



Original Article

Bell's Palsy in Elderly Taiwanese Patients with a History of Peptic Ulcer Disease: A Correlation Study

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SUMMARY

Background: This nationwide, retrospective cohort study was initiated to investigate the correlation between Bell's palsy (BP) and peptic ulcer disease (PUD).

Methods: The Taiwan National Health Insurance statistics were used in this large case-control study to investigate the correlation of BP in patients with a history of PUD. We included 69,340 patients in whom PUD was newly diagnosed between January 2000 and December 2005. The PUD patients were tracked until 31 December 2011 or when BP was first diagnosed. For comparison, 208,020 patients without PUD were randomly selected using a 1:3 case-control matching of age, gender and the year of diagnosis of PUD. The correlation of BP in patients with and without PUD was computed using Cox's proportional hazards model. The cumulative incidence of BP in both cohorts was estimated using the Kaplan-Meier method.

Results: Elderly patients aged 65 years or older with a history of PUD had a higher incidence rate of BP (at 1.21 per 1000 persons/year) compared to those without PUD (0.96 per 1000 persons/year). A significantly higher adjusted hazard ratio of 2.5 (95% CI 2.13–2.93; $p < 0.0001$) was found in this group as compared to patients aged 40–65 years.

Conclusions: A significant positive correlation between BP and a history of PUD was observed in elderly patients.

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1. Introduction

Bell's palsy (BP), a unilateral peripheral facial paralysis associated with isolated lower motor neuron facial weakness, represents more than 70% of acute idiopathic facial paralysis. The annual incidence rate varies between 11 and 40 cases per 100,000 people as reported in various countries.² The clinical manifestations include: sudden onset of unilateral facial hemiplegia, ipsilateral eyelid drooping, an inability to close the affected eye completely, a disappearance of the affected nasolabial folds, deviation of the mouth towards the unaffected side, dry eyes and ipsilateral impaired or loss of taste sensation.^{2,3} The highest incidence rate was noted in the 15–45 year-old age population regardless of race, geographical location or gender.⁴ Nevertheless, the etiology of BP remains unknown although there is speculation that infections of Herpes simplex virus or Herpes zoster virus may be associated.^{2,5–7}

Peptic ulcer disease (PUD) is a common digestive disorder characterized by erosions or ulcers on the esophageal, duodenal or gastric mucosa that typically extend into the deep layers of the gastrointestinal (GI) wall.^{8,9} It is a dynamic disease where the ulcers tend to heal and recur.¹⁰ The typical clinical manifestations include

dyspepsia, recurrent epigastric pain that progressively worsens after meals, epigastric distention, postprandial belching, gastroesophageal reflux, fatty food intolerance, nausea and vomiting. The gold standard in the diagnosis of PUD is endoscopic examination.¹¹ Wang et al. (2011) reported that 9.4% of patients in Taiwan were diagnosed with asymptomatic PUD.¹² The reported leading causes of PUD are *Helicobacter pylori* infections, corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin.^{13,14} Other causative factors include psychological stress and smoking.^{15,16} Pilotto et al. (2010) reported that a higher rate of hospitalization and mortality remained in older adults with PUD due to the increased prescriptions of GI-damaging drugs and the high prevalence of *H. pylori* infections.¹⁷

We performed a correlational study of PUD and BP using Taiwan National Health Insurance (NHI) nationwide statistics based on a hypothesis that there may be a positive correlation between BP and PUD. This hypothesis was derived from our clinical observations in the acupuncture and moxibustion applied on acupoints along the Stomach Meridian to treat GI disorders including PUD, as well as BP. The Stomach Meridian begins on the lateral side of the nose, distributes throughout the face and head, descends to the chest and abdomen, and finally ends at the toes. The symptoms of Stomach Meridian disorders include facial paralysis and GI dysfunction.¹⁸ An animal study concluded that moxibustion at Liangmen (ST 21) and Zusanli (ST 36) promotes the recovery of gastric mucosal lesion

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through inhibition of cell apoptosis and promotion of cell proliferation in stress-induced gastric ulcer.¹⁹ In a Clinical Practice Guideline of Acupuncture for Bell's Palsy published in 2016, Dicang (ST 4), Jiache (ST 6), Xiaguan (ST 7) are some of the main points recommended.²⁰ We therefore inspired to investigate the possible correlation between BP and PUD.

