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# Increased risk of systemic lupus erythematosus in pregnancy-induced hypertension

## A nationwide population-based retrospective cohort study

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**Abstract**

Dysregulation of the immune system plays a role in the pathogenesis of both, pregnancy-induced hypertension (PIH) and systemic lupus erythematosus (SLE). It is well known that SLE predisposes to be complicated with PIH. However, few studies have attempted to investigate whether PIH increased subsequent SLE risk.

The objectives of this study were to assess the association between PIH and subsequent SLE risk and identify predictive risk factors.

Patients with newly diagnosed PIH were selected from the Taiwan National Health Insurance Research Database (NHIRD) and compared with a matched cohort without PIH based on age and the year of delivery. The incidence of new-onset SLE 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 NHIRD, 29,091 patients with PIH and 116,364 matched controls were identified. The incidence of SLE was higher among patients with PIH than in the matched controls (incidence rate ratio [IRR] = 4.02, 95% confidence interval [CI] 3.98–4.05, $P < 0.0001$). The IRR for subsequent SLE development remained significantly higher in all stratifications during the follow-up years. The multivariate Cox regression model was performed and the results showed that PIH may be an independent risk factors for the development of subsequent SLE (hazard ratio [HR] = 2.87, 95% CI 2.07–3.98, $P < 0.0001$). Moreover, multivariate Cox regression model was used again among the PIH cohort only in order to identify the possible risk factors for subsequent SLE in the population with PIH.

Patients with PIH may have higher risk of developing newly diagnosed SLE than those without PIH. In addition, among individuals who have experienced PIH, those younger than 30 years, having experienced preeclampsia/eclampsia, single parity, preterm birth, or chronic kidney disease, may display an increased subsequent risk of SLE.

**Abbreviations:** AT1 = type-1 angiotensin II receptor, CI = confidence interval, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, GH = gestational hypertension, HR = hazard ratio, HTN = hypertension, ICD-9-CM = the International Classification of Diseases, Ninth Revision, Clinical Modification, IL = interleukin, IRR = incidence rate ratio, NHIRD = National Health Insurance Research Database, PIH = pregnancy-induced hypertension, SLE = systemic lupus erythematosus, Th = T-helper.

**Keywords:** eclampsia, hypertension in pregnancy, preeclampsia, pregnancy-induced hypertension, systemic lupus erythematosus

## 1. Introduction

Pregnancy-induced hypertension (PIH), which includes gestational hypertension (GH), preeclampsia, and eclampsia, is a major contributor to maternal morbidity and mortality.[1,2] GH is defined as a type of new-onset hypertension (HTN) that develops for the first time after 20 weeks of gestation, and disappears within 12 weeks postpartum. In addition, preeclampsia complicates approximately 3% to 5% of pregnancies.[3,4] Preeclampsia is characterized by the development of HTN and proteinuria after 20 weeks of gestation in previously normoten-

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sive women; eclampsia is characterized by the occurrence of a generalized tonic-clonic seizure that cannot be attributed to other causes within the course of preeclampsia.[5–7] Although the precise pathogenesis of preeclampsia has not been clearly defined, the central hypothesis strongly suggests that there are 2 stages in the pathogenesis of the disease. During 1st stage, the impaired invasion of the spiral arteries by trophoblasts prevents spiral artery remodeling, leading to utero-placental ischemia which is characterized by the production of angiogenic or antiangiogenic factors, reactive oxygen species, and inflammatory cytokines. During the 2nd stage, these factors, which have been released into the systemic maternal circulation, cause widespread endothelial dysfunction, microangiopathy, and vasospasm, which precede the onset of symptomatic clinical disease.[5,8–10]

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that predominantly affects young women of childbearing age.[11–13] The prevalence of SLE ranges from 20 to 150 cases per 100,000 populations and varies by race and ethnic background.[12,13] Genetic susceptibility, environmental effects, hormonal effects, viral infection, and immune disturbances play key roles on the pathogenesis of SLE. These factors act either sequentially or simultaneously on the immune system leading to the generation of autoantibodies, immune complexes, autoreactive T-cells, and inflammatory cytokines, which precede tissue damage and clinical manifestation.[14–16]

The incidence of SLE decreases before puberty and after menopause, and the severity of SLE often changes during pregnancy and throughout the menstrual cycle.[11,17] Data suggest that preeclampsia may be immunologically mediated.[8,18–20] Therefore, it is hypothesized that, dysregulation of the immune system, a characteristic of PIH, may increase a woman's risk for developing SLE. Clinical evidence supports this hypothesis. PIH and SLE share histological findings of the placenta.[21–23] In addition, both diseases are related to premature delivery and intrauterine growth restriction.[24–26] Moreover, preeclampsia is associated with lupus flares.[24,27] Very few studies have examined the relationship between PIH and the risk of SLE. Therefore, we conducted a nationwide population-based retrospective cohort study to investigate the risk for developing SLE among patients who have had PIH. Data from this study were collected over a 13-year observational period.

