Increased Risk of Intracranial Hemorrhage in Patients With Pregnancy-Induced Hypertension
A Nationwide Population-Based Retrospective Cohort Study

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Abstract: Pregnancy-induced hypertension (PIH) may be a major predictor of pregnancy-associated intracranial hemorrhage (ICH). However, the relationship between PIH and long-term ICH risk is unknown. The objective of the study was to determine the association between PIH and ICH and to identify the predictive risk factors. Patients with newly diagnosed PIH were recruited from the Taiwan National Health Insurance Research Database. PIH patients were divided into gestational hypertension (GH) and preeclampsia groups. The 2 groups were separately compared with matched cohorts of patients without PIH based on age and date of delivery. The occurrence of ICH was evaluated in both cohorts. The overall observational period was from January 1, 2000 to December 31, 2013. Among the 23.3 million individuals registered in the National Health Insurance Research Database, 28,346 PIH patients, including 7390 with GH and 20,956 with preeclampsia, were identified. The incidences of ICH were increased in both groups (incidence rate ratio [IRR] = 3.72 in the GH group, 95% confidence interval [CI] 3.63–3.81, P < 0.0001 and IRR = 8.21 in the preeclampsia group, 95% CI 8.12–8.31, P < 0.0001, respectively). In addition, according to the results of stratification of follow-up years, both groups were associated with a highest risk of ICH at 1 to 5 years of follow-up (IRR = 11.99, 95% CI 11.16–12.88, P < 0.0001 and IRR = 21.83, 95% CI 21.24–22.44, P < 0.0001, respectively). After adjusting for age, parity, severity of PIH, number of PIH occurrences, gestational age, and comorbidities in the multivariate survival analysis using Cox regression model, age ≥30 years (hazard ratio [HR] = 1.99, 95% CI 1.27–3.10, P = 0.0026), patients with preeclampsia (HR = 2.18, 95% CI 1.22–3.90, P = 0.0089), multiple PIH occurrences (HR = 4.08, 95% CI 1.85–9.01, P = 0.0005), hypertension (HR = 4.51, 95% CI 1.89–10.74, P = 0.0007), and obesity (HR = 7.21, 95% CI 1.58–32.84, P = 0.0107) were independent risk factors for the development of ICH among patients with PIH. Patients with PIH, especially those with older age, preeclampsia, and multiple PIH occurrences, may have an increased risk of developing ICH later in life.

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Abbreviations: CI = confidence interval, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, GH = gestational hypertension, HTN = hypertension, ICD-9-CM = International Classification of Diseases, Ninth Revision, clinical modification, ICH = intracranial hemorrhage, IRR = incidence rate ratio, NHIRD = National Health Insurance Research Database, NHRI = National Health Research Institute, PIH = pregnancy-induced hypertension, SD = standard deviation.

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INTRODUCTION

Pregnancy-induced hypertension (PIH), which includes gestational hypertension (GH) and preeclampsia, is a leading cause of maternal morbidity and mortality.1–4 Preeclampsia complicates approximately 3% to 5% of pregnancies,3,4 and is generally defined as the de novo development of hypertension and proteinuria arising after 20 weeks of gestation in previously normotensive women.5,6 Although the pathogenesis of preeclampsia remains unclear, the central hypothesis strongly suggests that impaired trophoblast invasion of the spiral arteries occurs during early pregnancy, which contributes to a failure in spiral artery remodeling and subsequent progressive insufficient utero-placental blood flow. As a consequence of placental ischemia, several antiangiogenic factors, reactive oxygen species, and inflammatory cytokines are released, leading to widespread endothelial dysfunction, microangiopathy, and vasospasm, which precede the onset of symptomatic clinical disease.7–11