2. Materials and Methods

The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) checklist for cohort studies was used to guide this nationwide, retrospective, case-controlled cohort study.

2.1. Data source

We analyzed data between 1996 and 2011 from the Longitudinal Health Insurance Database 2000 (LHID 2000) in the Taiwan National Health Insurance Research Database (NHIRD). It includes all the original claim data of one million randomly sampled beneficiaries enrolled in the period of 1996–2000. Each patient's identity is encrypted by the NHIRD to protect their privacy and security before being released for research use.

2.2. Ethics approval and consent to participate

This study proceeded with approval from the Institutional Review Board of China Medical University, Taichung, Taiwan (CMUH 104-REC2-115(CR-3)). The de-identified and encrypted dataset was obtained from NHIRD to protect the privacy of the enrollees. Hence, no informed consent was needed.

2.3. Cohort study subjects and variables

Our study analyzed 72,435 cases of newly diagnosed PUD (ICD-9-CM code: 533.XX) within the study period between January 2000 and December 2011. For comparison, 208,020 patients without PUD were randomly selected using a 1:3 case-control matching of age, gender and the year of diagnosis of PUD as the control group. The patients were tracked until 31 December 2011 or when BP (ICD-9-CM: 351.OX) was first diagnosed in the same patient. Eligible patients with the following factors were included in this study: at least three outpatient claim records or one inpatient claim record, a first prescription of H₂-blockers, proton pump inhibitors, antacids, sucralfate, bismuth, prostaglandin analogs, anticholinergics, triple therapy or quadruple therapy including antibiotics received between 2000 and 2005. We excluded the following patients from our study: (a) BP diagnosed before the occurrence of PUD in the patients, (b) patients younger than 18 years old, (c) incomplete demographic data in the patients' records and (d) patients with PUD diagnosed within 30 days from the date of BP first being identified.

The dependent variable was BP newly diagnosed in the first outpatient consultation or inpatient admission during the follow-up period until 31 December 2011. Other variables, such as age, gender and the Charlson comorbidity index (CCI), were included in the demographic characteristics of the study. The cohort was categorized into three age groups: 18–39 years, 40–65 years and > 65 years. The CCI was introduced in 1987 to provide a simple method for categorizing comorbidities based on an ICD diagnosis and predicting mortality for use in longitudinal studies.²¹ The overall health status of the patients was evaluated using the CCI by assigning an associated weight of one to six for each of the 16 categories of comorbidity. The sum of these weights was then calculated as a single

comorbidity score for each patient and used to determine the severity of their predicted outcomes. Diabetes mellitus, hypertension, dyslipidemia and *H.pylori* infections were selected as the comorbidities. Studies had suggested that diabetes mellitus is a risk factor for peptic ulcer bleeding and BP.^{22,23} Hypertension may also increase the risk of BP.²⁴ *H.pylori* infections, often implicated in PUD, was found to associate significantly with hypertension and dyslipidemia.^{25,26} A study had suggested that that a potential association between BP and use of statin in treatment of dyslipidemia.²⁷

2.4. Statistical analysis

For the analysis, continuous variables were compared using Student's *t*-test and the categorical variables were compared using Pearson's chi-square test. In addition, the cumulative incidence of BP for both cohorts were estimated using the Kaplan-Meier method; the log rank test was applied to assess the significance of the cumulative risk curve. The hazards ratio (HR) and 95% CI for patients with or without PUD was computed using Cox's proportional hazards model. A sensitivity analysis was conducted based on age and gender. All analyses were performed using SAS statistical software (Version 9.4 for Windows; SAS Institute, Inc., Cary, NC, USA). A *p*-value of less than 0.05 indicated statistical significance.

3. Results

In this research study, 69,340 patients were included after applying the exclusion criteria. Figure 1 provides the study cohort flowchart of patients' diagnoses with and without PUD derived from the LHID 2000 dataset.