## 2. Patients and methods

### 2.1. Data sources

The National Health Insurance program in Taiwan began in 1995, and approximately 98% of the population has this coverage. Data for this study were obtained from the National Health Insurance Research Database (NHIRD), which was established by the National Health Research Institute. This database contains insurance claims for 23.3 million beneficiaries from the years 2000 to 2013. The NHIRD safeguards the privacy of individuals and offers data to researchers who have ethical approval. We obtained anonymous data from NHIRD; therefore, the identities of the patients could not be determined. This study was approved by the Institutional Review Board at the Kaohsiung Veteran's General Hospital (VGHKS15-EM4-01).

### 2.2. Study design, participants and definitions of the clinical endpoints and follow-up

Patients with PIH who were over the age of 20 but younger than 50 years were evaluated according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), codes 642.3 to 642.6. Conditions examined in this study as well as their respective medical billing codes were as follows: GH (ICED-9-CM codes 642.30, 642.31, 642.32, 642.33, and 642.34), mild preeclampsia (ICD-9-CM codes 642.40, 642.41, 642.42, 642.43, and 642.44), severe preeclampsia (ICD-9-CM codes 642.50, 642.51, 642.52, 642.53, and 642.54) and eclampsia (ICD-9-CM codes 642.60, 642.61, 642.62, 642.63, and 642.64). To ensure diagnostic validity and to avoid any potential misclassifications, only patients with a diagnosis of PIH and inpatient hospitalization were selected. The overall observational period was from January 1, 2000 to December 31, 2013. Patients were ineligible for participation if they were diagnosed with SLE before January 1, 2000. The index date for the patients in the PIH cohort was the date of their initial PIH diagnosis. A total of 29,091 patients with PIH were assessed in this study. For each patient with PIH, 4 age- and the year of delivery-matched patients without PIH were randomly selected from the NHIRD and included in the comparison cohort. The study endpoint was defined as the date of SLE diagnosis (ICD-9-CM: 710.0) or death during the 13-year follow-up period (2000–2013). Pregnancy characteristics of the patients were recorded, including age, parity, gestational age, gestational number, and comorbidities. Parity, gestational age, and gestational number were determined based on ICD-9-CM codes for delivery (ICD-9-CM: 640–676), preterm birth (ICD-9-CM: 644.2x), and multiple gestation (ICD-9-CM: 651.xx), respectively. The comorbidities in our study included diabetes mellitus (DM) (ICD-9-CM: 250), HTN (ICD-9-CM: 401–405), coronary artery disease (ICD-9-CM: 410–414), dyslipidemia (ICD-9-CM: 272), chronic obstructive pulmonary disease (COPD) (ICD-9-CM: 491.2, 493.2, 496), chronic kidney disease (CKD) (ICD-9-CM: 585, 403), and cerebrovascular disease (ICD-9-CM: 430–437).

### 2.3. Statistical analysis

The incidence of newly diagnosed SLE among patients with PIH and controls was assessed. We calculated the incidence rate for SLE (per 10,000 person-years) as well as the incidence rate ratios (IRRs). The study groups were compared using the Chi-square test for categorical variables and independent *t* tests for continuous variables. A Kaplan–Meier analysis was used to calculate the cumulative incidence rates for SLE between the study and control cohorts, and the log-rank test was used to analyze the differences between survival curves. In addition, a Cox proportional hazards model was used to identify risk factors for SLE in patients displaying a history of PIH. Control variables, such as age, parity, gestational age, gestational number, the number of PIH occurrences, PIH severity, and common comorbidities, including DM, HTN, coronary artery disease, dyslipidemia, COPD, CKD, and cerebrovascular disease, were included as covariates in the univariate model. Variables examined in the univariate analysis that displayed a *P*-value less than 0.1 were included in the multivariate analysis. Statistical Analysis Software (SAS) version 9.4 (SAS System for Windows) was used for data analysis. Comparisons with a *P*-value less than 0.05 were considered significant.

