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The incidence of uveitis after systemic lymphoma in Taiwan

An 18-year nationwide population-based cohort study

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Abstract

Although uveitis can be an intraocular presentation of systemic lymphoma, it may be associated with direct lymphomatous infiltration and immune-mediated alterations. There have been no published studies describing the incidence of uveitis after systemic lymphoma. We conducted a nationwide cohort study to investigate the incidence of uveitis after systemic lymphoma diagnosis in Taiwan. Data were collected from the Taiwan National Health Insurance system and included patients newly diagnosed with systemic lymphoma between 2000 and 2017. We observed the risk of uveitis among study population since the index date until December 2017. The 1:8 of systemic lymphoma patient and paired comparison was identified by time distribution matching and individual paired with sex and age. Subsequent propensity score matching (PSM) was used to select the 1:1 of systemic lymphoma patient and paired comparison by greedy algorism with caliper of 0.05. The multiple Cox proportional hazard regression model was used to compare the developmental risk of uveitis (time-to-uveitis) between the systemic lymphoma and non-systemic lymphoma, while controlling for selected covariates. After time distribution matching, we selected 6846 patients with systemic lymphoma, and 54,768 comparisons. Among patients with systemic lymphoma groups, there were more men than women (52.94% vs 47.06%) and the mean age was 53.32 ± 21.22 years old. Systemic lymphoma incidence rates (per 10,000 person-months) of uveitis were 1.94 (95% confidence interval [CI], 1.60–2.35) in the systemic lymphoma cohort and 1.52 (95% CI, 1.42–1.63) in the non-systemic lymphoma cohort. Compared with the non-systemic lymphoma cohort, adjusted hazard ratio (aHR) of developing uveitis were 1.24 (95% CI, 1.00–1.52) in people with systemic lymphoma. But not significant in after PSM, aHR of developing uveitis were 1.17 (95% CI, 0.90–1.53). This 18-year nationwide population-based cohort study in Taiwan, showed that the risk of uveitis in patients' systemic lymphoma was not significantly higher than non-systemic lymphoma after PSM. In elderly and rheumatic patients with intraocular inflammation, it is important to first exclude uveitis masquerade syndrome, which could be a harbinger of intraocular involvement from systemic lymphoma. Further large-scale prospective clinical studies to investigate whether systemic lymphoma influences the incidence of uveitis are warranted.

Abbreviations: ASD = absolute standardized difference, aHR = adjusted hazard ratio, CI = confidence interval, ICD9-CM = International Classification of Diseases, 9th Revision, Clinical Modification, LHID = Longitudinal Health Insurance Database, NHIRD = National Health Insurance Research Database, PSM = propensity score matching.

Keywords: cohort study, intraocular inflammation, systemic lymphoma, uveitis

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CJL and CHC contributed equally to this work.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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1. Introduction

Lymphoma is a heterogeneous group of blood malignancies that develop from lymphocytes. Lymphomas are the ninth most common cancer and constitute 3.2% of malignant tumors, which also account for 2.7% of cancer deaths worldwide and can occur at any age.[1] Lymphomas are classified based on the normal counterpart, or cell of origin, from which they arise.[2] They may be broadly divided into non-Hodgkin (90%) and Hodgkin (10%) types. Most lymphomas (90%) are of B cell origin but can also be T cell or natural killer cell.[3] Each type of lymphoma grows at a different rate and responds differently to treatment.[2]

Uveitis refers to sight-threatening intraocular inflammation that affects both the uveal tract and adjacent structures including the sclera, cornea, vitreous, retina, and optic nerve.[4] Patients of uveitis comorbidant with systemic lymphoma have been reported.[4–9] Ocular symptoms of systemic lymphomas are non-specific and often mimic uveitis.[9–16] Malignant lymphomas involving the eye and surrounding structures are rare, representing less than 10% of extranodal lymphoma.[9] As the uvea is rich in blood vessels, immune system activation in 1 organ can result in hematogenous spread of inflammatory cells and cytokines into the eyes. In cases of intraocular involvement of systemic lymphoma, anterior or posterior intraocular inflammation may occur (masquerade syndrome).[9–16]