Table 1 provides the demographic and clinical characteristics of patients with and without PUD in the Taiwanese population. A higher percentage of female patients (52.78%) was diagnosed with PUD compared to the male patients (47.22%). The mean age of the PUD patients was 51.09 ± 16.79 years. The mean follow-up duration was 8.24 years for patients diagnosed with PUD and 8.11 years for those in the control group (data not shown). Generally, patients diagnosed with PUD were associated with higher prevalence of comorbidities (including diabetes mellitus, hypertension, dyslipidemia and *H.pylori* infections) as well as medications (including NSAIDs and

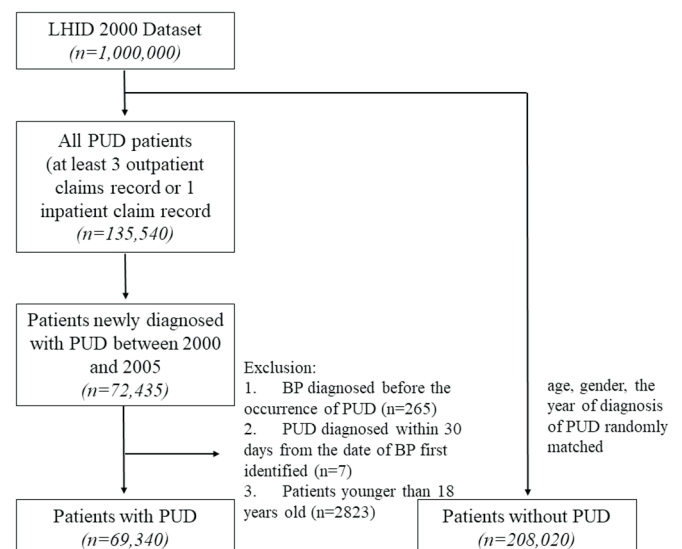


Figure 1. Study cohort flowchart of PUD and non-PUD patients derived from the LHID 2000 dataset. BP, Bell's palsy; PUD, peptic ulcer disease.

aspirin) compared to the control group. A significantly higher percentage of patients with previous histories of PUD were diagnosed with BP compared to the control group ($p < 0.001$).

Table 2 depicts the comparison of HR and 95% CI of BP occurring in patients with and without PUD. An incidence rate of newly diagnosed BP was 0.79 per 1000 persons/year in patients with PUD and 0.66 per 1000 persons/year in the control group. Compared to adults aged 65 and below, the elderly population previously diagnosed with PUD had a higher incidence rate of BP (1.21 per 1000 persons/year) and a multivariate HR of 1.24 (95% CI 1.02–1.51; $p < 0.05$). Compared to male patients, female patients had a significantly higher incidence rate of BP (0.85 per 1000 patients/year) and a multivariate HR of 1.27 (95% CI 1.10–1.48; $p < 0.01$).

Table 3 provides the comparison of the univariate and multivariate Cox regression analyses of the proportional hazards of patients with and without PUD from 2000 to 2011. BP diagnoses were significantly more likely to be associated with PUD patients than in

the control group (univariate HR 1.19; 95% CI 1.07–1.33; $p = 0.0016$). Similar results were shown in a multivariate Cox model in which the potential confounders (age, gender and CCI score) were controlled (multivariate HR 1.15; 95% CI 1.03–1.29; $p = 0.0104$). The elderly population (over 65 years old) had a significantly higher univariate HR of 2.75 and a multivariate HR of 2.5 compared to the adults in the younger age group ($p < 0.001$).

The average follow-up period for newly diagnosed BP was 4.52 years in patients with PUD and 4.56 years in the control group (data not shown). The Kaplan-Meier analysis was used to evaluate the survival curves of the two populations. Figure 2 illustrates a logrank test where the cumulative incidence rate of BP in the PUD population was higher than that of the control group ($p < 0.001$).

4. Discussion

This NHIRD analysis provides evidence to support our hypo-

Table 1
Demographic and clinical characteristics of patients with and without PUD.