**Table 1**

**Baseline characteristics of patients with PIH and matched cohort.**

| Parameters | PIH (n = 29,091) | | Matched cohort (n = 116,364) | | P |
|---|---|---|---|---|---|
| | n | % | n | % | |
| Age, years, mean ± SD | 30.97 ± 5.04 | | 30.83 ± 5.01 | | 0.999 |
| <30 | 12,692 | 43.63 | 50,768 | 43.63 | |
| ≥30 | 16,399 | 56.37 | 65,596 | 56.37 | |
| Parity | | | | | <0.0001 |
| 1 | 17,917 | 61.59 | 67,694 | 58.17 | |
| ≥2 | 11,174 | 38.41 | 48,670 | 41.83 | |
| Gestational age | | | | | <0.0001 |
| Term | 22,630 | 77.79 | 110,931 | 95.33 | |
| Preterm | 6461 | 22.21 | 5433 | 4.67 | |
| Gestational number | | | | | <0.0001 |
| Singleton | 27,386 | 94.14 | 114,237 | 98.17 | |
| Multiple | 1705 | 5.86 | 2127 | 1.83 | |
| Comorbidities | | | | | |
| Diabetes mellitus | 112 | 0.38 | 67 | 0.06 | <0.0001 |
| Hypertension | 253 | 0.87 | 88 | 0.08 | <0.0001 |
| Dyslipidemia | 94 | 0.32 | 104 | 0.09 | <0.0001 |
| Coronary artery disease | 25 | 0.09 | 76 | 0.07 | 0.2323 |
| COPD | 36 | 0.12 | 58 | 0.05 | <0.0001 |
| Chronic kidney disease | 132 | 0.45 | 120 | 0.10 | <0.0001 |
| Cerebrovascular disease | 51 | 0.18 | 86 | 0.07 | <0.0001 |

COPD = chronic obstructive pulmonary disease, PIH = pregnancy-induced hypertension, SD = standard deviation.

## 3. Results

### 3.1. Participant characteristics

A total of 29,091 patients with PIH and a matched cohort of 116,364 controls were examined in this study. Table 1 shows the demographic and comorbidity data for patients with PIH and the matched controls. The mean age of patients with PIH was 30.97 years. The majority of patients in both cohorts were older than 30 years (56.37%). The prevalence of single parity, preterm births, and multiple pregnancies were higher in the PIH group than in controls. Patients who experienced PIH also displayed a higher prevalence of the following comorbidities: DM, HTN, dyslipidemia, COPD, CKD, and cerebrovascular disease.

### 3.2. Incidence of SLE

The risk for SLE among patients that experienced PIH, stratified by age, parity, gestational age, gestational number, follow-up years, and comorbidities is indicated in Table 2. During the study period, the incidence rates for SLE in patients that experienced PIH and controls were 4.45 and 1.11 per 10,000 person-years, respectively. The risk for developing SLE was significantly higher

**Table 2**

**Incidence of SLE in patients with PIH and matched cohort.**

| Parameters | PIH (n = 29,091) | | Matched cohort (n = 116,364) | | IRR (95% CI) | P |
|---|---|---|---|---|---|---|
| | SLE no. | Per 10,000 person-year | SLE no. | Per 10,000 person-year | | |
| Total | 86 | 4.45 | 86 | 1.11 | 4.02 (3.98–4.05) | <0.0001 |
| Age, years | | | | | | |
| <30 | 52 | 5.58 | 34 | 0.91 | 6.14 (6.06–6.23) | <0.0001 |
| ≥30 | 34 | 3.40 | 52 | 1.29 | 2.63 (2.59–2.66) | <0.0001 |
| Parity, n | | | | | | |
| 1 | 61 | 6.04 | 55 | 1.45 | 4.17 (4.12–4.22) | <0.0001 |
| ≥2 | 25 | 2.71 | 31 | 0.78 | 3.47 (3.41–3.53) | <0.0001 |
| Gestational age | | | | | | |
| Term | 50 | 3.31 | 79 | 1.06 | 3.11 (3.07–3.14) | <0.0001 |
| Preterm | 36 | 8.55 | 7 | 2.07 | 4.14 (4.03–4.25) | <0.0001 |
| Gestational number | | | | | | |
| Singleton | 83 | 4.55 | 83 | 1.09 | 4.19 (4.15–4.23) | <0.0001 |
| Multiple | 3 | 2.76 | 3 | 2.33 | 1.18 (1.13–1.25) | <0.0001 |
| Follow-up years | | | | | | |
| ≤5 | 71 | 25.90 | 65 | 5.96 | 4.34 (4.30–4.39) | <0.0001 |
| 6–10 | 11 | 1.55 | 18 | 0.63 | 2.44 (2.38–2.50) | <0.0001 |
| >10 | 4 | 0.42 | 3 | 0.08 | 5.40 (5.15–5.66) | <0.0001 |
| Any comorbidities | 13 | 36.76 | 8 | 23.07 | 1.59 (1.55–1.64) | <0.0001 |

