Increased risk of intracerebral hemorrhage among patients with chronic osteomyelitis

*Chun-Hung Tseng, MD,^{1,2} Wei-Shih Huang, MD,^{1,2} Chih-Hsin Muo, MS,³ Yen-Jung Chang, PhD,⁴ and Fung-Chang Sung, PhD⁵

¹Department of Neurology and ³Management Office for Health Data, China Medical University Hospital, Taichung; ²School of Medicine and ⁵Institute of Clinical Medical Science, China Medical University College of Medicine, Taichung; and ⁴Department of Health Promotion and Health Education, National Taiwan Normal University, Taipei, Taiwan

OBJECT Inflammation may provoke cerebral arteriolar ectasia, inducing microaneurysm formation and further promoting intracerebral hemorrhage (ICH). Chronic osteomyelitis (COM) is an inflammatory disorder for which study of its role in ICH is lacking. This study explored whether COM increases the risk of ICH.

METHODS From Taiwan national insurance inpatient claims, 22,052 patients who were newly diagnosed with COM between 1997 and 2010 were identified; 88,207 age and sex frequency-matched subjects without COM were selected at random for comparison. Risks of ICH associated with COM and comorbidities, including hypertension, diabetes, hyperlipidemia, chronic kidney disease, and drug abuse, were assessed by the end of 2010.

RESULTS The incidence of ICH was 1.68 times higher in the COM cohort than in the comparison cohort, with an adjusted hazard ratio (HR) of 1.50 (95% CI 1.29–1.74) estimated in the multivariable Cox model. Age-specific analysis showed that the HR of ICH for COM patients decreased with age, with an adjusted HR of 3.28 (95% CI 1.88–5.75) in the < 40-year age group, which declined to 1.11 (95% CI 0.88–1.40) in the elderly. The incidence of ICH increased with the severity of COM; for those with severe COM the adjusted HR was 4.42 (95% CI 3.31–5.89). For subjects without comorbidities, the incidence of ICH was 1.20-fold (95% CI 1.00–1.45) higher in the COM cohort than in the comparison cohort.

CONCLUSIONS This study suggests for the first time that COM is an inflammatory factor associated with increased risk of ICH, especially in younger patients.

<http://thejns.org/doi/abs/10.3171/2014.11.JNS141269>

KEY WORDS inflammatory disease; chronic infection; chronic osteomyelitis; intracerebral hemorrhage; vascular disorders

STROKE, either ischemic stroke or intracerebral hemorrhage (ICH), is the leading cause of disability and one of the leading causes of death in adults.^{10,28,31} Patients with ICH are at higher risk of disability than those with ischemic stroke, inclusive of greater economic and health care burdens. Exhibiting in 10%–20% of all strokes, ICH has been associated with both noninfectious and infectious factors. Studies have shown that intravenous drug use–related systemic infections increase the risk of cerebral vascular infection and subsequent rupture of mycotic aneurysms in cerebral arterioles.^{9,15,32} Among noninfectious factors, pathological changes in the cerebral arterioles, including proliferation and death of arteriolar smooth

muscle cells and arteriolar ectasia with microaneurysm formation³¹ in the cerebral arterioles, may subsequently lead to the rupture of arteriolar microaneurysms, causing ICH.^{10,28,31} These noninfectious pathological changes can be triggered by some conventional risk factors for ICH, such as hypertension, diabetes, hyperlipidemia, and chronic kidney disease (CKD).^{16,18,20,21,24} However, risk factors for 10%–25% of ICH patients remain unclear, especially in the younger population.^{16,18,21,24}

Studies have documented well the role of chronic inflammation in triggering arterial ectasia and microaneurysm formation in the coronary artery.^{7,21,24} Studies have also associated ICH with similar chronic inflammatory

ABBREVIATIONS CKD = chronic kidney disease; COM = chronic osteomyelitis; HR = hazard ratio; ICH = intracerebral hemorrhage; IR = incidence rate; IRR = incidence rate ratio; NHI = National Health Insurance; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; VZV = varicella-zoster virus.

SUBMITTED June 11, 2014. **ACCEPTED** November 6, 2014.

INCLUDE WHEN CITING Published online May 29, 2015; DOI: 10.3171/2014.11.JNS141269.