Variables	PUD				p value ^a
	No (N = 208,020)		Yes (N = 69,340)		
	n	%	n	%	
Gender					0.99
Female	109,791	52.78	36,597	52.78	
Male	98,229	47.22	32,743	47.22	
Age, yr (Mean ± SD)	50.75 ± 16.88		51.09 ± 16.79		< 0.0001
18–39	57,744	27.76	19,248	27.76	0.99
40–65	100,350	48.24	33,450	48.24	
> 65	49,926	24	16,642	24	
CCI					< 0.0001
0	185,908	89	56,981	82.18	
1	12,115	6	6853	9.88	
> 2	9997	5	5506	7.94	
Comorbidity					
Diabetes mellitus	24,710	11.88	12,608	18.18	< 0.0001
Hypertension	55,209	26.54	25,113	36.22	< 0.0001
Dyslipidemia	31,513	15.15	17,361	25.04	< 0.0001
<i>H. pylori</i> infections	18	0.01	80	0.12	< 0.0001
Medications					
NSAIDs	198,809	95.57	68,773	99.18	< 0.0001
Low dose aspirin	62,207	29.90	28,467	41.05	< 0.0001
High dose aspirin	12,281	5.90	4438	6.40	< 0.0001
Dependent variable					
BP	1117	0.54	451	0.65	0.0006

Pearson's chi-square test is applied to compare the categorical variables. Continuous variable is given as mean ± SD.

^a Two sample t-test is performed.

BP, Bell's palsy; CCI, Charlson comorbidity index; PUD, peptic ulcer disease; SD, standard deviation.

Table 2
Comparison of HR and 95% CI of BP in patients with and without PUD (analysis according to gender and age).

Variables	PUD						Univariate HR (95% CI)	Multivariate HR (95% CI)
	No (N = 208,020)			Yes (N = 69,340)				
	No.	Patient/yr	IR ^d	No.	Patient/yr	IR ^d		
Total	1117	1,688,590	0.66	451	571,429	0.79	1.19 (1.07–1.33) ^b	1.15 (1.03–1.29) ^a
Gender								
Female	592	907,382	0.65	261	308,438	0.85	1.30 (1.12–1.50) ^c	1.27 (1.10–1.48) ^b
Male	525	781,208	0.67	190	262,991	0.72	1.07 (0.91–1.27)	1.05 (0.88–1.24)
Age, yr								
18–39	184	491,113	0.37	63	167,190	0.38	1.00 (0.75–1.34)	0.97 (0.73–1.29)
40–65	598	849,587	0.70	243	284,430	0.85	1.21 (1.04–1.41) ^a	1.18 (1.02–1.37) ^a
> 65	335	347,890	0.96	145	119,810	1.21	1.26 (1.04–1.53) ^a	1.24 (1.02–1.51) ^a

^a $p < 0.05$; ^b $p < 0.01$; ^c $p < 0.001$; ^d Incidence Rate (IR): Per 1000 persons/year.

CI, confidence interval; HR, hazard ratio; PUD, peptic ulcer disease.

Multivariate HR: PUD, age, gender, CCI score are adjusted in Cox proportional hazards regression.

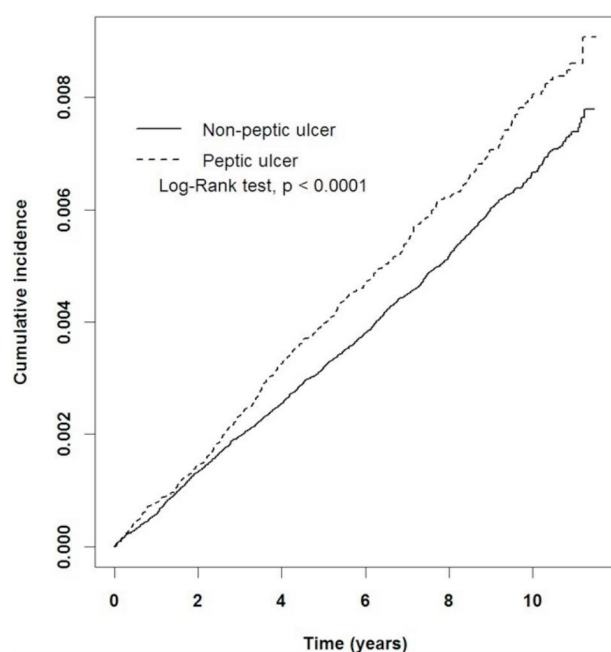
Table 3

Comparison of univariate and multivariate Cox regression analyses of proportional hazards of patients with and without PUD.

