Retrospective Study

Association of Higher Migraine Risk Among Female and Younger Chronic Osteomyelitis Patients: Evidence from a Taiwan Cohort of One Million

Jiunn-Horng Chen, MD, PhD[1,2], Shih-Chi Wu, MD[2,3], Chih-Hsin Muo, MSc[4,5], Chia-Hung Kao, MD[2,6], Chun-Hung Tseng, MD[2,7], and Chon-Haw Tsai, MD, PhD[2,7]

From: [1]Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan; [2]School of Medicine, College of Medicine, China Medical University, Taichung, Taiwan; [3]Trauma and Emergency Center, China Medical University Hospital, Taichung, Taiwan; [4]Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan; [5]College of Medicine, China Medical University, Taichung, Taiwan; [6]Department of Nuclear Medicine and PET Center, China Medical University Hospital, Taichung, Taiwan; [7]Department of Neurology, China Medical University Hospital, Taichung, Taiwan

Address Correspondence:
Chun-Hung Tseng, MD
Department of Neurology, China Medical University Hospital
2 Yuh-Der Road
Taichung 40447, Taiwan
E-mail: d8333@mail.cmuh.org.tw

Disclaimer: Drs. Jiunn-Horng Chen and Shih-Chi Wu contributed equally to this work. This study is supported partly by Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW104-TDU-B-212-113002), China Medical University Hospital, Academia Sinica Taiwan Biobank, Stroke Biosignature Project (BM104010092), NRPB Stroke Clinical Trial Consortium (MOST 103-2325-B-039-006), and CMU under the Aim for Top University Plan of the Ministry of Education, Taiwan. The grant funders had no role in the design of the study, management of the data, and decision of the manuscript submission for publication.

Manuscript received: 05-03-2017
Revised manuscript received: 09-09-2017
Accepted for publication: 09-22-2017

Free full manuscript: www.painphysicianjournal.com

Background: Inflammation may trigger migraine development through neurovascular reactions in the brain. Most of the migraine patients, particularly the younger ones, do not have any risk factors for this disease. Hence, we assessed whether chronic osteomyelitis (COM), a chronic inflammatory disease, increases the risk of migraine.

Objective: We aim to evaluate the risk of migraine among female and middle-age COM patients with a large patient sample.

Study Design: A retrospective cohort study was conducted in this study.

Setting: The data used in this study were extracted from the Taiwan National Health Insurance (NHI) Research Database.

Methods: A study group with 2,012 COM patients and 8,048 randomly chosen gender- and age-matched controls were chosen from the Taiwan NHI Research Database (NHIRD) from the start of 2000 to the end of 2009. The risk of migraine was estimated with Cox proportional regression model. Both COM and control groups were followed-up until the occurrence of migraine during the study period (2000–2011). Prevalent covariates, such as age, gender, hypertension, diabetes, hyperlipidemia, stroke, coronary artery disease, depression, anxiety, sleep disorder, bipolar disorder, and epilepsy, were included for further evaluation. The hazard ratio (HR) of migraine was measured with Cox proportional hazard regression model. The primary outcome was the overall migraine risk among COM patients, and the secondary outcome was the migraine risk among COM patients lacking the comorbidities. Additional outcomes included migraine risk among COM patients in different age and gender subgroups.

Results: The overall migraine risk was increased in COM patients (adjusted hazard ratio [aHR] 1.74, 95% confidence interval [CI] 1.14–2.65). Even without any prevalent comorbidities, COM patients still exhibited an increased risk of migraine (aHR 2.05, 95% CI 1.06–3.97) than the controls did. Moreover, this risk was relatively higher in COM patients aged < 40 and 45–54 years (aHR 2.07, 95% CI 0.97–4.46 and aHR 2.11, 95% CI 0.97–4.57, respectively) than in their counterparts. Female COM patients had a relatively higher migraine risk (aHR 1.85, 95% CI 1.05–3.24) than male patients did (aHR 1.68, 95% CI 0.89–3.16).

Limitations: The messages about personal behaviors were unavailable in the Taiwan NHIRD. Other neurovascular risk factors that might increase migraine cannot be excluded completely in this research.

Conclusion: An association between COM and increased risk of migraine was shown in this study. The results suggest that COM is a significant migraine predictor, and thus imply the necessity for rigorous migraine prevention in COM patients, especially female and younger ones.