Pregnancy-associated intracranial hemorrhage (ICH) is an uncommon but potentially life-threatening event that markedly contributes to maternal mortality. Preeclampsia is one of the risk factors for pregnancy-associated ICH.12–17 Patients with pregnancy-associated ICH have poorer prognoses for both the mother and fetus compared with other etiologies.12,18 Possible
effects of preeclampsia on systemic vessels include endothelial dysfunction, microangiopathy, and vasospasm. Additionally, high blood pressure persistently damages vessel walls and leads to rupture and bleeding. Concurrent ICH may be the end-stage manifestation of preeclampsia. In a study by Bateman et al., GH and preeclampsia/eclampsia were significant independent risk factors for ICH during pregnancy, and accounted for 30.5% of such cases. In a study by Oudghiri et al., a patient with preeclampsia at 31 weeks of gestation developed a spontaneous subdural hematoma. However, few studies have investigated the relationship between PIH and long-term ICH risk. In addition, the association between GH and subsequent ICH risk was seldom investigated. We hypothesized that a history of PIH, including GH and preeclampsia, increases the risk of subsequent ICH. To test our hypothesis, we designed a nationwide population-based matched cohort study to assess the incidence of ICH among women with a history of PIH.

METHODS

Data Sources
The National Health Insurance program in Taiwan was initiated in 1995, and approximately 98% of the population has utilized this coverage. The National Health Research Institute (NHRI) established a National Health Insurance research database (NHIRD), from which we obtained data for this study. This database contains insurance claims for 23.3 million beneficiaries from 2000 through 2013. The NHIRD safeguards the privacy of individuals and provides data to researchers who have ethical approval. We obtained anonymous data from NHIRD; therefore, the identities of the patients could not be determined. The Kaohsiung Veterans General Hospital (VGHKS15-EM4–01) Institutional Review Board approved this study.

Study Design and Participants
Patients with PIH who were &ge; 20 but &lt; 50 years of age were assessed according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 642.3 to 642.6, including patients with GH (ICD-9-CM codes 642.30, 642.31, 642.32, 642.33, and 642.34) and preeclampsia (ICD-9-CM codes 642.40, 642.41, 642.42, 642.43, 642.44, 642.50, 642.51, 642.52, 642.53, and 642.54). To ensure diagnostic validity and to avoid any potential misclassifications, only patients with a diagnosis of PIH and inpatient hospitalization were selected. Patients were not eligible for enrollment in this cohort study if they had a history of gestational diabetes mellitus or ICH. A total of 28,346 PIH patients were assessed for this study. PIH patients were divided into GH and preeclampsia groups. For each patient with GH or preeclampsia included in the PIH cohort, 4 age and the date of delivery-matched patients without PIH were randomly selected from the NHIRD and were included in the comparison cohort. GH group and preeclampsia group were matched with control groups separately. The reason we took the date of delivery for matching because the diagnostic criteria for PIH have changed over time. Furthermore, prevention and management strategies of PIH and diagnostic accuracy of ICH improved over time. Both the GH patients, or preeclampsia patients and comparison patients were followed until the development of ICH, death, or the end of 2013. In our study, sample size was determined to achieve 90% statistical power at 2-sided type I error rate of 5%. Under the assumption, 1:1 matching was not considered because the matching process would provide the maximum possible statistical power at around 65% while analyzing the risk of subsequent ICH development among the patients with GH. Therefore, 1:4 matching was used instead.

Definitions of the Clinical Endpoints and Follow-up
The index date for the patients in the PIH cohort was the date of initial PIH diagnosis. The study endpoint was defined as the date of ICH diagnosis (ICD-9-CM: 430–432) or death during the 13-year follow-up period (2000–2013). The pregnancy characteristics of the patients were recorded, including age, parity, gestational age, gestational number, and comorbidities. The comorbidities in our study included diabetes mellitus (ICD-9-CM: 250), hypertension (ICD-9-CM: 401–405), obesity (ICD-9-CM: 278.0), dyslipidemia (ICD-9-CM: 272), chronic kidney disease (ICD-9-CM: 585 and 403), and chronic obstructive pulmonary disease (COPD) (ICD-9-CM: 491.2, 493.2, and 496).

Statistical Analysis
The incidence of newly diagnosed ICH in the PIH patients and matched controls was assessed. We calculated ICH incidence rates (per 10,000 person-years) and incidence rate ratios (IRRs). The study groups were compared using the chi-square test for categorical variables. A Kaplan–Meier analysis was used to calculate the cumulative incidence rates for ICH between the study cohorts and matched cohorts, and the log-rank test was used to analyze the differences between survival curves. A Cox proportional-hazards model was used to identify the risk factors for ICH in patients with PIH. The qualifying criterion for inclusion in the multivariate analysis was a result in the univariate analysis, with a P value less than 0.1. SAS version 9.4 (SAS System for Windows) was used for data analysis. Comparisons with a P value &lt; 0.05 were considered significant.