DISCLOSURE This study was supported in part by China Medical University Hospital, Taichung, Taiwan, (Grant 1MS1), Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (Grant MOHW103-TDU-B-212-113002), Academia Sinica Taiwan Biobank, Stroke Biosignature Project (Grant BM103010096), and NRPB Stroke Clinical Trial Consortium (Grant MOST 103-2325-B-039 -006).

* Drs. Tseng and Huang contributed equally to this work.

cerebral arterioles due to viral infections of varicella-zoster virus (VZV)^{11,23} and HIV^{6,23} and autoimmune disorders such as rheumatoid arthritis (RA)^{13,37} and systemic lupus erythematosus (SLE).^{17,37} Hemorrhagic stroke is more prevalent in patients with RA. However, the mechanism of inflammation-related arteriolar ectasia and subsequent microaneurysm formation and rupture remains unclear.

Chronic osteomyelitis (COM) is a chronic inflammation caused by bone infection that may develop severe inflammatory conditions in the foci due to the formation of abscesses, bone debris, and sinus tracts.¹⁹ No study has indicated a link between this type of inflammatory disease and the risk of ICH. With the advantage of a large number of populations covered by the National Health Insurance (NHI) of Taiwan, this study used the inpatient claim database to investigate the correlation between COM and ICH in a 14-year follow-up period.

Methods

Data Source

This was a retrospective cohort study using all inpatient claims data acquired for the period of 1996–2010 from the insurance system, which was reformed in 1995 by the Ministry of Health in Taiwan, with more than 99% of the 23 million residents covered by 1999.^{14,33–35} Information available in the inpatient claims consists of patient demographic status, registered medical facilities, and treatment provided. The identification numbers of patients used for linking data files are scrambled before being released to users to protect the privacy of insured residents. Thus, this study needed no full review from the ethics review committee. Disease diagnoses were coded according to the ICD-9-CM. To prevent medical fraud in overbilling for health care or inappropriate claims based on unconfirmed diagnosis, the NHI has imposed rigorous rules on disease coding and has established an ad hoc committee to monitor medical claims. Violators receive penalties. The inpatient data are particularly reliable for studies to investigate the stroke risk in patients with COM.^{33–35}

Study Subjects

From the NHI inpatient database, patients with COM (ICD-9-CM code 730.1) newly diagnosed between January 1, 1997, and December 31, 2010, without a history of stroke (ICD-9-CM codes 430–438) were identified as the COM cohort. The first date of COM diagnosis was defined as the entry date. The comparison cohort, 4 times the size of the COM cohort, comprised subjects randomly selected from insured residents who had neither COM nor stroke and were matched by age, sex, and the entry date.

Outcome and Relevant Variables

Both the COM cohort and the comparison cohort were observed until the end of 2010 to estimate the incident cases with the diagnosis of ICH (ICD-9-CM code 431). Variables that were also relevant to ICH were age, sex, and comorbidities, such as hypertension (ICD-9-CM codes 401.0–405.99), diabetes (ICD-9-CM codes 250.00–250.93), hyperlipidemia (ICD-9-CM codes 272.0–272.4), CKD (ICD-9-CM code 585), and drug abuse (ICD-9-CM codes 304.00–304.03, 304.10–304.13, 304.20–304.23, 304.30–304.33, 304.40–304.43, 304.70–304.73, 305.20–

305.23, 305.40–305.43, 305.50–305.53, 305.60–305.63, 305.70–305.73, 965.00, 965.01, 965.02, 965.09, 967.0). Incident cases of ICH were also measured in association with these factors.

Statistical Analysis

The chi-square test and t-test were used to evaluate the distributions of discrete and continuous variables, respectively, between the COM cohort and the comparison cohort. The incidence of ICH was measured per 1000 person-years, counted from the entry dates to the first dates of the occurrence of ICH, withdrawal from the insurance program, death, or the end of 2010. Poisson regression analysis estimated the COM cohort-to-comparison cohort incidence rate ratio (IRR) and 95% CI by sex, age, and comorbidities. Further analysis plotted the cumulative proportional incidences of ICH using the Kaplan-Meier model for both cohorts and applied the log-rank test to examine the difference. The Cox proportional hazards regression model was used to study the corresponding hazard ratios (HRs) of ICH. The Cox model also measured HRs by age group (< 40, 40–54, 55–64, and ≥ 65 years) for the relation with sex and comorbidity. Additional analysis estimated the HRs derived from the joint effect of COM and comorbidities.