No published study has investigated the incidence of uveitis after systemic lymphoma. Therefore, we conducted a nationwide cohort study by analyzing the claims data from the Taiwan National Health Insurance Research Database (NHIRD) during a follow-up period from 2000 to 2017 with ICD-9 codes to explore the risk of uveitis in patients with systemic lymphoma and non-systemic lymphoma in the Taiwanese population.

2. Materials and methods

2.1. Data source

Taiwan's Bureau of National Health Insurance set up the NHIRD based on the single-payer National Health Insurance program. This program was inaugurated on March 1, 1995 and provides coverage to over 99% of all residents in Taiwan. We obtained a Longitudinal Health Insurance Database 2005 version (LHID), which includes 2,000,000 insurant Registry for Beneficiaries. All medical claims included both inpatient and outpatient visits and medical treatment for each insurant from January 1, 2000 to December 31, 2017 that were contained in the LHID. To comply with the Personal Information Protection Act, the identification of each insurant in the LHID was re-coded. This study was also approved by the Institutional Review Board of Chung Shan Medical University Hospital (IRB CS1-20108), Taiwan.

2.2. Study subject

We collected patients who were newly diagnosed with systemic lymphoma (the International Classification of Diseases, 9th and 10th Revision, Clinical Modification [ICD-9-CM codes: 200, 201, 202, ICD-10-CM codes: C80, C81, C82, C83, C84, C85, C86, C88]) from 2000 to 2017. Patients with at least 1 medical visit or 1 hospital admission for systemic lymphoma were defined as new cases and the first date of diagnosis with systemic lymphoma was defined as the index date. Those with a diagnosis of systemic lymphoma prior to 2000 were excluded. The endpoint was a new diagnosis of uveitis (ICD-9-CM codes: 360.12, 363.0x, 363.1x, 363.20, 363.21, 363.22, 364.0x, 364.1x, 364.2x, 364.3, ICD-10-CM codes: H44.11, H30, H20). The follow-up was at the start of the index date until the first occurrence of uveitis, death, or December 31, 2017. Those with a history of uveitis before index date were excluded. Index date before 2000, and after 2016 were also excluded.

Controls were randomly selected from a population without histories of systemic lymphoma. The systemic lymphoma cohort was time distribution matching with the non-systemic lymphoma cohort to give a start point at a ratio of 1:8 by age (±1 years old) and sex. To prevent potential confounding bias, the systemic lymphoma cohort was matched with the non-systemic lymphoma cohort by propensity score matching (PSM) with a greedy matching algorithm at a 1:1 ratio, caliper of 0.05. Co-morbidities included hypertension, diabetes mellitus, stable coronary artery disease, hyperlipidemia, congestive heart failure, acute myocardial infarction, rheumatic disease, liver disease, liver cirrhosis, HIV, and tuberculosis.

2.3. Endpoint, demographic characteristics, and systemic lymphoma

The clinical endpoint was a diagnosis of uveitis. Patients with at least 2 medical visits for uveitis, which were separated for at least 7 days, were defined as the endpoint to ensure validity. All study subjects were followed from the index date until the first occurrence of uveitis, death, or December 31, 2017. In this study, the demographic characteristics included age group ($\leq$20, 21–40, 41–65, and $>$65 years old), gender, marital status, and education at the index date.

2.4. Statistical analysis

A chi-square test was used for the difference of demographic characteristics between the systemic lymphoma cohort and comparison cohort. The uveitis survival rates in the 2 groups were calculated using the Kaplan–Meier method and the log-rank test. The multiple Cox proportional hazard regression model was used to compare the incidence risk of uveitis (time-to-uveitis) between the systemic lymphoma and non-systemic lymphoma, while controlling for selected covariates.