RESULTS

Participant Characteristics
A total of 28,346 patients with PIH (including 7390 with GH and 20,956 with preeclampsia) and matched cohort of 113,384 subjects (including 29,560 matched with GH patients and 83,824 matched with preeclampsia patients) were identified for this study. Table 1 presents the demographics and comorbidities of the PIH patients and matched subjects. The mean patient ages were 31.19 ± 4.98 and 30.94 ± 5.05 years for GH and preeclampsia groups, respectively. The majority of patients were older than 30 years in both the GH (58.81%) and preeclampsia (55.97%) groups. When compared with matched cohorts, patients in both the GH and preeclampsia groups had lower parity, higher preterm birth, and higher multiple pregnancy rates. Furthermore, patients with GH had a higher prevalence of diabetes mellitus (DM), hypertension (HTN), obesity, and dyslipidemia; patients with preeclampsia had a higher prevalence of DM, HTN, obesity, dyslipidemia, chronic kidney disease, and COPD.

Incidence of ICH
Table 2 shows the risk for ICH in PIH patients stratified by age and follow-up years. In GH group, during the 13-year follow-up period, the incidence rates for ICH in patients with GH and the matched...
### TABLE 1. Baseline Characteristics of Patients With Pregnancy-induced Hypertension* and matched cohort

| Parameters                  | Gestational Hypertension | Matched Cohort | P  | Preeclampsia    | Matched Cohort | P  |
|-----------------------------|--------------------------|----------------|----|----------------|----------------|----|
|                             | Study Cohort             | Matched Cohort | P  | Study Cohort    | Matched Cohort | P  |
| Age, yrs, mean ± SD         | 31.19 ± 4.98             | 31.03 ± 4.94   | 0.999 | 30.94 ± 5.05   | 30.82 ± 5.02   | 0.999 |
| <30                         | 3044                     | 12,176         | 41.19 | 9226           | 36,904         | 44.03 |
| ≥30                         | 4346                     | 17,384         | 58.81 | 11,730         | 46,920         | 55.97 |
| Parity, n                   |                          |                |     |                |                |     |
| 1                           | 4578                     | 17,902         | 60.56 | 12,920         | 48,454         | 57.8 |
| ≥2                          | 2812                     | 11,658         | 39.44 | 8036           | 35,370         | 42.2 |
| Gestational age             |                          |                |     |                |                |     |
| Term                        | 6365                     | 28,212         | 95.44 | 15,635         | 79,877         | 95.29 |
| Preterm                     | 1025                     | 1348           | 4.56  | 5321           | 3947           | 4.71  |
| Gestational number          |                          |                |     |                |                |     |
| Singleton                   | 7080                     | 29,032         | 98.21 | 19,600         | 82,320         | 98.21 |
| Multiple                    | 310                      | 528            | 1.79  | 1356           | 1504           | 1.79  |
| Comorbidities               |                          |                |     |                |                |     |
| Diabetes mellitus           | 23                       | 19             | 0.06  | 85             | 58             | 0.07 |
| Hypertension                | 57                       | 20             | 0.07  | 205            | 71             | 0.08 |
| Obesity                     | 18                       | 13             | 0.04  | 46             | 31             | 0.04 |
| Dyslipidemia                | 25                       | 22             | 0.07  | 73             | 79             | 0.09 |
| Chronic kidney disease      | 2                        | 5              | 0.02  | 24             | 5              | 0.01 |
| COPD                        | 4                        | 8              | 0.03  | 10             | 15             | 0.02 |

Preeclampsia is primarily defined as gestational hypertension plus proteinuria (300 mg/24 h).
COPD = chronic obstructive pulmonary disease, SD = standard deviation.
*Gestational hypertension and preeclampsia are hypertensive disorders induced by pregnancy.
Chi-square test.