Data analysis also evaluated the ICH risk associated with the severity of COM. We calculated the length of hospital stay due to COM during the follow-up period for each patient to represent the severity, which was divided by the total length of follow-up time to present the life time portion of hospitalization.^{14,33–35} Patients were classified by COM severity into tertiles; patients in the lower tertile were considered as having mild COM, those in the second tertile as having moderate COM, and those in the higher tertile as having severe COM. Incidence of ICH was estimated for each level, and HR was measured by comparison with the control cohort.

Results

Males dominated the study cohorts (66.5%), and nearly one-third of subjects were elderly (Table 1). Compared with the control cohort, the COM cohort had a higher prevalence of common comorbidities relating to the development of ICH, including hypertension, diabetes, hyperlipidemia, and CKD ($p < 0.0001$).

The overall incidence of ICH was 1.68 times greater in the COM cohort than in the comparison cohort (2.23 and 1.34 per 1000 person-years, respectively) (Table 2). The incidence was slightly higher for males than for females in both cohorts. The incidence increased with age, but the age-specific COM cohort-to-comparison cohort IRR decreased as age increased: 3.67 (95% CI 2.14–6.29) for those < 40 years old and 1.20 (95% CI 0.96–1.50) for the elderly. The incidence of ICH was higher for subjects with comorbidities in both cohorts; it was greater for those in the COM cohort, particularly in those with CKD. The COM cohort-to-comparison cohort IRR for subjects without these comorbidities was 1.20 (95% CI 1.00–1.45) (Table 2). The Kaplan-Meier plot showed that the cumulative proportional ICH incidence was 1.1% greater for the COM cohort than the comparison cohort (log-rank, $p < 0.0001$) (Fig. 1).

TABLE 1. Demographic factors and comorbidities in COM and comparison cohorts

Variable	Control (n = 88,207)		COM (n = 22,052)		p Value*
	n	%	n	%	
Sex					0.98
Women	29,505	33.5	7376	33.5	
Men	58,702	66.5	14,676	66.5	
Age in yrs					0.96
<40	19,127	21.7	4782	21.7	
40–54	23,600	26.8	5900	26.8	
55–64	15,888	18.0	3971	18.0	
≥65	29,582	33.6	7399	33.6	
Comorbidity*					
Hypertension	6661	7.55	4672	21.2	<0.0001
Diabetes	3944	4.47	4948	22.4	<0.0001
Hyperlipidemia	1549	1.76	1232	5.59	<0.0001
CKD	540	0.61	839	3.80	<0.0001
Drug abuse	148	0.67	34	0.04	<0.0001

* Chi-square test.

The multivariable Cox proportional hazards regression was used and the overall adjusted HR for ICH was 1.50 (95% CI 1.29–1.74) for the COM cohort after controlling for sex, age, and comorbidities (Table 3). The data stratified by age showed a higher risk of ICH for younger COM patients, with adjusted HRs of 3.28 (95% CI 1.88–5.75) for the youngest group and 1.11 (95% CI 0.88–1.40) for the elderly (Table 3). Hypertension also had a stronger relationship with ICH in young subjects, while diabetes and CKD exhibited a stronger relationship in the middle age groups

(i.e., 40- to 54-year and 55- to 64-year age groups). Figure 2 demonstrates the ICH hazards measured for joint effects associated with COM and comorbidities of hypertension, diabetes, and CKD. Compared with subjects without these disorders, subjects with all these disorders had an adjusted HR of 9.52 (95% CI 5.20–17.5) (Fig. 2).

Examining the association between the severity of COM and hazards of ICH revealed a dose-response relationship: the incidence of ICH increased with severity of COM (Table 4). Compared with the control cohort, the adjusted HR for COM patients by severity increased from 0.98 (95% CI 0.98–1.38) for those in the mild group, to 2.31 (95% CI 1.75–3.07) for those in the moderate group and 4.42 (95% CI 3.31–5.89) for those in the severe group.