Key words: Inflammation, migraine, chronic osteomyelitis, Taiwan National Health Insurance Research Database

Pain Physician 2018; 21:E149-E156

Migraine is one of the most common disorders of the nervous system and might cause different levels of disability (1-4). The early detection of risk factors is critical for preventing migraine and thereby reducing migraine-related socioeconomic burdens and public health issues (1-4). Migraine could be caused by certain mechanisms through immune responses (5-8), inflammatory processes (5,6,8), or neurovascular reactions (5-7) that inflict visual sensitivity and cause vasogenic pain characteristics of migraine. Similarly, the risk of migraine might increase with certain traditional neurovascular risk factors, such as hypertension (9-12), diabetes (9-12), hyperlipidemia (9,10,12), stroke (4,9-11,13), and coronary artery disease (CAD) (14-16), as well as some neuropsychological factors, such as depression (3,4,6,10-13), anxiety (3,4,6,12,13), sleep disorder (4,6,11-13), bipolar disorder (15,16), and epilepsy (14-16). The prevalence of migraine ranges from 10–25% (1-3,17-19), and despite several efforts, no clear etiology can be determined for most patients with migraine (4,17,18). Therefore, further meticulous research is required to explore the risk factors for migraine in addition to the well-manifested ones such as hypertension (9-12), diabetes (9-12), hyperlipidemia (9,10,12), stroke (4,9-11,13), CAD (14-16), depression (3,4,6,10-13), anxiety (3,4,6,12,13), sleep disorder (4,6,11-13), bipolar disorder (15,16), and epilepsy (14-16).

Through the neurovascular effects of chronic inflammatory processes on the brain, migraine has been reported in certain infectious diseases, such as Helicobacter pylori (HP) (20,21) and human immunodeficiency virus (HIV) infections (22,23), and certain autoimmune disorders, such as multiple sclerosis (MS) (24,25) and systemic lupus erythematosus (SLE) (25,26). The pathogenic effect of chronic inflammation on the brain is considered as an evidenced mechanism in the pathogenesis of migraine (5,6,8). Nevertheless, the extent to which these diseases delineate the contributions of chronic inflammations in developing migraine through possible inflammation-related neurovascular effects on the brain, in addition to the conventional risk factors, such as hypertension, diabetes, hyperlipidemia, stroke, depression, anxiety, and sleep disorder, remains unclear.

Chronic osteomyelitis (COM), a disorder characterized by severe chronic inflammation due to bone infection, may persist for weeks, months, or even years. COM may continue to exhibit pathogenic features with strong inflammatory activity at the infection sites because of the generation of abscesses, bone debris, and sinus tracts (27). In our prior studies, we found that COM, a well-known chronic inflammatory disease, was associated with the risk of some cardiovascular diseases, such as ischemic stroke (28), hemorrhagic stroke (29), CAD (30), and atrial fibrillation (31), as well as a lot of neuropsychological disorders, e.g., dementia (32), depression (33), and epilepsy (34). Although COM is a rare disease, it is interesting to us to explore the correlation between COM and other diseases and to further imply the necessary disease prevention in the COM patients. To our knowledge, rare studies have investigated the association between COM and the development of migraine. In the present retrospective cohort study, we used the data of enrollees from the National Health Insurance (NHI) claims database available in Taiwan to determine the association between COM and the risk of migraine in a cohort of one million enrollees for a 12-year period from January 1, 2000 to December 31, 2011.

Methods

Data Source

This retrospective cohort study used the beneficiary list of Longitudinal Health Insurance Database (LHID), with one million enrollees extracted from the National Health Insurance (NHI) Research Database (NHIRD) in the period of 2000–2011 (28-34). The Taiwan NHI program was set up in 1995, and it covers more than 98% of the total 23 million Taiwanese people. Patient identification numbers in the NHI were scrambled before data collection. Therefore, informed consent from the patients included in the study was not necessary. The present study was approved by the Research Ethics Committee at China Medical University (CMUH104-REC2-115). The diseases evaluated in the present study were coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

Study Patients

From the LHID claims database, we used the data of enrollees who were newly diagnosed with COM (ICD-9-CM code 730.1) from January 1, 2000 to December 31, 2009, but had no medical history of migraine before their diagnoses of COM. Only those who had the COM diagnoses for at least 3 times during the study period (2000–2011) were thought to have COM. The dates of their first diagnosis of COM were defined as the entry dates. Finally, 2,012 patients with COM formed the study group. The control group comprised randomly

selected age- and gender-matched individuals without COM and migraine, with corresponding entry dates 4 times the size (1:4) of the study group (n = 8,048) from the NHIRD.