### TABLE 2. Incidence Risk Ratios of Intracranial Hemorrhage in Patients With Pregnancy-induced Hypertension and Matched Cohort

| Parameters                  | Study Cohort | Matched Cohort | IRR* (95% CI) | P   |
|-----------------------------|--------------|----------------|---------------|-----|
|                             | ICH No.      | Per 10,000 Person-yrs | ICH No. | Per 10,000 Person-yrs | IRR* (95% CI) | P   |
| Gestational hypertension    |              |                 |              |     |
| Total                       | 13           | 2.89            | 14           | 0.78 | 3.72 (3.63–3.81) | <0.0001 |
| Age, yrs                    |              |                 |              |     |
| <30                         | 2            | 0.98            | 3            | 0.37 | 2.66 (2.52–2.82) | <0.0001 |
| ≥30                         | 11           | 4.49            | 11           | 1.12 | 4.01 (3.91–4.12) | <0.0001 |
| Follow-up yrs               |              |                 |              |     |
| <1                          | 2            | 55.83           | 6            | 41.72 | 1.34 (1.27–1.41) | <0.0001 |
| 1–5                         | 3            | 4.00            | 1            | 0.33 | 11.99 (11.16–12.88) | <0.0001 |
| ≥5                          | 8            | 2.15            | 7            | 0.47 | 4.58 (4.43–4.73) | <0.0001 |
| Preeclampsia                |              |                 |              |     |
| Total                       | 94           | 6.61            | 46           | 0.80 | 8.21 (8.12–8.31) | <0.0001 |
| Age, yrs                    |              |                 |              |     |
| <30                         | 26           | 3.76            | 13           | 0.47 | 8.03 (7.87–8.20) | <0.0001 |
| ≥30                         | 68           | 9.30            | 33           | 1.12 | 8.29 (8.18–8.40) | <0.0001 |
| Follow-up yrs               |              |                 |              |     |
| <1                          | 21           | 237.19          | 10           | 28.71 | 8.26 (8.07–8.46) | <0.0001 |
| 1–5                         | 33           | 18.16           | 6            | 0.83 | 21.83 (21.24–22.44) | <0.0001 |
| ≥5                          | 40           | 3.25            | 30           | 0.61 | 5.37 (5.29–5.45) | <0.0001 |

CI = confidence interval, ICH = intracranial hemorrhage, IRR = incidence risk ratio, PIH = pregnancy-induced hypertension.
*The incidence risk ratios of developing ICH between the patients with PIH and matched cohort were calculated by the MedCalc Statistical Software version 12.7.8.
cohorts were 2.89 and 0.78 per 10,000 person-years, respectively. Patients with GH had a significantly higher risk of ICH than patients without GH (IRR = 3.72, 95% confidence interval [CI] 3.63–3.81, \( P < 0.0001 \)). After stratifying patients according to age, both patients aged <30 years (IRR = 2.66, 95% CI 2.52–2.82, \( P < 0.0001 \)) and aged ≥30 (IRR = 4.01, 95% CI 3.91–4.12, \( P < 0.0001 \)) had a higher risk of ICH than matched cohorts. After stratifying patients according to follow-up duration, the ICH risk was the most pronounced in the 1 to 5-year follow-up (IRR = 11.99, 95% CI 11.16–12.88, \( P < 0.0001 \)). According to a Kaplan–Meier analysis, GH patients were associated with higher cumulative incidence rates for ICH than patients in the comparison cohort (log-rank \( P = 0.0002 \)) in Figure 1.

In preeclampsia group, during the 13-year follow-up period, the incidence rates for ICH in patients with preeclampsia and matched subjects were 6.61 and 0.80 per 10,000 person-years, respectively. Patients with preeclampsia had a significantly higher risk of ICH than those without preeclampsia (IRR = 8.21, 95% CI 8.12–8.31, \( P < 0.0001 \)). After stratifying patients according to age, both patients aged <30 years (IRR = 8.03, 95% CI 7.87–8.20, \( P < 0.0001 \)) and aged ≥30 (IRR = 8.29, 95% CI 8.18–8.40, \( P < 0.0001 \)) had a higher risk of ICH than matched cohorts. We also stratified the patients according to follow-up duration and observed that the IRRs were most pronounced in the 1 to 5-year follow-up (IRR = 21.83, 95% CI 21.24–22.44). Based on a Kaplan–Meier analysis, the log-rank test indicated that patients with preeclampsia had significantly higher cumulative incidence rates of ICH than patients in the matched cohort (log-rank \( P < 0.0001 \)) in Figure 2.