Discussion

Previous studies have reported that patients with VZV^{11,23} and HIV^{6,23} infections and inflammatory disorders, such as RA^{13,37} and SLE,^{17,37} are at an increased risk of ICH. In the present population study, we compared the ICH risk between COM patients and subjects without the disease in a 14-year follow-up period. The incidence of ICH was 68% greater for COM patients than controls (Table 2). A dose-response relationship was observed between the ICH risk and the severity of COM. With an incidence of 2.23 per 1000 person-years in the COM cohort, COM may contribute a great ICH risk to the general population. Chan et al. recently reported that the incidence of spontaneous ICH in the entire population of Taiwan is 40.77 cases per 100,000 population per year.⁵ The ICH incidence in Taiwan is likely higher than that in the Western populations (10–30 cases per 100,000 population per year).²⁷

Nearly one-third of our study population was male. This is consistent with previous reports that middle-aged

TABLE 2. Incidence rate of ICH and COM cohort-to-comparison cohort incidence rate ratio by demographic factor and comorbidity

Variable	Control Cohort			COM Cohort			IRR (95% CI)
	No. of Events	P-Yrs	IR	No. of Events	P-Yrs	IR	
Overall	754	561,195	1.34	273	122,225	2.23	1.68 (1.46–1.92)*
Sex							
Female	222	181,405	1.22	85	39,478	2.15	1.78 (1.38–2.28)*
Male	532	379,790	1.40	188	82,747	2.27	1.63 (1.38–1.93)*
Age in yrs							
<40	28	140,409	0.20	25	3480	0.72	3.67 (2.14–6.29)*
40–54	142	158,087	0.90	83	34,657	2.39	2.69 (2.05–3.52)*
55–64	170	104,663	1.62	70	21,949	3.19	1.99 (1.51–2.63)*
≥65	414	158,036	2.62	95	30,938	3.07	1.20 (0.96–1.50)
Comorbidity							
None	627	519,565	1.21	133	91,671	1.45	1.20 (1.00–1.45)
Hypertension	93	28,177	3.30	87	16,985	5.12	1.56 (1.17–2.09)†
Diabetes	45	16,604	2.71	98	19,559	5.01	1.86 (1.30–2.64)*
Hyperlipidemia	15	6993	2.15	17	4647	3.66	1.73 (0.86–3.46)
CKD	11	1928	5.70	19	2161	8.79	1.52 (0.72–3.20)
Drug abuse	1	609	1.64	0	149	0.00	

IR = incidence rate per 1000 person-years; IRR = incidence rate ratio; P-Yr = person-year.

* $p < 0.001$.† $p < 0.01$.

FIG. 1. Comparison of ICH-free rates between COM and comparison cohorts using the Kaplan-Meier model.

men are at higher risk for COM.^{30,38} A Colombian study reported that 72% of the COM patients are men and are usually 40 years or older.³⁸ However, there is only a minor difference in incidences of ICH between males and females for each cohort, indicating no difference in the risk of ICH between males and females with COM. The results of a multivariable Cox model demonstrated an elevated HR for males compared with females, which may be associated with factors other than COM.

Age is the most important risk factor for ICH.^{1,26,29,36} The incidence of ICH increased with age in both the COM

and comparison cohorts in this study. However, the COM cohort-to-comparison cohort estimated age-specific HR was higher in the younger groups, with the highest IRR of 3.67 noted in the < 40-year group, which declined steadily to 1.20 in the elderly group (Table 2). Comorbidities are known to be less prevalent in the younger population. COM is thus a more prominent risk factor for younger patients than for older patients. Therefore, younger COM patients are at relatively higher risk of developing ICH than older COM patients. It is important to note that in this study the risk of ICH increased steadily with the progression of COM severity. These findings intensify the causality of COM in the development of ICH.

Comorbidities for ICH

Many studies have associated the risk for ICH with older age, male sex, and comorbidities of hypertension, diabetes, hyperlipidemia, CKD, and drug abuse.^{1–4,8,9,15,22,25,32} Figure 2 shows that COM and hypertension are independent predictors for ICH risk. The joint effect increased the HR further to 9.52 (95% CI 5.20–17.5) for COM patients with comorbidities of hypertension, diabetes, and CKD. Hypertension exhibits a more prominent role than COM does in the relationship with ICH.

Strengths and Limitations

This study has the advantages of using a large study population and the longitudinal design with few losses to follow-up. The large sample size allows a stratified data analysis to be performed to observe variations among groups, such as by sex, age, severity of COM, and comorbidities. The dose-response relationship relating to COM severity strengthens the validity of this study. Comorbidities modify the relationship between COM and ICH and underline the joint effect on ICH. Insurance claims for in-

TABLE 3. Multivariable Cox proportional hazard regression analysis estimated predictor of ICH by age