Outcome and Relevant Variables

The study end-point was the diagnosis of migraine (ICD-9-CM codes 346.xx) during the study period (2000–2011). In order to make the diagnoses of migraine as correct as possible, only those who had the migraine diagnoses for at least 3 times during the study period were considered to be the migraine patients in this study. The relevant variables for migraine were age, gender, and comorbidities, including hypertension (ICD-9-CM codes 401–405), diabetes (ICD-9-CM code 250), hyperlipdiemia (ICD-9-CM code 272), stroke (ICD-9-CM codes 430–438), depression (ICD-9-CM codes 296.2, 296.3, 296.82, 300.4, 390, 390.1, 309.28, and 311), anxiety (ICD-9-CM codes 300.0–300.3, 308.3, and 309.81), sleep disorder (ICD-9-CM codes 307.4 and 780.5), bipolar disorder (ICD-9-CM code 345), CAD (ICD-9-CM codes 410–414), and epilepsy (ICD-9-CM codes 296.4–296.8).

Statistical Analysis

The chi-square test and t-test were used to determine the differences among discrete and continuous variables between the COM and control groups. Person-years were computed from the entry dates to the first date of migraine onset, withdrawal from the insurance program, death, or the end of 2011. The gender- and age-specific incidence rates (per 1,000 person-years) of migraine were estimated between the COM and control groups. A Cox proportional regression model was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for determining the risk of migraine in both the groups. The correlation of demographic factors and comorbidities with the risk of migraine was compared between the COM and control groups. The HRs for migraine were stratified by age, gender, and comorbidities in both of the groups. The association between migraine and migraine-associated risk factors in 2 groups was assessed. To estimate the association between the severity of COM and the risk of migraine, the severity of COM was stratified as whether the patients with COM required outpatient treatment alone or hospitalization. The migraine-free rates were plotted using the Kaplan-Meier model, and the differences between both of the groups were analyzed with the log-rank test. All statistical analyses were performed using SAS Version 9.3 (SAS Institute, Inc., Cary, NC), and R software (R Foundation for Statistical Computing, Vienna, Austria) was used to plot the Kaplan-Meier curves. A 2-tailed *P*-value of < 0.05 was considered significant.

Results

The risk of COM was higher in men than in women (62.7% vs. 37.3%) (Table 1). The prevalence of the relevant comorbidities was higher in the COM group than in the control group ($P < 0.0001$), except anxiety and bipolar disorder (Table 1). The overall incidence rate of migraine was 3.19 and 1.67 per 1,000 person-years in the COM and control groups, respectively (Table 2). After adjusting for age, gender, and the relevant comorbidities with Cox proportional regression model, the risk of migraine was 1.74-fold significantly higher in the COM group (95% CI 1.14–2.65) compared to the control group. The COM patients had a higher migraine incidence than the comparisons in both genders. However, only female COM patients had a significant migraine risk than their counterparts (aHR 1.85, 95%

Table 1. *Demographic factors and comorbidities in COM and control groups.*

	Control n = 8,048		COM n = 2,012		*P*-Value
	n	%	n	%	
Gender					
Female	3,000	37.3	750	37.3	0.99
Male	5,048	62.7	1,262	62.7	
Age (yrs)					
< 40	1,620	20.1	405	20.1	0.99
40–54	1,964	24.4	491	24.4	
≥ 55	4,464	55.5	1,116	55.5	
Mean (SD)#	55.7	(18.5)	56.2	(18.4)	0.37
Comorbidity					
Diabetes	1,108	13.8	563	28.0	< 0.0001
Stroke	437	5.43	197	9.79	< 0.0001
Depression	354	4.40	135	6.71	< 0.0001
Anxiety	764	9.49	217	10.8	0.08
Hyperlipidemia	1,729	21.5	526	26.1	< 0.0001
Hypertension	2,983	37.1	964	47.9	< 0.0001
Sleep disorder	1,390	17.3	493	24.5	< 0.0001
Bipolar disorder	8	0.40	26	0.32	0.61
CAD	521	25.9	1,585	19.7	< 0.0001
Epilepsy	44	2.19	75	0.93	< 0.0001

Chi-square test and #t-test.
COM= chronic osteomyelitis; SD= standard deviation;
CAD= coronary artery disease

Table 2. *Incident rates and aHRs of migraine in COM and control groups, stratified by gender and age.*