To prevent potential confounding bias, the systemic lymphoma cohort was matched with the non-systemic lymphoma cohort by PSM with a greedy matching algorithm at a 1:1 ratio, caliper of 0.05. The goal is to approximate a random experiment, eliminating many of the problems that come with observational data analysis. P values $<.05$ were statistically significant for this study. All analyses were performed using SAS statistical software, version 9.4 (SAS Institute, Inc., Cary, NC).

3. Results

In this retrospective cohort study, a total number of 6846 patients with systemic lymphoma were enrolled in the study group, while another 54,768 individuals were sex age (±1 years old) matching at index date enrolled into the control group. After 1:1 PSM matching by sex, age, marital status, education, and co-morbidities yielded 6811 systemic lymphoma and non-systemic lymphoma. The flowchart of patient selection is shown in Figure 1. The baseline characteristics of all patients with systemic lymphoma and non-systemic lymphoma group in Table 1.

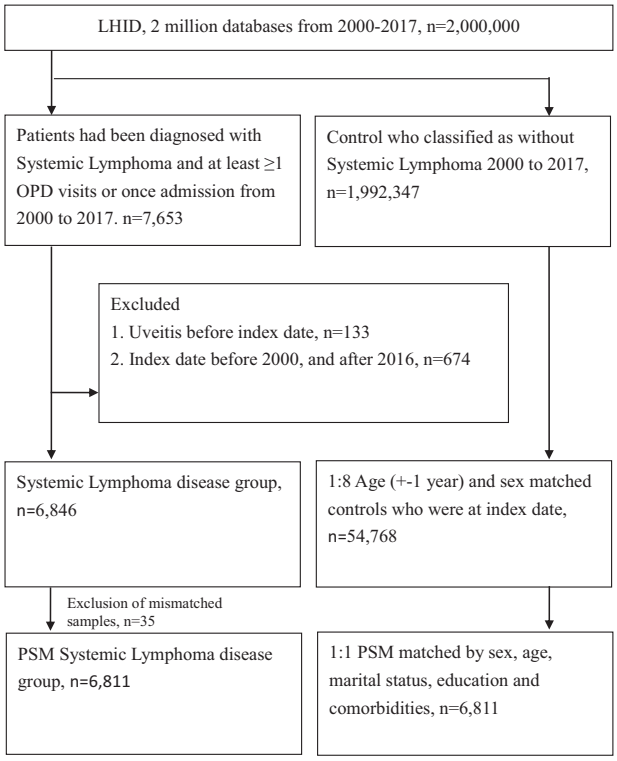

Figure 1. The flowchart of patient selection. LHID = Longitudinal Health Insurance Database, OPD = Outpatient department, PSM = propensity score matching.

After time distribution matching, among patients with systemic lymphoma presenting, there were more men than women (52.94% vs 47.06%) and the mean age was 53.32 ± 21.22 (mean ± standard deviation) years old. After 1:1 PSM, we used absolute standardized difference assess balance in among 2 groups, the absolute standardized difference of <0.1 was mean a small difference (Table 1).

During the follow-up period, for patients with systemic lymphoma the incidence rate was 1.94 (95% confidence interval [CI]: 1.60–2.35) per 10,000 person-months, and without systemic lymphoma the incidence rate was 1.52 (95% CI: 1.42–1.63) per 10,000 person-months, there was significant difference of crude relative risk 1.27 (95% CI: 1.04–1.56). But after PSM the crude relative risk was not significantly 1.09 (95% CI: 0.83–1.41), the incidence rate was 1.95 (95% CI: 1.61–2.36), and 1.78 (95% CI: 1.48–2.13) per 10,000 person-months. The trend was similar in different models after adjusting for multiple potential risk factors including demographic data, systemic diseases, and socioeconomic status (Table 2).