Demographic characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	p value	HR	95% CI	p value
PUD						
No	1.00	reference		1.00	reference	
Yes	1.19	(1.07–1.33)	0.0016	1.15	(1.03–1.29)	0.0104
Gender						
Female	1.02	(0.93–1.13)	0.65	1.04	(0.94–1.15)	0.4126
Male	1.00	reference				
Age, yr						
18–39	1.00	reference				
40–65	1.98	(1.72–2.28)	< 0.0001	1.93	(1.67–2.22)	< 0.0001
> 65	2.75	(2.36–3.21)	< 0.0001	2.50	(2.13–2.93)	< 0.0001
CCI						
0	1.00	reference				
1	2.07	(1.77–2.42)	< 0.0001	1.65	(1.40–1.94)	< 0.0001
> 2	1.52	(1.22–1.89)	0.0002	1.18	(0.94–1.47)	0.1496

CCI, Charlson comorbidity index; CI, confidence interval; HR, hazard ratio; PUD, peptic ulcer disease.

Multivariate HR: PUD, age, gender, CCI score are adjusted in Cox proportional hazards regression.

**Figure 2.** Cumulative incidence rate of BP in the PUD and non-PUD population. BP, Bell's palsy; PUD, peptic ulcer disease.

thesis that there may be positive correlation between BP and PUD. Our findings include:

4.1. Age group distribution

We observed that PUD was predominant in the middle-aged population (40–65 years old) with a high incidence rate of 48.24%. However, as shown in Table 3, the elderly (over 65 years old) had a significantly higher HR of 2.75 times that of the youngest age group (18–39 years old). The incidence rate in the elderly population was 1.21 per 1000 persons/year, which was considerably higher than in people less than 65 years old (Table 2). The univariate HR of BP in elderly patients with a previous history of PUD was 1.26 times greater than that of patients in the 18–39 age group. These findings suggest that elderly patients over 65 years old with a history of PUD may be more susceptible to BP in Taiwan, although studies do show that BP occurs frequently in 15–45 year-old patients.²⁸ Other studies have suggested that an increased risk of PUD in older populations may be

associated with the deterioration of gastric mucosa and prescriptions for ulcer-inducing drugs.^{29,30} Viral infections or autoimmune diseases have also been postulated as possible pathological causes. Hence, this higher susceptibility of BP in middle-aged and elderly populations could be due to changes in immunity with advancing age and increasing susceptibility to infections.^{31,32}

4.2. Gender differences

We identified that 52.78% of females and 47.22% of males were diagnosed with PUD. This coincides with some studies that have determined a significantly higher ratio of females suffering from PUD compared to males.^{33,34} We speculated that one of the possible causes for a PUD diagnosis in young female populations could be due to an increased intake of NSAIDs or acetaminophen during dysmenorrhea. The prevalence rate of dysmenorrhea is approximately 25%. Other studies have reported that as many as 67.2–84% of young female adults suffer from dysmenorrhea.^{35,36} NSAIDs are frequently prescribed, but this could cause peptic ulcers due to an increased susceptibility to mucosal injury.³⁷ Another risk factor for PUD includes psychological stress.³⁸ Low-stress resilience in adolescents could be associated with a higher risk of PUD in subsequent adulthood. Table 2 also shows that females with PUD have a higher incidence rate of BP compared to males (0.85 compared to 0.72 per 1000 persons/year, respectively). The univariate and multivariate HRs show a significant difference between male and female populations.

We attempted to address the putative clinical significance and the meaning of the correlation between PUD and BP. A recent review suggested that the etiology of BP includes anatomical structure, viral infection, vascular ischemia, inflammation and acute cold exposure.³⁹ Plasecki pointed out that a failure of gastric mucosal blood supply was suspected in PUD, while other studies also suggested that the disturbed gastric blood circulation is closely associated with the pathogenesis of gastric lesions induced by *H. pylori*, alcohol and NSAIDs.^{40–43} We speculated that the decreased blood supply to the facial nerve may be related to the reduced gastric mucosal blood flow in patients with PUD. It is interesting to note that the ancient traditional Chinese medicine (TCM) references, *Huang Di Nei Jing*, had also discussed that the clinical characteristics of Stomach meridian disorder includes deviated mouth and abdominal distention since this meridian distributes throughout the face and head, descends to the chest and abdomen, then to the legs and toes.⁴⁴ Con-

