Response to: 'Correspondence on 'Increased risk of systemic lupus erythematosus in patients with autoimmune haemolytic anaemia' by Huang and Zhang

We thank Huang and Zhang¹ for their interest in our article entitled 'Increased risk of systemic lupus erythematosus (SLE) in patients with autoimmune hemolytic anaemia (AIHA): a nationwide population-based cohort study'.² In our article, we used nationwide longitudinal population-based data to explore the incidence of systemic lupus erythematosus (SLE) in patients with autoimmune haemolytic anaemia (AIHA) and demonstrated that patients with AIHA are at a very high risk of incidental SLE.² Huang and Zhang¹ have put forward valuable comments and opinions on our article.

First, Huang and Zhang¹ proposed that patients with childhood-onset SLE may be more likely to develop AIHA than adulthood-onset patients, and suggested that we describe the incidence of AIHA in patients with SLE of different age groups. Given that it is impossible to provide such information using our original data, we conducted another nationwide cohort study to investigate the risk of AIHA in patients with SLE stratified by age groups (ie, <18 years and ≥18 years). Using the 1997–2013 Taiwanese National Health Insurance Research Database (NHIRD), we identified 6781 newly diagnosed patients with SLE from 2006 to 2013 and randomly selected 130 340 age, sex-matched (1:20) individuals without SLE from one million representative populations. From the cohort, we used propensity score matching (PSM) (1:2) for age, sex, comorbidities and potential confounders (online supplemental table 1). Before PSM, 123 (1.9%) patients with SLE and 1 (0.001%) individual without SLE had a history of AIHA ($p<0.001$). After excluding those with a history of AIHA, the incidence rates with 95% CIs of AIHA were 26.82 (26.80 to 26.83) cases per 100 000 person-months in patients with SLE

and 0.046 (0.045 to 0.046) individuals without SLE (incidence rate ratio 88.68, 95%CI 185.81 to 1865.06) (table 1). After adjusting for potential confounders, including demographic variables, medical use and comorbidities, the risk of AIHA was markedly increased in patients with SLE (adjusted HR 550.63, 95%CI 172.64 to 1756.25) (online supplemental table 2). However, age was not associated with the risk of AIHA. Among patients with SLE before PSM, the incidence of AIHA was not significantly different between patients with childhood-onset SLE and patients with adulthood-onset SLE (table 2).

Second, Huang and Zhang¹ also suggest that comparison be made on the incidences of SLE between patients with AIHA with idiopathic thrombocytopenic purpura (ITP), patients with AIHA without ITP and patients with ITP without AIHA. We found that of the 1:20 age-matched and sex-matched patients with AIHA ($n=731$), 56 (7.66%) had a history of ITP and 675 (92.34%) had no comorbid ITP. The incidences of SLE were 383.15 cases per 100 000 person-months and 404.47 cases per 100 000 person-months in patients with AIHA with and without ITP, respectively (incidence rate ratio 0.95, 95% CI 0.44 to 2.03). Among ITP patients without AIHA, Zhu *et al*³ recently reported that the incidence of SLE was 52.45 cases per 100 000 person-months using the NHIRD. Also, we agree with Huang and Zhang¹ that both AIHA and ITP are associated with antiphospholipid antibodies.⁴ Unfortunately, the NHIRD lacks laboratory data. Therefore, future human and animal studies were warranted to elucidate the mechanistic role of antiphospholipid antibodies on the development of AIHA and ITP.

Finally, Huang and Zhang¹ were concerned with the validity of AIHA diagnosis by ICD-9 code and suggested checking the autoantibodies to confirm AIHA diagnosis. Given that the NHIRD lacks autoantibodies data, we only considered patients whose AIHA diagnosis was made during hospitalisation but not in outpatient visits only, as patients with AIHA, to improve the validity of AIHA