CI = confidence interval, IRR = incidence rate ratio, PIH = pregnancy-induced hypertension, SLE = systemic lupus erythematosus.

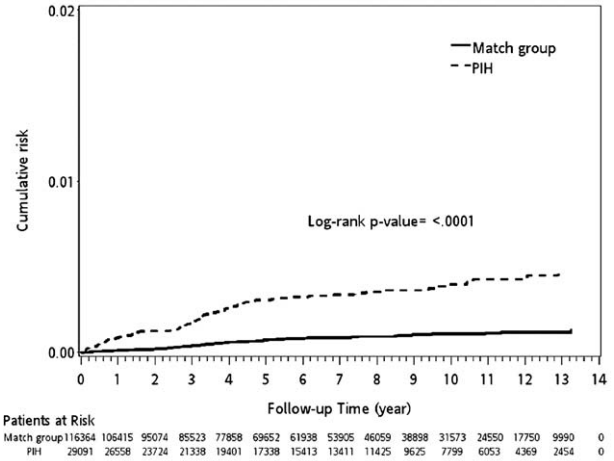


**Figure 1.** The cumulative incidence of SLE in patients with PIH (dashed line) and matched controls (solid line). PIH = pregnancy-induced hypertension, SLE = systemic lupus erythematosus.

for patients that experienced PIH than for patients in the control group (IRR = 4.02, 95% confidence interval [CI] 3.98–4.05, $P < 0.0001$). When stratified by age, parity, gestational age, gestational number, follow-up years, and any comorbidities, patients who had experienced PIH displayed a significantly higher risk of SLE than patients who did not in all stratified subgroups.

According to the Kaplan–Meier analysis, patients with PIH displayed a higher cumulative incidence rate of SLE than those in the matched control cohort (log-rank $P < 0.0001$) (Fig. 1). In addition, after stratifying the data by age, the Kaplan–Meier analysis showed that among patients with a history of PIH, both those under the age of 30 (log-rank $p < 0.0001$) as well as those 30 years of age and older (log-rank $P < 0.0001$), displayed a greater cumulative incidence rate of SLE than patients in the comparison cohort (see Fig. 2A and B).

### 3.3. Risks factors for SLE among patients with PIH and comparison cohort

As shown in Table 3, multivariate survival analysis using Cox model indicated that PIH, not the other possible confounding factors, as an independent risk factor for the development of subsequent SLE (hazard ratio [HR] 2.87, 95% CI 2.07–3.98, $P < 0.0001$).

### 3.4. Risks factors for SLE in patients with PIH

Patients with PIH were divided into 2 groups (i.e., preeclampsia/eclampsia vs GH) based on disease severity (see Table 4). As demonstrated in the multivariate analysis, age <30 years (HR = 2.24, 95% CI 1.43–3.50, $P = 0.0004$), single parity (HR = 2.41, 95% CI 1.39–4.15, $P = 0.0016$), a history of severe PIH (HR = 2.07, 95% CI 1.03–4.16, $P = 0.0407$), preterm birth (HR = 2.24, 95% CI 1.44–3.48, $P = 0.0003$), and CKD (HR = 23.04, 95% CI 11.49–46.18, $P < 0.0001$) were independent risk factors for the subsequent development of SLE among patients with a history of PIH.