	Control		COM		aHR# (95% CI)
	Event	IR	Event	IR	
Overall	75	1.67	32	3.19	1.74 (1.14–2.65)*
Gender					
Female	40	2.42	18	4.78	1.85 (1.05–3.24)*
Male	35	1.23	14	2.23	1.68 (0.89–3.16)
Age (yrs)					
< 40	20	1.88	10	3.85	2.07 (0.97–4.46)
40–54	21	1.75	10	3.80	2.11 (0.97–4.57)
≥ 55	34	1.52	12	2.53	1.48 (0.76–2.87)
Comorbidity					
No	33	1.41	12	2.92	2.05 (1.06–3.97)*
Yes	42	1.95	20	3.37	1.74 (1.02–2.96)*

#aHR: mutually adjusted for gender, age, hypertension, diabetes, stroke, depression, hyperlipidemia, sleep disorder, coronary artery disease, and epilepsy. * P < 0.05. COM= chronic osteomyelitis; IR= incidence rate per 1,000 person-years; aHR= adjusted hazard ratio; CI= confidence interval

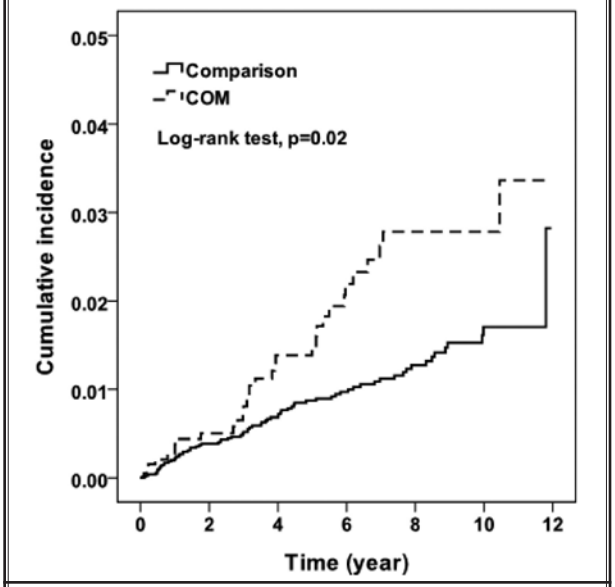

Fig. 1. *The comparison of migraine-free rates between COM group and control cohort using the Kaplan-Meier model.*

CI 1.05–3.24). The age-specific incidence of migraine was decreased with aging in both groups. However, the COM patients in the younger age groups had a greater risk of migraine (aHR 2.07, 95% CI 0.97–4.46 for age < 40 years and aHR 2.11, 95% CI 0.97–4.57 for age 40–54 years, respectively) comparative with their counterparts. In the Kaplan-Meier assessment, the risk of migraine increased during the follow-up period in both groups. Nevertheless, the migraine-free rate was significantly higher in the control group than in the COM group (log-rank $P = 0.02$) (Fig. 1).

Either with or without relevant comorbidities for migraine, COM patients had a higher incidence for migraine than comparisons, and either with or without comorbidities, COM patients still had a significantly higher migraine risk (aHR 2.05, 95% CI 1.06–3.97 and aHR 1.74, 95% CI 1.02–2.96, respectively) than their counterparts (Table 2). In the analyses of comorbidity stratification, COM patients with sleep disorder were found to have a 3.85-folded risk for migraine than the controls (95% CI 1.75–8.46) (Table 3). However, the comparison patients with stroke and sleep disorder had higher risk for migraine (aHR 2.66, 95% CI 1.12–6.33 and aHR 2.58, 95% CI 1.48–4.51, respectively) (Table 3). In severity analyses, comparative with the controls, COM patients requiring outpatient treatment alone and requiring hospitalization exhibited a higher risk of migraine (patients with COM requiring outpatient treatment alone: aHR 1.73, 95% CI 1.03–2.89; patients with COM requiring hospitalization: aHR 1.76, 95% CI 0.96–3.20) (Table 4).

Discussion

In addition to the traditional risk factors for migraine, such as hypertension (9-12), diabetes (9-12), stroke (4,9-11,13), hyperlipidemia (9,10,12), CAD (14-16), depression (3,4,6,10-13), anxiety (3,4,6,12,13), sleep disorder (4,6,11-13), bipolar disorder (15,16), and epilepsy (14-16), previous studies have revealed that

several infectious diseases, such as HP (20,21) and HIV infections (22,23), and certain autoimmune disorders, such as MS (24,25) and SLE (25,26), could increase the risk of migraine. With an advantage of the availability of a large patient population extracted from the Taiwan NHIRD, we investigated whether patients with COM, a condition characterized by continuous, chronic, and severe inflammation, had higher risk of migraine. Subgroup analyses with relevant comorbidities for migraine were also arranged.