The multiple Cox proportional hazard regression model showed the adjusted hazard ratio (aHR) of uveitis for patients with systemic lymphoma was 1.24 (95% CI: 1.00–1.52) in before PSM, after PSM the aHR of uveitis for patients with systemic lymphoma was 1.17 (95% CI: 0.90–1.53). After PSM, patients aged 41 to 65 years (aHR: 3.05, 95% CI: 1.32–7.03) and age greater than 66 years old group (aHR: 3.31, 95% CI: 1.39–7.85) risk of uveitis was significantly higher than age ≤20 years old group, and patients with rheumatic disease (aHR: 1.85, 95% CI: 1.03–3.32) risk of uveitis was significantly higher than without rheumatic disease (Table 3).

4. Discussion

In this study, the occurrence of uveitis was significantly higher in those with systemic lymphoma compared to non-lymphoma individuals, after adjusting for multiple potential risk factors in the different models. However, after PSM, patients with systemic lymphoma were found to have no significantly higher incidence of uveitis, with the crude relative risk was 1.09 (95% CI: 0.83–1.41).

We can offer some speculations regarding the relationship between systemic lymphoma and uveitis. First, intraocular involvement of systemic lymphoma can present as intraocular inflammation simulating uveitis (masquerade syndromes) with manifestations including vitritis, intermediate uveitis, or subretinal plaque-like lesions.[2] When ophthalmologists encounter patients with intraocular inflammation in Taiwan, the ICD-9 diagnostic codes of uveitis would be usually used to indicate a diagnosis on a reimbursement claim for the arrangement of further examinations.

Another possible indirect connection are patients with sarcoidosis. Several studies strongly support the increased risk of lymphoma in patients with sarcoidosis.[17,18] The underlying sarcoidosis can present as sarcoid uveitis during any stage of the disease. The term "sarcoidosis–lymphoma syndrome" was first suggested by Bichel and Brincker[19] in the 1960s and additional descriptions of this connection have been published.[20]

Several possible pathophysiologic mechanisms may explain the relationship between sarcoidosis and lymphoma. Global regulatory T-cell subset amplification can be found in sarcoidosis, which enhances proliferation of naïve and effector T cells producing interleukin-2. Interleukin-2 furthermore acts as a growth factor for B cells, and the proliferation might override endogenous regulatory mechanisms, eventually leading to their transformation into malignant B cells, which results in systemic lymphoma.[18] This hypothesis is hard to be verified in our studies due to the scarcity of sarcoidosis in Taiwan. In a report from the Taiwanese NHIRD, Taiwan has an overall sarcoidosis prevalence of 2.17 per 100,000 people per year, which is much lower than the prevalence in northern European databases (11–19 per 100,000 per year).[21–23]

Other diseases that correlated with the occurrence of uveitis after systemic lymphoma prior to PSM were diabetes mellitus, stable CAD, hyperlipidemia, and rheumatic diseases. However, after PSM, only rheumatic diseases showed a significant correlation with uveitis. The association between rheumatic diseases and uveitis is reasonable since several rheumatic diseases are the etiologies of uveitis.

Age over 41-years-old was another risk factor identified in our study, which corresponded to the previous epidemiological study.[24,25] Several types of lymphoma can involve the eye and mimic uveitis. Systemic non-Hodgkin lymphoma mostly occurs in people aged 60 and older and more frequently involve the eye than Hodgkin lymphoma. Ocular involvement in Hodgkin lymphoma is relatively rare and usually occurs late in the course of the disease which demonstrates a bimodal distribution, with those between 20 and 30 years and those over 55 years of age having a higher risk.[2,3,10,11]

Prior studies concerning the epidemiology of uveitis have been involved different methodologies and databases. The incidence of uveitis has been estimated to be between 0.14 and 0.43 per 10,000 people per month, which was much lower than our present study (1.52–1.95 per 10,000 of population per month).[26,27] Even in the population older than 65 years, the

Table 1

Baseline characteristics.