## 4. Discussion

We present a population-based study designed to determine if PIH serves as a risk factor for SLE. In our approach, we examined individuals who experienced PIH and a matched control cohort over a follow-up period of 13 years. Several risk factors and possible confounding factors for developing SLE were included in our study. Patients who experienced PIH showed a higher prevalence of the comorbid conditions compared with the control group. The Cox regression model was performed to avoid the influence of these variables while we tried to investigate the association between PIH and the subsequent SLE risk. Results from this analysis showed that a higher incidence of subsequent SLE was observed among patients with PIH. PIH may be an independent risk factors for the development of subsequent SLE. In addition, among individuals that experienced PIH, more severe forms of PIH (i.e., preeclampsia/eclampsia), were associated with a greater risk for developing SLE than less severe forms of PIH, such as GH. Additionally, PIH patients who were aged less than 30 years and had single parity had a higher risk of developing SLE than those who were older than 30 years of age and had multiparity. Furthermore, preterm birth and CKD were independent risk factors for the development of SLE among patients that experienced PIH.

SLE, an autoimmune disease that can affect multiple organs, is caused by genetic, environmental, hormonal, viral, and immune factors, which lead to dysregulation of the immune system.[11,14,16] B-cells are pivotal in the pathogenesis of SLE. In

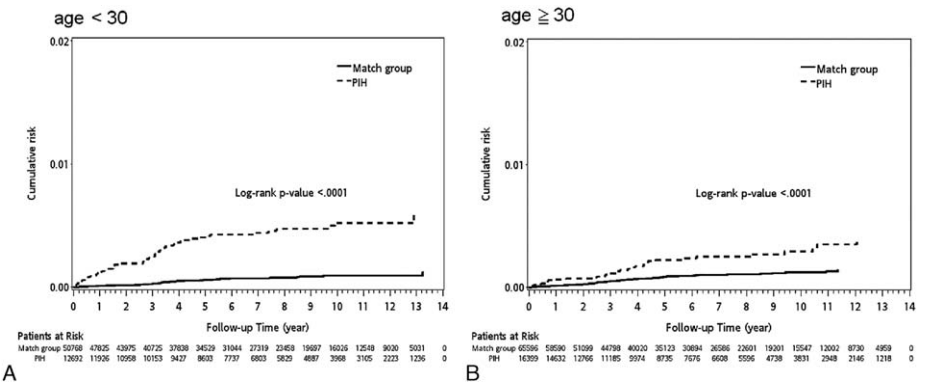


**Figure 2.** The cumulative incidence of SLE, stratified by age, in patients with PIH (dashed line), and matched controls (solid line). (A) age < 30 (B) age ≥ 30. PIH = pregnancy-induced hypertension, SLE = systemic lupus erythematosus.

**Table 3**

**Analyses of risk factors for SLE among the patients with PIH and comparison cohort.**

| | Univariate analysis | | Multivariate analysis* | |
|---|---|---|---|---|
| | HR (95% CI) | P | HR (95% CI) | P |
| PIH | | | | |
| Yes vs No | 4.01 (2.98–5.41) | <0.0001 | 2.87 (2.07–3.98) | <0.0001 |
| Age, years | | | | |
| <30 vs ≥30 | 1.11 (0.82–1.5) | 0.4972 | 1.40 (1.03–1.91) | 0.0333 |
| Parity | | | | |
| 1 vs ≥2 | 2.05 (1.49–2.83) | <0.0001 | 2.00 (1.43–2.79) | <0.0001 |
| Gestational age | | | | |
| Preterm vs term | 3.87 (2.74–5.46) | <0.0001 | 2.09 (1.42–3.06) | 0.0002 |
| Gestational number | | | | |
| Singleton vs multiple | 0.71 (0.31–1.59) | 0.3995 | 1.49 (0.65–3.44) | 0.3479 |
| Hypertension | | | | |
| Yes vs No | 19.36 (9.09–41.24) | <0.0001 | 2.16 (0.91–5.13) | 0.0800 |
| Dyslipidemia | | | | |
| Yes vs No | 9.32 (2.31–37.55) | 0.0017 | 1.50 (0.36–6.30) | 0.5821 |
| Chronic kidney disease | | | | |
| Yes vs No | 72.95 (44.2–120.42) | <0.0001 | 30.53 (17.04–54.71) | <0.0001 |

CI = confidence interval, HR = hazard ratio, PIH = pregnancy-induced hypertension, SLE = systemic lupus erythematosus.

