.9%)	372 (9.768%)	175 (11.8%)

Length of Misdiagnosis (Quarters)				
0	29147 (88.4%)	29147 (100.0%)	0 (0.0%)	0 (0%)
1	476 (1.4%)	0 (0.0%)	476 (12.439%)	112 (7.6%)
2	234 (0.7%)	0 (0.0%)	234 (6.109%)	75 (5.1%)
3	253 (0.8%)	0 (0.0%)	253 (6.658%)	80 (5.4%)
4	311 (0.9%)	0 (0.0%)	311 (8.109%)	114 (7.7%)
5	367 (1.1%)	0 (0.0%)	367 (9.655%)	127 (8.6%)
6	416 (1.3%)	0 (0.0%)	416 (10.83%)	177 (11.9%)
7	637 (1.9%)	0 (0.0%)	637 (16.658%)	275 (18.6%)
8	1147 (3.5%)	0 (0.0%)	1147 (29.986%)	522 (32.2%)

SD = standard deviation; EPO = exclusive provider organization; PPO = preferred provider organization; HMO = health maintenance organization; POS = point or service; CDHP = consumer directed health plan; HDHP = high deductible health plan; CCI = charlson comorbidity index

[±]*Variable was used in the generalized linear model for adjusted analysis*

Table 2: Diagnosis Characteristics

Diagnosis Characteristics (Correct Migraine Diagnosis and Misdiagnosis)	All Patients (N = 32988)	Correct Diagnosis (N = 29147)	Misdiagnosis (N = 3841)	Multiple Misdiagnosis Subgroup (N = 1482)
	n (%)	n (%)	n (%)	n(%)
Migraine Diagnosing Provider				
Neurologist	3432 (10.4%)	2548 (8.7%)	884 (23.0%)	416 (28.1%)
Emergency Medicine	2684 (8.1%)	2499 (8.6%)	185 (4.8%)	49 (3.3%)
Otolaryngology (ENT)	501 (1.5%)	426 (1.5%)	75 (1.9%)	34 (2.3%)
PA or NP (unspecified specialty)	1682 (5.1%)	1472 (5.1%)	210 (5.5%)	76 (5.1%)
PCP*	15069 (45.7%)	13604 (46.7%)	1465 (38.1%)	506 (34.1%)
Other**	9620 (29.2%)	8598 (29.5%)	1022 (26.6%)	401 (27.1%)
Migraine Diagnosis Setting				
Emergency Room	4737 (14.4%)	4415 (15.3%)	322 (8.4%)	79 (5.3%)
Inpatient	2378 (7.2%)	2113 (7.3%)	265 (6.9%)	101 (6.8%)
Urgent Care	375 (1.1%)	352 (1.2%)	23 (0.6%)	9 (0.6%)
Outpatient Neurologist	3212 (9.7%)	2354 (8.1%)	858 (22.3%)	406 (27.4%)
Outpatient PCP	15069 (45.7%)	13604 (46.7%)	1465 (38.1%)	401 (27.1%)
Other Setting***	7217 (21.9%)	6309 (21.6%)	908 (23.6%)	486 (32.8%)
Misdiagnosis Diagnosing Provider				
Neurologist	-	-	162 (4.2%)	88 (5.9%)
Emergency Medicine	-	-	258 (6.7%)	101 (6.8%)
Otolaryngology (ENT)	-	-	78 (2.0%)	31 (2.1%)
PA or NP (unspecified specialty)	-	-	206 (5.4%)	88 (5.9%)
PCP*	-	-	1691(44.0%)	602 (40.6%)
Other**	-	-	1446 (37.6%)	572 (38.6%)
Misdiagnosis Diagnosis Setting				
Emergency Room	-	-	438 (11.4%)	168 (11.3%)
Inpatient Hospital	-	-	93 (2.4%)	35 (2.4%)
Urgent Care	-	-	161 (4.2%)	44 (3.0%)
Outpatient Neurologist	-	-	148 (3.9%)	80 (5.4%)
Outpatient PCP	-	-	1691 (44.0%)	602 (40.6%)
Other Outpatient Provider***			1310 (34.1%)	553 (37.3%)

PA = Physician's Assistant, NP = Nurse Practitioner, PCP = Primary Care Provider, ENT = Ear, Nose, and Throat

**PCP: medical doctor, internal medicine, multispecialty physician group, family practice, geriatric medicine, geriatric hospital, gynecologist*

***Other providers: pain medicine, rheumatologist, neurosurgery, head and neck surgery, and other non-specified specialties*

***Other Setting(diagnosing setting): other/unknown, skilled nursing facility, nursing facility, hospice, patient home, assisted living, walk-in retail health clinic*