Consistent with several prior investigations (35,36), the COM was predominantly noted in men, and most COM patients were aged ≥ 40 years (Table 1). These findings demonstrated the data reliability of the COM population derived from the Taiwan NHIRD. The diagnosis of COM was associated with a higher risk of migraine (aHR 1.74, 95% CI 1.14–2.65) (Table 2). Although the COM group revealed a male predominance, COM increased the risk of migraine in both male and female patients (Table 2).

Age is one of the crucial risk factors for migraine (1,2,6-9,11,12). In both the COM and control groups, most of the migraine events occurred at age < 54 years (Table 2), and the migraine incidence decreased gradually with the increase of age (from 3.85 per 1,000 person-years in patients aged < 40 years to 2.53 per 1,000 person-years in patients aged ≥ 55 years in the COM group) (Table 2). Nevertheless, the relative risk of migraine was higher among the relatively younger COM patients, especially among those in the middle age (aHRs of 2.07 and 2.11 in the patients aged < 40 and 40–54 years, respectively) (Table 2). Because the incidence of the relevant comorbidities known to increase the risk of migraine was lower in the relatively younger patients, in these "relatively neat" younger patients, COM served as a more critical risk factor than in the relatively older patients, in whom the incidence of comorbidities was higher and thus might have played more crucial roles in the development of migraine (Tables 2 and 3). Comparative with the control group, the migraine risk increased in COM patients requiring outpatient treatment alone and those requiring hospitalization, with aHR 1.73, 95% CI 1.03–2.89 and aHR 1.76, 95% CI 0.96–3.20, respectively (Table 4). These findings strengthen the causality of COM in the development of migraine.

Comorbidities for Migraine

Several risk factors have been documented for migraine (1-5,8-13). Among these, younger age (1-5,8,9,11-13), female gender (1-5,8-13), hypertension (9-12), diabetes (9-12), hyperlipidemia (9,10,12), stroke (4,9-11,13), CAD (14-16), depression (3,4,6,10-13), anxiety (3,4,6,12,13), sleep disorder (4,6,11-13), bipolar disorder (15,16), and epilepsy (14-16) have been reported to exert varying effects. The risk of migraine increased to various levels in both the COM and control groups based on the presence of the various relevant comorbidities (Table 3). COM patients without the relevant comorbidities exhibited a higher risk of migraine (aHR 2.05, 95% CI 1.06–3.97) than did their counterparts (Table 2). These findings suggest that COM is an independent predictor of migraine, particularly among female and middle-age patients (Table 2).

Table 3. *aHRs of migraine in COM and control groups, stratified by comorbidities.*

Comorbidity	Control		COM	
	aHR#	(95% CI)	aHR#	(95% CI)
Diabetes	1.00	(0.48–2.10)	0.40	(0.13–1.25)
Stroke	2.66	(1.12–6.33)*	0.62	(0.08–4.88)
Depression	0.63	(0.19–2.09)	0.71	(0.19–2.66)
Hyperlipidemia	1.15	(0.62–2.15)	1.89	(0.75–4.76)
Hypertension	1.03	(0.54–1.95)	0.61	(0.23–1.63)
Sleep disorder	2.58	(1.48–4.51)***	3.85	(1.75–8.46)***
CAD	0.93	(0.47–1.85)	1.42	(0.54–3.76)
Epilepsy	2.71	(0.64–11.6)	2.73	(0.58–12.7)

#aHR: mutually adjusted for gender, age, hypertension, diabetes, stroke, depression, hyperlipidemia, sleep disorder, coronary artery disease, and epilepsy.
* P < 0.05, *** P < 0.001
COM= chronic osteomyelitis; aHR= adjusted hazard ratio; CI= confidence interval

Table 4. *Incidence rates and aHRs of migraine, stratified by severities of COM.*

COM Severity	n	Event	IR	aHR# (95% CI)
Compared group	8,048	75	1.67	1.00
COM with OPT	1,081	19	3.41	1.73 (1.03–2.89)*
COM with Hosp	931	13	2.91	1.76 (0.96–3.20)
P for trend				0.02