* Adjusted for age, parity, gestational age, gestational number, and comorbidities, including hypertension, dyslipidemia, chronic kidney disease, diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease, and cerebrovascular disease.

addition to producing antibodies, B-cells are also involved in the activation of T-cells, cytokine secretion, and the modulation of dendritic cells; B-cells also act as antigen-presenting cells.[28] T-cells are also critical for SLE pathogenesis as they regulate B-cell responses and infiltrate target organs.[29,30] SLE is regarded as a T-helper (Th)-2-driven disease and displays and increased serum concentration of interleukins (ILs) 4, 6, and 10.[31] Moreover, B-lymphocyte stimulators, IL 17, IL 18, type I interferons, and tumor necrosis factor (TNF) α are also implicated in the inflammatory process and disease pathogenesis of SLE.[32] In addition, deficiencies in components of the complement system are prone to develop SLE.[33]

**Table 4**

**Analyses of risk factors for subsequent SLE among the patients with PIH.**

| | Multivariable analysis* | |
|---|---|---|
| Parameters | HR (95% CI) | P |
| Age, years | | |
| <30 vs ≥30 | 2.24 (1.43–3.50) | 0.0004 |
| Parity | | |
| 1 vs ≥2 | 2.41 (1.39–4.15) | 0.0016 |
| Gestational age | | |
| Preterm vs term | 2.24 (1.44–3.48) | 0.0003 |
| Gestational number | | |
| Singleton vs multiple | 2.39 (0.74–7.68) | 0.1435 |
| PIH severity | | |
| PE/Eclampsia vs GH | 2.07 (1.03–4.16) | 0.0407 |
| Number of PIH occurrences | | |
| ≥2 vs 1 | 1.13 (0.47–2.72) | 0.7874 |
| Hypertension | | |
| Yes vs No | 1.81 (0.65–5.02) | 0.2535 |
| Chronic kidney disease | | |
| Yes vs No | 23.04 (11.49–46.18) | <0.0001 |

CI = confidence interval, GH = gestational hypertension, HR = hazard ratio, PE = preeclampsia, PIH = pregnancy-induced hypertension, SLE = systemic lupus erythematosus.

* Adjusted for age, parity, gestational age, gestational number, PIH severity, number of PIH occurrences, and comorbidities, including diabetes mellitus, hypertension, dyslipidemia, coronary artery disease, chronic obstructive pulmonary disease, chronic kidney disease, and cerebrovascular disease.

Over the past 2 decades, studies have provided evidence that PIH is an immunological disorder.[8,19] The release of inflammatory cytokines, type-1 angiotensin II receptor (AT1) autoantibodies, angiogenic and antiangiogenic factors, and syncytiotrophoblast-derived particles into the maternal circulation lead to systemic endothelial damage and clinical features of PIH.[8] B-cells are also pivotally responsible for the pathophysiology of preeclampsia as they produce autoantibodies.[34] Anti-AT1 autoantibodies, which can activate AT1 in endothelial cells, vascular smooth muscle cells, and mesangial cells, contribute to PIH by inducing oxidative stress, promoting the production of antiangiogenic factors, and by activating the complement component C3.[18,35,36] The degree of B-cell activation and the level of anti-AT1 autoantibodies may be associated with the severity of PIH.[37] It has been proposed that a Th1/Th2 imbalance mediates the pathogenesis of PIH, with a shift toward the Th1 response.[38] As a result, Th1 cytokines, including IL-1, IL-2, and Interferon-γ, are predominant in PIH. In addition to Th1 cytokines, various inflammatory cytokines, such as IL-6, IL-8, IL-18, and TNF-β, derived from activated neutrophils and monocytes, have been demonstrated to play a role in etiology of PIH.[39,40]

A study conducted by Minamiguchi et al[21] indicated that the degree of C4d immunoreactivity was associated with low placental weight and histological placental abnormalities among individuals with PIH, as well as among those with SLE. Activation of the complement cascade may result in placental dysfunction in cases of PIH and in cases of SLE. Moreover, laminin chains and antilaminin autoantibodies appeared to play a role in the pathogenesis of preeclampsia and lupus nephritis.[41–43] As immune dysfunction has been observed among individuals that have experienced PIH and those with SLE, we thought that there might be a relationship between them. It has been established that pregnant patients with SLE are likely to develop PIH.[26,44] Additionally, PIH is associated with increased risk for lupus flares during pregnancy or postpartum.[24,27] However, only a few studies have examined whether