Table 3: All-Cause Healthcare Resource Utilization: Any Misdiagnosis vs. Correct Diagnosis

All-Cause Healthcare Resource Utilization	Total (N = 32988)	Misdiagnosis (N = 3841)	Correct Diagnosis (N = 29147)	Incidence Rate Ratio	Incidence Rate Ratio	95% Confidence Interval
	Mean (SD)	Mean (SD)	Mean (SD)	Unadjusted	Adjusted	Adjusted
Inpatient Admissions[¥] (per person-months)	0.01 (0.06)	0.03 (0.13)	0.01 (0.03)	2.90***	1.61***	[1.47 – 1.74]
ED Visits[¥] (per person-months)	0.04 (0.10)	0.09 (0.22)	0.03 (0.07)	2.76***	1.92***	[1.82 – 2.03]
Neurologist Visits[¥] (per person-months)	0.02 (0.09)	0.09 (0.23)	0.01 (0.049)	7.42***	5.92***	[5.37 – 6.54]
Outpatient Visits[¥] (per person-months)	1.18 (1.25)	1.91 (1.68)	1.07 (1.14)	1.78***	1.67***	[1.62 – 1.72]
Prescriptions Filled [¥] (per person-months)	1.52 (1.77)	2.25 (2.20)	1.42 (1.68)	1.58***	1.52***	[1.47 – 1.57]

**p<0.05, **p<0.01, ***p<0.001*

[±]*Adjusted for age, gender, region, plan type, Charlson comorbidity score*

[¥]*GLM, negative binomial distribution, log-link*

Table 4: All-Cause Direct Healthcare Costs: Any Misdiagnosis vs. Correct Diagnosis

All-Cause Direct Healthcare Costs	Total (N = 32988)	Misdiagnosis (N = 3841)	Correct Diagnosis (N = 29147)	Incidence Rate Ratio	Incidence Rate Ratio	Confidence Interval
	Mean (SD)	Mean (SD)	Mean (SD)	Unadjusted	Adjusted	Adjusted
Inpatient Admissions Cost[§] (per person-months)	$334 ($2,428)	$943 ($6192)	$254 ($1252)	3.71***	3.22***	[2.79 – 3.73]
ED Visit Cost[§] (per person-months)	$59 ($249)	$146 ($622)	$48 ($136)	3.03***	2.66***	[2.44 – 2.91]
Neurologist Visit Cost[§] (per person-months)	$7 ($111)	$26 ($197)	$4 ($94)	5.46***	2.28***	[1.55 – 3.24]
Outpatient Visit Cost[Ω] (per person-months)	$545 ($1,574)	$1,035 ($2,685)	$481 ($1,349)	2.15***	2.06***	[1.91 – 2.23]
Prescriptions Cost[Ω] (per person-months)	$187 ($999)	$266 ($2,04)	$177 ($763)	1.50**	1.36***	[1.13 – 1.63]

**p<0.05, **p<0.01, ***p<0.001*

[‡]*Adjusted for age, gender, region, plan type, Charlson comorbidity score*

[§]*Two-part model; part-1: logit, part-2: gamma with log-link*

[Ω]*GLM, gamma distribution, log-link*

Table 5: All-Cause Healthcare Resource Utilization: Multiple Misdiagnosis vs. Correct Diagnosis

All-Cause Healthcare Resource Utilization (Multiple Misdiagnosis Subgroup)	Multiple Misdiagnosis (N = 1482)	Correct Diagnosis (N = 29147)	Incidence Rate Ratio	Incidence Rate Ratio	95% Confidence Interval
	Mean (SD)	Mean (SD)	Unadjusted	Adjusted	Adjusted
Inpatient Admissions[¥] (per person-months)	0.035 (0.16)	0.010 (0.03)	3.50***	1.68***	[1.49 – 1.90]
ED Visits[¥] (per person-months)	0.102 (0.23)	0.0345 (0.07)	2.95***	2.17***	[2.00 – 2.35]
Neurologist Visits[¥] (per person-months)	0.11 (0.24)	0.012 (0.049)	9.16***	7.75***	[6.72 – 8.98]
Outpatient Visits[¥] (per person-months)	2.19 (1.85)	1.07 (1.14)	2.04***	1.87***	[1.76 – 1.99]
Prescriptions Filled [¥] (per person-months)	2.46 (2.31)	1.42 (1.68)	1.73***	1.61***	[1.49 – 1.73]

**p<0.05, **p<0.01, ***p<0.001*

[±]Adjusted for age, gender, region, plan type, Charlson comorbidity score

[¥]GLM, negative binomial distribution, log-link

Table 6: All-Cause Direct Healthcare Costs: Multiple Misdiagnosis vs. Correct Diagnosis