#aHR: mutually adjusted for gender, age, hypertension, diabetes, stroke, depression, hyperlipidemia, sleep disorder, coronary artery disease, and epilepsy.
* P < 0.05
COM= chronic osteomyelitis; IR= incidence rate per 1,000 person-years; aHR= adjusted hazard ratio; CI= confidence interval; COM with OPT= chronic osteomyelitis patients with outpatient treatment only; COM with Hosp= chronic osteomyelitis patients with hospitalization ever

Strengths and Limitations

This population-based cohort study has certain strengths. First, data of the patients with COM and the age- and gender-matched controls were extracted from a large database of over 23 million enrollees of the Taiwan NHI program that covered more than 98% of the Taiwanese population. The insurance claims for reimbursement for medical management are strictly controlled and supervised by Taiwan NHI to forbid healthcare frauds. The disease diagnoses without the valid supports of clinical findings may be considered medical frauds by Taiwan NHI, with a penalty of 100-fold of the payment claimed by the treating hospital or physicians. The NHI monitoring system intensifies the credibility of the diagnoses recorded on the insurance claims. The demographic profiles revealing the female predominance and age distribution profiles in migraine are the same as those reported in previous researches (1-5,8,9,11-13). The disclosure of well-categorized risk factors for migraine, including hypertension (9-12), diabetes (9-12), hyperlipidemia (9,10,12), stoke (4,9-11,13), CAD (14-16), depression (3,4,6,10-13), anxiety (3,4,6,12,13), sleep disorder (4,6,11-13), bipolar disorder (15,16), and epilepsy (14-16), in combination with the augmented incidence rates of migraine in both COM and control groups also reinforces the trustworthiness of the data used in this study. Second, the large sample size adequately facilitated the classification of the study cohort into subgroups for further statistical analyses and enabled us to determine the effects of COM on the development of migraine, particularly in the relatively younger patients, in whom the etiology of migraine may be less obvious. The length of follow-up showing time- and severity-dependent effects on the risk of migraine magnifies the contribution of COM as a risk factor for migraine. Finally, the increased incidence of comorbidities, such as hypertension, diabetes, hyperlipidemia, stroke, depression, and sleep disorder, which are well-known risk factors for migraine, among patients with COM indicates that the underlying chronic inflammation may also expose such patients to a higher risk of developing the comorbidities of migraine.

However, this study still has several limitations. First, we could not exclude the compound potentiality that other neurovascular risk factors, such as the medications used for COM, decreased physical activities, and altered immunity, might also increase the risk of migraine. Thus, except the risk factors of migraine determined in the present study, other underlying neurovascular factors might confound the migraine development besides COM. Second, in this study, we could not address all the potential variables and risk factors that might influence the incidence of migraine in the cohort. Third, since the data of personal habits that might affect health, e.g., smoking and alcohol consumption were not available in the Taiwan NHIRD; the effects of these health-affecting factors on migraine development among the COM group could not be determined. However, since COM augmented the risk of migraine in patients with both genders (Table 3) and the smoking rate among the adult women in Taiwan was extremely low (< 4.3%) (37), it implies that smoking is less likely to be a confounding factor that considerably augments the risk of migraine among COM patients. The relatively higher risk of migraine in younger COM patients (especially those in the middle age) (Table 2), who exhibit potentially less cumulative cigarette and alcohol exposures than do the relatively older patients, also reveals that cigarette smoking and alcohol consumption play less critical roles in the development of migraine in patients with COM. Fourth, the present study findings revealed the increased risk of migraine in COM patients, in whom the prevalence of comorbidities was higher than in the controls (Table 1). However, the present study demonstrated that, even without the risk factors for migraine, COM still imposed a higher risk of migraine. Although COM patients had higher risk for migraine, the causal relationship between COM and migraine remains to be elucidated. Further investigations are required to explore such crucial issue.

Conclusion

The results of the present study revealed that COM is a risk factor for migraine. The relative contribution of COM as a risk factor for migraine was more remarkable in women and younger patients (especially in the middle age). Therefore, preventive evaluations must be meticulously conducted to determine the presence of risk factors for migraine in patients with COM, particularly female patients and those of younger age.

Acknowledgement

The authors would like to thank the National Health Research Institutes in Taiwan for providing insurance claims data for analysis. We also thank Professors Chung Y. Hsu, Fung-Chang Sung, and Chi-Pang Wen for their valuable comments.