experiencing PIH is associated with an increased risk for developing SLE in the future. A Danish population-based cohort study revealed that the risk for developing any autoimmune disease was significantly increased among women with gestational hypertensive disorders (IRR = 1.21; 95% CI 1.16–1.26). Stronger associations were observed in some specific autoimmune diseases, including SLE and these associations persisted for more than 5 years after child birth.[45] Cooper et al[46] demonstrated that having a history of preeclampsia was associated with an increased risk for experiencing SLE when preeclampsia occurred at a minimum of 3 years before patients were diagnosed with SLE (odds ratio = 3.7). In our study, when compared to the control cohort patients, those with a history of PIH exhibited a 4.02-fold increase in the incidence rate of SLE (95% CI 3.98–4.05, $P < 0.0001$). The risk persisted for more than 10 years postpartum (see Table 2). The Kaplan–Meier analysis revealed that among individuals that had a history of PIH, both those under the age of 30 and those 30 years of age and older displayed a higher cumulative incidence rate for SLE than individuals who did not have a history of PIH (see Fig. 2A and B). Additionally, as shown in Tables 3 and 4, our data revealed that PIH, especially preeclampsia or eclampsia, was associated with an increased risk for developing SLE. As a result, it is reasonable to believe that abnormal immune responses, such as autoantibodies, inflammatory cytokines, and complement deficiency, which are all induced by PIH, could persist in the maternal circulation for many years postpartum and may be implicated in the pathogenesis of SLE later in life.

Few studies have examined the perinatal or reproductive risk factors for the development of SLE. Simard et al indicated that participants that experienced a preterm birth had a statistically significant, 1.9-fold higher incidence of SLE (95% CI 1.2–3.0).[47] A population-based nested case–control study showed that there was a 2.4-fold increased odd of SLE among males born preterm (95% CI 1.09–5.36).[48] Our multivariate analysis revealed that patients with preterm birth displayed a significant 2.09-fold increased HR for SLE (95% CI 1.42–3.06) (see Table 3). The mechanisms underlying the association between preterm birth and SLE are poorly understood. It is possible that alterations in the immune system that are associated with preterm delivery may be implicated in an increased risk for developing autoimmune diseases. For example, C4d immunoreactivity is related to low placental weight and preterm birth[21,22] and is also involved in the pathogenesis of SLE.[21] Interestingly, a population-based cohort study indicated that nulliparous women and 1-child mothers display a markedly increased risk for developing SLE.[49] An increased risk for SLE was also observed among patients with single parity in our study (see Table 3). However, other studies have reported that parity is not correlated with SLE.[46,50]

Based on the age at diagnosis onset, patients with SLE can be categorized into 3 groups: juvenile-onset ($\leq$18 years), adult-onset (19–50 years), and late onset (>50 years).[51] Most of the patients with SLE in our study displayed adult-onset SLE, the largest subgroup of SLE.[52] As shown in Table 3, age less than 30 years old was an independent risk factor for the development of adult-onset SLE. Interestingly, the distribution of ages, among women with SLE, differs by race. A study conducted by Pons-Estel et al[12] showed that the highest age-specific incidence rate for SLE was found in women under the age 40 in the United States, but was observed in women over the age 40 in the United Kingdom, Sweden, and Iceland.

This study was a longitudinal, large population-based design. Thus, some limitations inherent to the adoption of insurance claims databases must be considered. First, the diagnosis of PIH in the NHIRD was according to the ICD-9-CM codes. Information on blood pressure, proteinuria, and other symptoms could not be obtained from the database. Second, several demographic variables were not present in the database, such as socioeconomic status, body mass index, lifestyle, smoking status, and family medical history. These factors could have been used to assess other factors that may be associated with PIH or SLE. Third, the diagnostic criteria for PIH have changed over the years, this could lead to population heterogeneity across studies and may limit comparisons. Fourth, although patients were excluded if they were diagnosed with SLE, preclinical lupus would be difficultly identified in the registered database, which probably led to subsequent PIH development and progressed to SLE many years postpartum. Thus, we had to interpret the data cautiously.

In conclusion, patients that have experienced PIH may have a higher risk for developing SLE later in life. In addition, patients with severe forms of PIH may have a greater risk for developing SLE than patients that experienced less severe forms of PIH. Moreover, younger age, single parity, preterm birth, and CKD were also independent risk factors for the subsequent development of SLE among patients that experienced PIH.

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