Variable	HR (95% CI)				
	<40 Yrs	40–54 Yrs	55–64 Yrs	≥65 Yrs	All Age Groups*
COM	3.28 (1.88–5.75)†	1.88 (1.38–2.55)†	1.42 (1.04–1.93)‡	1.11 (0.88–1.40)	1.50 (1.29–1.74)†
Age in yrs					
<40					1.00
40–54					3.91 (2.90–5.28)†
55–64					6.31 (4.68–8.52)†
≥65					9.05 (6.79–12.1)†
Sex					
Female	1.00	1.00	1.00	1.00	1.00
Male	1.77 (0.80–3.93)	2.27 (1.58–3.27)†	1.81 (1.36–2.41)†	1.21 (1.01–1.44)‡	1.49 (1.30–1.71)†
Comorbidity (yes vs no)					
Hypertension	7.37 (2.20–24.8)§	2.74 (1.73–4.33)†	1.64 (1.09–2.46)‡	1.43 (1.13–1.82)§	1.59 (1.31–1.91)†
Diabetes	1.53 (0.33–7.10)	2.29 (1.47–3.55)†	2.33 (1.59–3.43)†	1.03 (0.75–1.40)	1.55 (1.26–1.91)†
Hyperlipidemia		0.97 (0.49–1.93)	0.63 (0.29–1.38)	0.92 (0.54–1.56)	0.90 (0.62–1.30)
CKD	2.08 (0.23–18.5)	2.36 (1.10–5.06)‡	2.96 (1.48–5.90)§	1.91 (1.03–3.52)‡	2.45 (1.67–3.59)†
Drug abuse		1.48 (0.21–10.6)			1.36 (0.19–9.68)

* Mutually adjusted for age, sex, hypertension, diabetes, hyperlipidemia, CKD, and drug abuse in Cox proportional hazards regression.

† $p < 0.001$.

‡ $p < 0.05$.

§ $p < 0.01$.

FIG. 2. Age- and sex-adjusted HRs of ICH measured by joint effects of COM and comorbidities.

patient reimbursements are under strict superintendence and monitoring by the NHI to prevent health care fraud. The NHI inspection system strengthens the diagnosis established on insurance claims.

However, there are limitations as well in this study. First, information on some vascular risk factors, such as physical activity, smoking, drinking, and other lifestyles and medications, was unavailable in the claims data. Data on indwelling lines, injections, and other management, including wound debridement and hyperbaric therapy, for COM treatment were not documented. We were unable to control these factors in the data analysis for the association with ICH. However, less than 4.5% of women smoke in Taiwan.⁵ Since the incidence of ICH in males and females is similar, smoking and drinking are unlikely to alter the association between COM and ICH. Information on COM subclassified by the anatomical location of the infection was also unavailable in our data. We were unable to evaluate whether the ICH risk associated with COM is different between the spine and other locations.

Second, it is unclear whether COM is the cause of ICH or only an association in this retrospective cohort study. Patients who are in the hospital receiving medical therapy (such as subcutaneous heparin and indwelling lines) are more likely to experience ICH. Although the cohorts were

frequency matched by age and sex, there are both known and unknown significant differences between the cohorts. Patients with COM who likely spent an increased period in the hospital were compared with patients with potentially primarily outpatient diagnoses.

The present study intended to evaluate the risk of ICH in patients with COM. We noted higher prevalence rates of comorbidities in patients with COM than in the comparison cohort. However, after controlling for these comorbidities, the risk of ICH remains higher in the COM cohort than in the comparison cohort. Therefore, COM is likely a disorder related to an increased ICH risk and deserves further study.

Conclusions

The present study demonstrated a novel finding in the risk of ICH for patients with COM. The results reveal that the risk increases with the severity of COM and number of comorbidities. Younger age and severe cases deserve greater attention. Additional study is needed for other populations to prove our findings. The study findings could be adopted in ICH prevention measures for patients with COM, especially for patients at a younger age.

Acknowledgments

We thank the National Health Research Institutes in Taiwan for making the insurance claims data available for analyses. We also thank Professors Chung Y. Hsu, Chi-Pang Wen, and Dennis P. H. Hsieh for their critical comments.