**Risk Factors for ICH in Patients With PIH**

As demonstrated in the multivariate analyses, the independent risk factors for the development of ICH among the PIH patients included age ≥30 years (hazard ratio [HR] = 1.99, 95% CI 1.27–3.10, \( P = 0.0026 \)), multiple PIH occurrences (HR = 4.08, 95% CI 1.85–9.01, \( P = 0.0005 \)), PIH severity (HR = 2.18, 95% CI 1.22–3.90, \( P = 0.0089 \)), hypertension (HR = 4.51, 95% CI 1.89–10.74, \( P = 0.0007 \)), and obesity (HR = 7.21, 95% CI 1.58–32.84, \( P = 0.0107 \)). However, multiparity was a protective factor against ICH among patients with PIH (HR = 0.25, 95% CI 0.13–0.48, \( P < 0.0001 \)).

**DISCUSSION**

The estimated pregnancy-associated ICH rates range from 3.8 to 18.1 per 100,000 deliveries. Mortality rates resulting from pregnancy-associated ICH range from 9% to 38%,13–16,18 and permanent neurologic deficits occur in 40% of patients. Preeclampsia plays a pivotal role in the development of pregnancy-associated ICH. The possible contributions8,12,18,23–25 included endothelial dysfunction, microangiopathy, and vasospasm of brain vessels; increased cerebral perfusion pressure and brain capillary permeability; disturbances of cerebral blood flow auto-regulation and subsequent cerebral hyperperfusion leading to vasodilation and brain edema; and thrombocytopenia or coagulation factors (as predisposing factors). Notably, preeclampsia is an important etiology of pregnancy-associated ICH. Eclampsia or preeclampsia rates reported in pregnant women with ICH range from 14% to 57.5%.14,16,21 Bateman et al demonstrated that GH (odds ratio [OR] 2.41, 95% CI 1.62–3.59) and preeclampsia/eclampsia (OR 10.39, 95% CI 8.32–12.98) were independent predictors of pregnancy-related intracerebral hemorrhage.15 Although the ICH associated with preeclampsia is typically intraparenchymal, subdural hematomas or subarachnoid hemorrhages have also been observed19,21,26 including our study. However, most studies followed patients for only 6 weeks after delivery. Thus, the long-term ICH risks after PIH are unknown. After a follow-up of 13 years, the present study indicated an ICH incidence that was 3.72-fold higher in the GH cohort (95% CI 3.63–3.81, 0.0001).
most important risk factor for ICH is hypertension.\textsuperscript{32–35} A systematic review and meta-analysis revealed hypertension was a central contributor of subarachnoid hemorrhages.\textsuperscript{36} Obesity seems to have an impact on the risk of ICH. A multicenter, observational study conducted by Pezzini et al\textsuperscript{27} indicated that obesity was associated with increased risk of deep intracerebral hemorrhage, but had no effect on the risk of lobar intracerebral hemorrhage. A single-center prospective study showed that extremes of body mass index (BMI), which included low BMI (<18.5 kg/m\textsuperscript{2}) and very high BMI (>30.0 kg/m\textsuperscript{2}), increased risk of deep intracerebral hemorrhage, but not lobar intracerebral hemorrhage.\textsuperscript{38} Matsukawa et al\textsuperscript{39} demonstrated that patients with pontine hemorrhage had a higher proportion of obese individuals. As demonstrated in our multivariate analyses, hypertension (HR 4.51, 95\% CI 1.89–10.74, \textit{P} = 0.0007) and obesity (HR 7.21, 95\% CI 1.58–32.84, \textit{P} = 0.0107) were independent risk factors for ICH among PIH patients. PIH is also a pivotal risk factor for ICH. As shown in Table 3, our analysis revealed increased PIH severity and occurrences were associated with higher ICH risk among patients with PIH. Additionally, age \textgreater{} 30 years was an independent risk factor for ICH in PIH patients (HR 1.99, 95\% CI 1.27–3.10, \textit{P} = 0.0026) (Table 3). Advanced maternal age is also an independent predictor of pregnancy-related ICH.\textsuperscript{15} A systematic review and meta-analysis conducted by van Asch et al\textsuperscript{11} demonstrated that the incidence of ICH increases with age. However, in our study, multiparity was protective against ICH (HR 0.25, 95\% CI 0.13–0.48, \textit{P} < 0.0001) (Table 3). Our result contrasts the findings of Jung et al,\textsuperscript{40} who indicated that an increased number of childbirth was related to an increased risk of ICH. More studies are needed to clarify this discrepancy.