Author Contributions

J-H Chen, S-C Wu, C-H Kao, C-H Tseng, and C-H Tsai designed the study. C-H Muo collected the necessary data and performed the statistical analyses. J-H Chen, C-H Muo, and C-H Tseng drafted the manuscript. C-H Tseng did the critical revision of the manuscript. All authors approved the final version submitted for publication.

Funding support

This study is supported partly by Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW104-TDU-B-212-113002), China Medical University Hospital, Academia Sinica Taiwan Biobank, Stroke Biosignature Project (BM104010092), NRPB Stroke Clinical Trial Consortium (MOST 103-2325-B-039-006), and CMU under the Aim for Top University Plan of the Ministry of Education, Taiwan. The grant funders had no role in the design of the study, management of the data, and decision of the manuscript submission for publication.

Conflict of Interest

Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

References

1. Ferrari MD. The economic burden of migraine to society. *Pharmacoeconomics* 1998; 13:667-676.
2. Leonardi M, Steiner TJ, Scher AT, Lipton RB. The global burden of migraine: Measuring disability in headache disorders with WHO's Classification of Functioning, Disability and Health (ICF). *J Headache Pain* 2005; 6:429-440.
3. Blumenfeld AM, Varon SF, Wilcox TK, Buse DC, Kawata AK, Manack A, Goadsby PJ, Lipton RB. Disability, HRQoL and resource use among chronic and episodic migraineurs: Results from the International Burden of Migraine Study (IBMS). *Cephalalgia* 2010; 31:301-315.
4. Bigal ME, Lipton RB. The epidemiology, burden, and comorbidities of migraine. *Neurol Clin* 2009; 27:321-334.
5. Arulmozhi DK, Veeranjaneyulu A, Bodhankar SL. Migraine: Current concepts and emerging therapies. *Vascul Pharmacol* 2005; 43:176-187.
6. Galletti F, Cupini LM, Corbelli I, Calabresi P, Sarchielli P. Pathophysiological basis of migraine prophylaxis. *Prog Neurobiol* 2009; 89:176-192.
7. Aurora SK. Pathophysiology of migraine and cluster headaches. *Semin Pain Med* 2004; 2:62-71.
8. Martelletti P, Zicari A, Realacci M, Fiore G, De Filippis S, Stirparo G, Denora P, Solimeo MD, Rinaldi C, Morrone S, Giacovazzo M. Expression of NOS-2, COX-2 and Th1/Th2 cytokines in migraine. *J Headache Pain* 2001; 2:S51-S56.
9. Bigal ME, Kurth T, Santanello N, Buse D, Golden W, Robbins M, Lipton RB. Migraine and cardiovascular disease: A population-based study. *Neurology* 2010; 74:628-635.
10. Tzourio C, Gagnière B, El Amrani M, Alpérovitch A, Bousser MG. Relationship between migraine, blood pressure and carotid thickness. A population-based study in the elderly. *Cephalalgia* 2003; 23:914-920.
11. Fernández-de-las-Peñas C, Hernández-Barrera V, Carrasco-Garrido P, Alonso-Blanco C, Palacios-Ceña D, Jiménez-Sánchez S, Jiménez-García R. Population-based study of migraine in Spanish adults: Relation to socio-demographic factors, lifestyle and co-morbidity with other conditions. *J Headache Pain* 2010; 11:97-104.
12. Bond DS, Roth J, Nash JM, Wing RR. Migraine and obesity: Epidemiology, possible mechanisms and the potential role of weight loss treatment. *Obes Rev* 2011; 12:e362-e371.
13. Negro A, D'Alonzo L, Martelletti P. Chronic migraine: Comorbidities, risk factors, and rehabilitation. *Intern Emerg Med* 2010; 5:S13-S19.
14. Diener HC, Küper M, Kurth T. Migraine-associated risks and comorbidity. *J Neurol* 2008; 255:1290-1301.
15. Scher AI, Bigal ME, Lipton RB. Comorbidity of migraine. *Curr Opin Neurol* 2005; 18:305-310.
16. Chen YC, Tang CH, Ng K, Wang SJ. Comorbidity profiles of chronic migraine sufferers in a national database in Taiwan. *J Headache Pain* 2012; 13:311-319.
17. Ducros A, Tournier-Lasserve E, Bousser MG. The genetics of migraine. *Lancet Neurol* 2002; 1:285-293.
18. Lyngberg AC, Rasmussen BK, Jørgensen T, Jensen R. Has the prevalence of migraine and tension-type headache changed over a 12-year period? A Danish population survey. *Eur J Epidemiol* 2005; 20:243-249.
19. Miranda H, Ortiz G, Figueroa S, Peña D, Guzmán J. Prevalence of headache in Puerto Rico. *Headache* 2003; 43:774-778.
20. Tunca A, Türkay C, Tekin O, Kargili A, Erbayrak M. Is Helicobacter pylori infection a risk factor for migraine ? A case-control study. *Acta Neurol Belg* 2004; 104:161-164.
21. Hosseinzadeh M, Khosravi A, Saki K, Ranjbar R. Evaluation of Helicobacter pylori infection in patients with common migraine headache. *Arch Med Sci* 2011; 7:844-849.
22. Kirkland KE, Kirkland K, Many WJ Jr, Smitherman TA. Headache among patients with HIV disease: Prevalence, characteristics, and associations. *Headache* 2012; 52:455-466.
23. Sheikh HU, Cho TA. Clinical aspects of headache in HIV. *Headache* 2014; 54:939-945.