All-Cause Direct Healthcare Costs (Multiple Misdiagnosis Subgroup)	Multiple Misdiagnosis (N = 1482)	Correct Diagnosis (N = 29147)	Incidence Rate Ratio	Incidence Rate Ratio	Confidence Interval
	Mean (SD)	Mean (SD)	Unadjusted	Adjusted	Adjusted
Inpatient Admissions Cost[§] (per person-months)	$862 ($4098)	$254 ($1251)	3.39***	2.94***	[2.39 – 3.62]
ED Visit Cost[§] (per person-months)	$172 ($868)	$48 ($136)	3.56***	2.82***	[2.47 – 3.22]
Neurologist Visit Cost[§] (per person-months)	$33 ($258)	$5 ($94)	6.93***	2.14***	[1.28 – 3.51]
Outpatient Visit Cost[Ω] (per person-months)	$1126 ($2321)	$481 ($1,349)	2.34***	2.12***	[1.90 – 2.37]
Prescriptions Cost[Ω] (per person-months)	$329 ($3070)	$177 ($763)	1.86*	1.46***	[1.11 – 1.92]

**p<0.05, **p<0.01, ***p<0.001*

[±]*Adjusted for age, gender, region, plan type, Charlson comorbidity score*

[§]*Two-part model; part-1: logit, part-2: gamma with log-link*

[Ω]*GLM, gamma distribution, log-link*

Table 7: Headache-Related Healthcare Resource Utilization

Headache-Related Health Care Resource Utilization			Headache-Related Cost		
	Misdiagnosis	Multiple Misdiagnosis (≥2 Misdiagnosis)		Misdiagnosis	Multiple Misdiagnosis (≥2 Misdiagnosis)
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)
Headache-Related Inpatient Admissions (per person-months)	0.01 (0.09)	0.01 (0.09)	**Headache-Related Inpatient Admission Cost (per person-months)**	$11 ($186)	$19 ($279)
Headache-Related ED Visits (per person-months)	0.04 (0.20)	0.04 (0.19)	**Headache-Related ED Visit Cost (per person-months)**	$59 ($395)	$59 ($417)
Headache-Related Neurologist Visits (per person-months)	0.02 (0.11)	0.04 (0.14)	**Headache-Related Neurologist Visit Cost (per person-months)**	$5 ($30)	$7 ($26)
Headache-Related Outpatient Visits (per person-months)	0.33 (0.57)	0.37 (0.56)	**Headache-Related Outpatient Visit Cost (per person-months)**	$139 ($612)	$143 ($430)

***Headache-related visit: any visit associated with an ICD-10-CM diagnosis of headache*

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9. APPENDICES

Appendix A: ICD-10-CM Diagnosis Codes

ICD-10-CM Code	Diagnosis	Code Description
Migraine		
G43.XX	**Migraine**	**Migraine**
G43.00	**Episodic Migraine**	Migraine without aura, not intractable
G43.001		Migraine without aura, not intractable with status migrainosus
G43.009		Migraine without aura, not intractable without status migrainosus
G43.011		Migraine without aura, intractable, with status migrainosus
G43.019		Migraine without aura, intractable without status migrainosus
G43.101		Migraine with aura, not intractable with status migrainosus
G43.109		Migraine with aura, not intractable without status migrainosus
G43.111		Migraine with aura, intractable with status migrainosus
G43.119		Migraine with aura, intractable without status migrainosus
G43.809		Other migraine, not intractable, without status migrainosus
G43.A0		Cyclical vomiting, not intractable
G43.B0		Ophthalmoplegic migraine, not intractable
G43.C0		Periodic headache syndromes in child or adult, not intractable
G43.D0		Abdominal migraine, not intractable
G43.819		Other migraine, not intractable, without status migrainosus
G43.A1		Cyclical vomiting, intractable
G43.B1		Ophthalmoplegic migraine, intractable
G43.C1		Periodic headache syndromes in child or adult, intractable
G43.D1		Abdominal migraine, intractable
G43.801		Other migraine, not intractable, with status migrainosus
G43.811		Other migraine, intractable, with status migrainosus
G43.409		Hemiplegic migraine, not intractable without status migrainosus
G43.419		Hemiplegic migraine, intractable without status migrainosus
G43.401		Hemiplegic migraine, not intractable with status migrainosus
G43.411		Hemiplegic migraine, intractable with status migrainosus
G43.829		Menstrual migraine, not intractable, without status migrainosus
G43.839		Menstrual migraine, intractable, without status migrainosus
43.821		Menstrual migraine, not intractable, with status migrainosus
G43.831		Menstrual migraine, intractable, with status migrainosus
G43.509		Persistent migraine aura without cerebral infarction, not intractable, without status migrainosus
G43.501		Persistent migraine aura without cerebral infarction, without mention of intractable migraine with status migrainosus
G43.511		Persistent migraine aura without cerebral infarction, with intractable migraine, so stated, with status migrainosus
G46.609		Persistent migraine aura with cerebral infarction, without mention of intractable migraine, without mention of status migrainosus
G43.619		Persistent migraine aura with cerebral infarction, with intractable migraine, so stated, without mention of status migrainosus
G43.601		Persistent migraine aura with cerebral infarction, without mention of intractable migraine with status migrainosus
G43.611		Persistent migraine aura with cerebral infarction, with intractable migraine, so stated, with status migrainosus
G43.809		Other forms of migraine, without mention of intractable migraine without mention of status migrainosus