ceptually, in TCM, the stomach transforms food into nutrients to provide a source of energy and blood to the body.⁴⁵ A decrease in energy and blood supply to the face and body may occur in stomach dysfunction such as PUD. Malnutrition was common in PUD patients, particularly when they had peptic ulcer hemorrhage.⁴⁶ We suggest that future clinical or animal studies should focus on the possible link between etiology, drug-induced morbidity or systemic factors such as gut microbiome of PUD and BP.

4.3. Strength and limitations of study

The strength of our study is that a large nationally represented population was used to determine a potential association between PUD and BP. This provided adequate power to detect minor differences in outcomes. However, several limitations to this study should be addressed.

4.3.1. Limited data access

Our data access was limited. We could only access the dataset with the follow-up period until 31 December 2011. More recent datasets up to 2013 were unavailable at the time of study.

4.3.2. Data exclusion

Even though the NHI provided comprehensive coverage in Taiwan, not all patients with PUD and BP sought medical assistance and, therefore, such data were excluded.

4.3.3. Lack of comprehensive patient information

A lack of comprehensive patient information like dietary preferences or family histories could yield biased results since there may be comorbidities or risk factors related to BP.

4.3.4. Incomplete data

We had to exclude some incomplete data due to omissions in the input of ICD-9 diagnostic codes.

4.3.5. Exclusion of other evaluations

We had excluded the evaluation of the different pathogenesis and clinical entities of gastric, duodenal and esophageal ulcers as well as other co-morbidities and risk factors such as stress, smoking, co-administration of anti-platelets and anti-coagulation agents. These factors could impact the results of the study. Thus, future studies that would include these considerations may be warranted to confirm our observations.

4.3.6. Unknown confounding factors

Unknown confounding factors may exist despite the meticulous protocol design.

Moreover, we identified some factors that might influence the results in this large-scale cohort study:

a. The accurate assignment of the ICD-9 diagnostic codes

The precise diagnosis of PUD and BP by experienced clinicians, and the accurate assignment of the ICD-9 diagnostic codes in electronic medical records (EMRs), could greatly influence the results of this analysis. In local hospitals and clinics, similar diagnostic criteria for the conditions are established using international clinical practice guidelines as references. With the stringent, regular EMR audits conducted by hospitals and the Bureau of NHI, this study was based on the presumption that the conditions were accurately diagnosed and that correct ICD-9 diagnostic codes were assigned in the EMR. Incomplete data of ICD-9 diagnostic codes in the database were omitted from this study.

b. The rigor of the data

To strengthen the rigor of our data and avoid potential errors or omissions in the process, the selection criteria for this study included the following: (a) patients had to have at least three outpatient claim records or one inpatient claim record, and (b) patients had to have received a first prescription, between 2000 and 2005, of drugs for PUD treatment. This ensured that selected subjects were confirmed with the diagnosis of PUD.

c. Inclusion and exclusion

The use of steroidal medications in the treatment of BP could induce or worsen PUD.² Therefore, we excluded patients with BP diagnosed before the occurrence of PUD and patients diagnosed with PUD within 30 days of the date that BP was first identified. In addition, patients younger than 18 years old were excluded as the incidence rate in children is reported to be lower than in adults.⁴⁷ The control group of non-PUD patients was randomly selected from the same dataset using the criteria of age, gender and year of diagnosis of PUD. A 1:3 case-control matching was applied to ensure that the proportions of gender and age distribution in both groups remained the same to avoid any biases.

Further investigation may be merited to use more recent datasets to compare the trend of incidence rates of BP in patients with PUD. A future study could analyze the association between drug-induced PUD and BP, which we have excluded from the scope of our study.

5. Conclusions

A significant positive correlation between BP and a history of PUD was observed in elderly patients. Further research is required to clarify whether prior PUD is a true risk factor that increases the susceptibility of BP.

Data availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of interest

None declared.

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