References

1. Abbott RD, Curb JD, Rodriguez BL, Masaki KH, Popper JS, Ross GW, et al: Age-related changes in risk factor effects on the incidence of thromboembolic and hemorrhagic stroke. *J Clin Epidemiol* 56:479-486, 2003
2. Ariesen MJ, Claus SP, Rinkel GJE, Algra A: Risk factors for intracerebral hemorrhage in the general population: a systematic review. *Stroke* 34:2060-2065, 2003
3. Bos MJ, Koudstaal PJ, Hofman A, Breteler MMB: Decreased glomerular filtration rate is a risk factor for hemorrhagic but not for ischemic stroke: the Rotterdam Study. *Stroke* 38:3127-3132, 2007

TABLE 4. Incidence and hazard ratio for ICH by severity of COM

COM Severity*	No. of Events	P-Y	IR	Adjusted HR (95% CI)†
Compared group	754	561,195	1.34	1.00
Mild (T ₁)	161	99,702	1.61	0.98 (0.98-1.38)
Moderate (T ₂)	56	1492	3.79	2.31 (1.75-3.07)‡
Severe (T ₃)	56	7731	7.24	4.42 (3.31-5.89)‡
p for trend				<0.0001

T₁ = first tertile; T₂ = second tertile; T₃ = third tertile.

* COM severity is defined as the total length of hospital stay due to COM during the follow-up duration divided by the length of follow-up duration.

† Adjusted HR: adjusted for age, sex, hypertension, diabetes, hyperlipidemia, chronic kidney disease and drug abuse in Cox proportional hazards regression.

‡ p < 0.001.