G43.819		Other forms of migraine, with intractable migraine, so stated, without mention of status migrainosus
G43.801		Other forms of migraine, without mention of intractable migraine, with status migrainosus
G43.811		Other forms of migraine, with intractable migraine, so stated, with status migrainosus
G43.909		Migraine, unspecified, not intractable, without status migrainosus
G43.919		Migraine, unspecified, intractable, without status migrainosus
G43.901		Migraine, unspecified, not intractable, with status migrainosus
G43.911		Migraine, unspecified, intractable, with status migrainosus
G43.70	**Chronic Migraine**	Chronic migraine without aura, without mention of intractable migraine
G43.709		Chronic migraine without aura, without mention of intractable migraine without mention of status migrainosus
G43.719		Chronic migraine without aura, with intractable migraine, so stated, without mention of status migrainosus
G43.701		Chronic migraine without aura, without mention of intractable migraine, with status migrainosus
G43.71		Chronic migraine without aura, with intractable migraine
G43.711		Chronic migraine without aura, with intractable migraine, so stated, with status migrainosus
Headache		
G44.209	**Headache**	Tension-type headache, unspecified, not intractable
G44.219		Episodic tension-type headache, not intractable
G44.221		Chronic tension-type headache, intractable
G44.229		Chronic tension-type headache, not intractable
G44.89		Other headache syndrome
G44.001		Cluster headache syndrome, unspecified, intractable
G44.009		Cluster headache syndrome, unspecified, not intractable
G44.011		Episodic cluster headache, intractable
G44.019		Episodic cluster headache, not intractable
G44.1		Vascular headache, not elsewhere classified
R51.		Headache
Sinusitis		
J01.XX	**Sinusitis**	Acute sinusitis
J32.XX		Chronic Sinusitis
Cervical Pain		
M54.2	Cervicalgia	Cervical Pain

Appendix B: Charlson Comorbidity Index Comorbidities

Comorbidity	Score
Prior myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Rheumatologic disease	1
Peptic ulcer disease	1
Mild liver disease	1
Diabetes	1
Cerebrovascular event	2
Moderate-to-severe renal disease	2
Diabetes with chronic complications	2
Cancer without metastases	2
Leukemia	2
Lymphoma	2
Moderate or severe liver disease	3
Metastatic solid tumor	6
Acquired Immune-Deficiency Syndrome	6

Appendix C: Dataset Variables

Variable	Description
ADMDATE	Date of Admission
AGE	Age of Patient
DAYSUPP	Days Supply
DISDATE	Date of Discharge
DX1-5	Diagnosis 1-5
ENROLID	Enrollee ID
NDCNUM	National Drug Code
PAY	Payment
PDX	Diagnosis Principle
PLANTYP	Plan Indicator
REGION	Region
SEX	Gender of Patient
STDPROV	Provider Type
STDPLAC	Place of Service
SVCDATE	Service Date

Appendix C: Healthcare Resource Utilization and Costs Regression Models

Outcome Category	Captured by	Data Type	Distribution of Incidence rates	Measure of outcome	Stat test for unadjusted outcomes	Regression GLM (family, link)
Health Care Resource Utilization						
Inpatient Admissions	# of visits / person-day (months)	Count	Negative Binomial	Incidence Rate Ratio	2 sample Poisson rate test	GLM (negative binomial, log)
Emergency Department Visits						
Neurologist Visits						
Outpatient visits						
Prescription Fills						
Costs						
Inpatient Admission Costs	$'s spent / person-day (months)	Continuous	Gamma	Incidence Rate Ratio	2 sample t-test for means	2-Part Model
Emergency Department Visits Costs						2-Part Model
Neurologist Visits Cost						2-Part Model
Outpatient Visits Costs						GLM (gamma, log)
Prescription Fills Cost						GLM (gamma, log)