24. Nicoletti A, Patti F, Lo Fermo S, Liberto A, Castiglione A, Laisa P, Garifoli A, La Naia F, Maimone D, Sorbello V, Contrafatto D, Zappia M. Headache and multiple sclerosis: A population-based case-control study in Catania, Sicily. *Cephalalgia* 2008; 28:1163-1169.
25. Sarchielli P, Alberti A, Coppola F, Gallai V. Dysimmune disorders and migraine: Is there a possible common denominator? *J Headache Pain* 2004; 5:S81-S84.
26. Glanz BI, Venkatesan A, Schur PH, Lew RA, Khoshbin S. Prevalence of migraine in patients with systemic lupus erythematosus. *Headache* 2001; 41:285-289.
27. Lankarani-Fard A, Liu PY, Fang MA. Osteomyelitis and septic arthritis. In: Yoshikawa TT, Norman DC (eds). *Infectious Disease in the Aging: A Clinical Handbook*. Humana Press, New York 2009, pp 201-217.
28. Tseng CH, Chen JH, Muo CH, Chang YJ, Sung FC, Hsu CY. Increased risk of ischaemic stroke among patients with chronic osteomyelitis: A population-based cohort study in Taiwan. *Eur J Neurol* 2015; 22:633-639.
29. Tseng CH, Huang WS, Muo CH, Chang YJ, Sung FC. Increased risk of intracerebral hemorrhage among patients with chronic osteomyelitis. *J Neurosurg* 2015; 123:1528-1533.
30. Hsiao LC, Muo CH, Chen YC, Chou CY, Tseng CH, Chang KC. Increased risk of coronary heart disease in patients with chronic osteomyelitis: A population-based study in a cohort of 23 million. *Heart* 2014; 100:1450-1454.
31. Hsiao LC, Muo CH, Chou CY, Tseng CH, Chen MF, Chang KC. Chronic osteomyelitis is associated with increased risk of new-onset atrial fibrillation: Evidence from a nationwide cohort of 23 million people. *Can J Cardiol* 2016; 32:1388-1395.
32. Tseng CH, Huang WS, Muo CH, Kao CH. Increased risk of dementia among chronic osteomyelitis patients. *Eur J Clin Microbiol Infect Dis* 2015; 34:153-159.
33. Tseng CH, Huang WS, Muo CH, Chang YJ, Kao CH. Increased depression risk among patients with chronic osteomyelitis. *J Psychosom Res* 2014; 77:535-540.
34. Tseng CH, Huang WS, Muo CH, Kao CH. Increased risk of epilepsy among patients diagnosed with chronic osteomyelitis. *Epilepsy Res* 2014; 108:1427-1434.
35. Smith IM, Austin OM, Batchelor AG. The treatment of chronic osteomyelitis: A 10-year audit. *J Plast Reconstr Aesthet Surg* 2006; 59:11-15.
36. Zuluaga AF, Galvis W, Saldarriaga JG, Agudelo M, Salazar BE, Vesga O. Etiologic diagnosis of chronic osteomyelitis: A prospective study. *Arch Intern Med* 2006; 166:95-100.
37. Taiwan Health Promotion Administration. Taiwan tobacco control annual report 2014. *Taipei: Taiwan Ministry of Health and Welfare* 2014; http://tobacco.hpa.gov.tw/Upload/FTB/UpFiles/2014%E8%8F%B8%E5%AE%B3%E9%98%B2%E5%88%B6%E5%B9%B4%E5%A0%B1(%E8%8B%B1%E6%96%87%E7%89%88).pdf.