Table 1 Incidence of AIHA in the study groups before and after PSM

	Before PSM (1:20 age–sex matching)		1:2 PSM	
	Non-SLE	SLE	Non-SLE	SLE
All				
n	130 339	6394	11 738	5869
Follow-up (person-months)	6 586 011	290 881	594 290	266 895
SLE	3	78	1	70
Incidence rate* (95% CI)	0.046 (0.045–0.046)	26.82 (26.80 to 26.83)	0.17 (0.17 to 0.17)	26.23 (26.21 to 26.25)
Crude relative risk (95% CI)	Reference	588.68 (185.81 to 1865.06)	Reference	155.87 (21.65 to 1122.10)
Adjusted HR (95% CI)	Reference	550.63 (172.65 to 1756.25)†	Reference	149.24 (20.76 to 1072.90)‡
Age <18 years				
n	15 440	749	1396	698
Follow-up (person-months)	842 289	38 137	76 401	35 421
SLE	0	12	0	11
Incidence rate* (95% CI)	0	31.47 (31.41 to 31.52)	0	31.06 (31.00 to 31.11)
Crude relative risk (95% CI)	Reference	Cannot estimate	Reference	Cannot estimate
Adjusted HR (95% CI)	Reference	Cannot estimate	Reference	Cannot estimate
Age ≥18 years				
n	114 899	5645	10 342	5171
Follow-up (person-months)	5 743 721	252 744	517 888	231 475
SLE	3	66	1	59
Incidence rate* (95% CI)	0.0522 (0.0520 to 0.0524)	26.11 (26.09 to 26.13)	0.19 (0.19 to 0.19)	25.49 (25.47 to 25.51)
Crude relative risk (95% CI)	Reference	499.96 (157.20 to 1590.12)	Reference	132.00 (18.29 to 952.76)
Adjusted HR (95% CI)	Reference	460.24 (143.69 to 1474.12)†	Reference	126.02 (17.47 to 909.10)‡

*Incidence rate, cases per 100 000 person-months.

†Cox proportional hazard regressions for estimation of HR on AIHA with SLE exposure adjusted for demographic variables, medical use and comorbidities at baseline.

‡Conditional Cox model for estimation of HR on AIHA with SLE exposure alone.

AIHA, autoimmune haemolytic anaemia; PSM, propensity score matching; SLE, systemic lupus erythematosus.

Table 2 Incidence of AIHA in patients with SLE before PSM

	Before PSM (1:20 age–sex matching)	
	<18 years	≥18 years
n	749	5645
Follow-up person-months	38 137	252 744
SLE	12	66
Incidence rate* (95% CI)	31.47 (31.41 to 31.52)	26.11 (26.09 to 26.13)
Crude relative risk (95% CI)	Reference	0.83 (0.45 to 1.54)
Adjusted HRT (95% CI)	Reference	1.02 (0.52 to 1.97)

*Incidence rate, cases per 100 000 person-months.

†Cox proportional hazard regressions for estimation of HR on SLE with AIHA exposure adjusted for demographic variables, medical utilisation and comorbidities at baseline.

AIHA, autoimmune haemolytic anaemia; PSM, propensity score matching; SLE, systemic lupus erythematosus.

diagnosis. This is also the reason why the case number of patients with AIHA in a nationwide dataset was relatively small, leading to a wide range of 95%CI of HR. We also acknowledge that the extremely high HR of SLE risk in patients with AIHA compared with individuals without AIHA can be explained, at least in part, that some patients with AIHA were actually in the early stage of SLE. We tried to improve the validity of AIHA diagnosis by the exclusion of those (n=36) who did not receive corticosteroid or immunosuppressant therapy within 6 months after AIHA diagnosis and found a consistent result using the age-matched and sex-matched populations (adjusted HR 151.11, 95%CI 92.46 to 246.95). Furthermore, Huang and Zhang¹ suggested stratified analyses based on different time intervals to investigate potential time-varying effects. According to the Kaplan-Meier curves that displayed the cumulative incidence of SLE, we examined the risks of SLE associated with AIHA during the time intervals within the first 2 years and after 2 years of follow-up. We found that in the propensity score-matched population, the HRs for SLE development were 202.97 (95% CI 28.28 to 1456.57) and 47.11 (95% CI 6.25 to 355.25) during the first 2 years and after 2 years, respectively.

In conclusion, patients with AIHA had increased risk of SLE particularly in the first 2 years. The risk did not differ between patients with AIHA with and without a history of ITP. We also found a markedly increased risk of AIHA in patients with SLE, and the risk was not significantly different between patients with childhood-onset SLE and patients with adulthood-onset SLE. We suggested that clinicians conduct comprehensive assessment regarding SLE-related clinical and laboratory characteristics to avoid delayed diagnosis of SLE and to improve patient care.

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