4. Bozluolcay M, Nalbantoglu M, Gozubatik-Celik RG, Benbir G, Akalin MA, Erkol G: Hypercholesterolemia as one of the risk factors of intracerebral hemorrhage. *Acta Neurol Belg* **113**:459–462, 2013
5. Chan CL, Ting HW, Huang HT: The incidence, hospital expenditure, and 30 day and 1 year mortality rates of spontaneous intracerebral hemorrhage in Taiwan. *J Clin Neurosci* **21**:91–94, 2014
6. Dobbs MR, Berger JR: Stroke in HIV infection and AIDS. *Expert Rev Cardiovasc Ther* **7**:1263–1271, 2009
7. Dogan A, Tuzun N, Turker Y, Akcay S, Kaya S, Ozaydin M: Matrix metalloproteinases and inflammatory markers in coronary artery ectasia: their relationship to severity of coronary artery ectasia. *Coron Artery Dis* **19**:559–563, 2008
8. Emerging Risk Factors Collaboration, Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, et al: Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* **375**:2215–2222, 2010
9. Esse K, Fossati-Bellani M, Traylor A, Martin-Schild S: Epidemic of illicit drug use, mechanisms of action/addiction and stroke as a health hazard. *Brain Behav* **1**:44–54, 2011
10. Ferro JM: Update on intracerebral haemorrhage. *J Neurol* **253**:985–999, 2006
11. Gilden D, Cohrs RJ, Mahalingam R, Nagel MA: Varicella zoster virus vasculopathies: diverse clinical manifestations, laboratory features, pathogenesis, and treatment. *Lancet Neurol* **8**:731–740, 2009
12. Health Promotion Administration, Ministry of Health and Welfare: **Taiwan Tobacco Control Annual Report 2012**. Taipei: Health Promotion Administration, Ministry of Health and Welfare, 2012
13. Holmqvist M, Gränsmark E, Mantel A, Alfredsson L, Jacobsson LTH, Wallberg-Jonsson S, et al: Occurrence and relative risk of stroke in incident and prevalent contemporary rheumatoid arthritis. *Ann Rheum Dis* **72**:541–546, 2013
14. 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* **100**:1450–1454, 2014
15. Kalita J, Goyal G, Kumar P, Misra UK: Intracerebral hemorrhage in young patients from a tertiary neurology center in North India. *J Neurol Sci* **336**:42–47, 2014
16. Karatay M, Mehmetoğlu R, Erdem Y, Gülensoy B, Taşcıoğlu T, Sertbaş İ, et al: The relation between surgically treated spontaneous intracerebral hematomas and mortality: retrospective evaluation of 72 cases. *Türk Nöroloji Dergisi* **18**:83–87, 2012
17. Krishnan E: Stroke subtypes among young patients with systemic lupus erythematosus. *Am J Med* **118**:1415.e1–1415.e7, 2005
18. Lai SL, Chen ST, Lee TH, Ro LS, Hsu SP: Spontaneous intracerebral hemorrhage in young adults. *Eur J Neurol* **12**:310–316, 2005
19. 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**. New York: Humana Press, 2009, pp 201–217
20. Lavados PM, Sacks C, Prina L, Escobar A, Tossi C, Araya F, et al: Incidence of lobar and non-lobar spontaneous intracerebral haemorrhage in a predominantly Hispanic-Mestizo population—the PISCIS stroke project: a community-based prospective study in Iquique, Chile. *Neuroepidemiology* **34**:214–221, 2010
21. Li JJ, Nie SP, Qian XW, Zeng HS, Zhang CY: Chronic inflammatory status in patients with coronary artery ectasia. *Cytokine* **46**:61–64, 2009
22. Mayo NE, Nadeau L, Daskalopoulou SS, Côté R: The evolution of stroke in Quebec: a 15-year perspective. *Neurology* **68**:1122–1127, 2007
23. Nagel MA, Mahalingam R, Cohrs RJ, Gilden D: Virus vasculopathy and stroke: an under-recognized cause and treatment target. *Infect Disord Drug Targets* **10**:105–111, 2010
24. Nichols L, Lagana S, Parwani A: Coronary artery aneurysm: a review and hypothesis regarding etiology. *Arch Pathol Lab Med* **132**:823–828, 2008
25. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al: Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet* **376**:112–123, 2010
26. Park JK, Kim HJ, Chang SJ, Koh SB, Koh SY: Risk factors for the hemorrhagic stroke in Wonju, Korea. *Yonsei Med J* **39**:229–235, 1998
27. Qureshi AI, Mendelow AD, Hanley DF: Intracerebral haemorrhage. *Lancet* **373**:1632–1644, 2009
28. Qureshi AI, Tuhir S, Broderick JP, Batjer HH, Hondo H, Hanley DF: Spontaneous intracerebral hemorrhage. *N Engl J Med* **344**:1450–1460, 2001
29. Smadja D, Cabre P, May F, Fanon JL, René-Corail P, Riocreux C, et al: ERMANCIA: Epidemiology of Stroke in Martinique, French West Indies. Part I: methodology, incidence, and 30-day case fatality rate. *Stroke* **32**:2741–2747, 2001
30. Smith IM, Austin OMB, Batchelor AG: The treatment of chronic osteomyelitis: a 10 year audit. *J Plast Reconstr Aesthet Surg* **59**:11–15, 2006
31. Sutherland GR, Auer RN: Primary intracerebral hemorrhage. *J Clin Neurosci* **13**:511–517, 2006
32. Tamrazi B, Almast J: Your brain on drugs: imaging of drug-related changes in the central nervous system. *Radiographics* **32**:701–719, 2012
33. Tseng CH, Chen JH, Muo CH, Chang YJ, Sung FC, Hsu CY: Increased risk of ischaemic stroke amongst patients with chronic osteomyelitis: a population-based cohort study in Taiwan. *Eur J Neurol* **22**:633–639, 2015
34. Tseng CH, Huang WS, Muo CH, Kao CH: Increased risk of epilepsy among patients diagnosed with chronic osteomyelitis. *Epilepsy Res* **108**:1427–1434, 2014
35. Wang IK, Muo CH, Chang YC, Liang CC, Chang CT, Lin SY, et al: Association between hypertensive disorders during pregnancy and end-stage renal disease: a population-based study. *CMAJ* **185**:207–213, 2013
36. Zhang J, Wang Y, Wang GN, Sun H, Shi JQ, et al: Clinical factors in patients with ischemic versus hemorrhagic stroke in East China. *World J Emerg Med* **2**:18–23, 2011
37. Zöller B, Li X, Sundquist J, Sundquist K: Risk of subsequent ischemic and hemorrhagic stroke in patients hospitalized for immune-mediated diseases: a nationwide follow-up study from Sweden. *BMC Neurol* **12**:41, 2012
38. Zuluaga AF, Galvis W, Saldarriaga JG, Agudelo M, Salazar BE, Vesga O: Etiologic diagnosis of chronic osteomyelitis: a prospective study. *Arch Intern Med* **166**:95–100, 2006

Author Contributions

Conception and design: Sung, Tseng, Huang. Acquisition of data: Sung. Analysis and interpretation of data: Sung, Muo, Chang. Drafting the article: Tseng, Huang, Muo, Chang. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Sung. Statistical analysis: Sung, Muo, Chang. Study supervision: Sung.

Correspondence

Fung-Chang Sung, Institute of Clinical Medical Science, China Medical University College of Medicine, 91 Hsueh-Shih Rd., Taichung 40402, Taiwan. email: fcsung1008@yahoo.com.