### TABLE 3. Analyses of Risk Factors for Subsequent Intracranial Hemorrhage Among the Patients With Pregnancy-induced Hypertension

| Parameters                                | HR (95\% CI)       | \textit{P}  |
|-------------------------------------------|--------------------|------------|
| **Age, yrs**                              |                    |           |
| \textgreater{} 30 vs \textless{} 30      | 1.99 (1.27–3.10)   | 0.0026    |
| **Number of PIH occurrences**             |                    |           |
| \textgreater{} 2 vs 1                     | 4.08 (1.85–9.01)   | 0.0005    |
| **Parity**                                |                    |           |
| \textgreater{} 2 vs 1                     | 0.25 (0.13–0.48)   | \textless{}0.0001 |
| **Gestational age**                       |                    |           |
| Preterm vs term                           | 1.37 (0.91–2.05)   | 0.1352    |
| **PIH severity**                          |                    |           |
| Preeclampsia vs GH                        | 2.18 (1.22–3.90)   | 0.0089    |
| **Diabetes mellitus**                     |                    |           |
| Yes vs no                                 | 1.35 (0.18–9.87)   | 0.7709    |
| **Hypertension**                          |                    |           |
| Yes vs no                                 | 4.51 (1.89–10.74)  | 0.0007    |
| **Obesity**                               |                    |           |
| Yes vs no                                 | 7.21 (1.58–32.84)  | 0.0107    |
| **Dyslipidemia**                          |                    |           |
| Yes vs no                                 | 0.6 (0.07–5.14)    | 0.6420    |
| **Chronic kidney disease**                |                    |           |
| Yes vs no                                 | 2.31 (0.28–18.8)   | 0.4351    |

\textit{CI} = confidence interval, GH = gestational hypertension, HR = hazard ratio, ICH = intracranial hemorrhage, PIH = pregnancy-induced hypertension.

\textsuperscript{a}A Cox proportional-hazards model was used to identify the potential risk factors for ICH in patients with PIH. The qualifying criterion for inclusion in the multivariate analysis was a result in the univariate analysis with a \textit{P} value less than 0.1 (not shown in the table).
This study was a longitudinal, large population-based design. Nonetheless, several limitations inherent to the use of insurance claims databases must be considered. First, the diagnosis of PIH in the NHIRD was based on the ICD-9-CM code. Information on blood pressure, proteinuria, and symptoms could not be obtained from the database. Second, many demographic variables were not present in the database, such as socioeconomic status, BMI, lifestyle, smoking status, and family medical history. These factors could have been useful for assessing other factors that may be associated with PIH or ICH. Third, information on the cause of ICH was not available; consequently, we cannot conclude that the etiology of ICH is related to PIH or other factors, such as arteriovenous malformations or cerebral aneurysms. Finally, the diagnostic criteria for PIH have changed over the years, which could lead to heterogeneous populations across studies and may limit comparisons. Despite these limitations, our study was based on a nationwide, population-based database that included nearly all of Taiwan’s residents. The large sample size in our study contributed to its substantial statistical power and revealed an obvious association between PIH and ICH with minimal selection biases.

CONCLUSIONS

In conclusion, PIH was associated with a significant increase in ICH risk later in life. Preeclampsia may have higher ICH risk than GH. In addition, older age, multiple PIH occurrences, hypertension, and obesity were independent risk factors for ICH.

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