	Age-sex matching 8:1			After PSM 1:1		
	Uveitis without systemic lymphoma	Uveitis with systemic lymphoma	ASD	Uveitis without systemic lymphoma	Uveitis with systemic lymphoma	ASD
N	54,768	6846		6811	6811	
Year of index			0.0000			0.0000
2000–2004	14,336 (26.18%)	1792 (26.18%)		1784 (26.19%)	1787 (26.24%)	
2005–2008	12,208 (22.29%)	1526 (22.29%)		1508 (22.14%)	1520 (22.32%)	
2009–2012	11,832 (21.6%)	1479 (21.6%)		1479 (21.71%)	1466 (21.52%)	
2013–2016	16,392 (29.93%)	2049 (29.93%)		2040 (29.95%)	2038 29.92%)	
Sex			0.0000			0.006
Female	25,776 (47.06%)	3222 (47.06%)		3192 (46.87%)	3215 (47.2%)	
Male	28,992 (52.94%)	3624 (52.94%)		3619 (53.13%)	3596 (52.8%)	
Age at index (mean ± SD)	53.29 ±21.21	53.32 ±21.22	0.0000	54.29 ±21.01	53.37 ±21.22	0.029
≤20	4552 (8.31%)	569 (8.31%)		543 (7.97%)	567 (8.32%)	
21–40	10,505 (19.18%)	1318 (19.25%)		1233 (18.1%)	1303 (19.13%)	
41–65	21,859 (39.91%)	2715 (39.66%)		2703 (39.69%)	2703 (39.69%)	
>65	17,852 (32.6%)	2244 (32.78%)		2332 (34.24%)	2238 (32.86%)	
Marital status			0.047			0.024
Unmarried	13,105 (23.93%)	1598 (23.34%)		1482 (21.76%)	1577 (23.15%)	
Married	34,396 (62.8%)	4344 (63.45%)		4414 (64.81%)	4335 (63.65%)	
Divorced	2866 (5.23%)	404 (5.9%)		401 (5.89%)	401 (5.89%)	
Widowed	4401 (8.04%)	500 (7.3%)		514 (7.55%)	498 (7.31%)	
Education			0.044			0.047
Elementary school or below	24,757 (45.2%)	2972 (43.41%)		3048 (44.75%)	2961 (43.47%)	
Junior high school	8623 (15.74%)	1090 (15.92%)		1028 (15.09%)	1084 (15.92%)	
Senior high school	13,916 (25.41%)	1796 (26.23%)		1775 (26.06%)	1788 (26.25%)	
University/college or above	7472 (13.64%)	988 (14.43%)		960 (14.09%)	978 (14.36%)	
Co-morbidities						
Hypertension	14,426 (26.34%)	2287 (33.41%)	0.154	2397 (35.19%)	2278 (33.45%)	0.036
Diabetes mellitus	6780 (12.38%)	1199 (17.51%)	0.144	1235 (18.13%)	1193 (17.52%)	0.016
Stable CAD	4574 (8.35%)	798 (11.66%)	0.110	831 (12.2%)	793 (11.64%)	0.017
Hyperlipidemia	7234 (13.21%)	1082 (15.8%)	0.073	1141 (16.75%)	1081 (15.87%)	0.023
Congestive heart failure	1614 (2.95%)	394 (5.76%)	0.138	391 (5.74%)	390 (5.73%)	0.000
AMI	184 (0.34%)	43 (0.63%)	0.042	37 (0.54%)	42 (0.62%)	0.009
Rheumatic disease	482 (0.88%)	193 (2.82%)	0.144	180 (2.64%)	190 (2.79%)	0.009
Liver disease	4155 (7.59%)	1305 (19.06%)	0.342	1324 (19.44%)	1280 (18.79%)	0.016
Liver cirrhosis	406 (0.74%)	215 (3.14%)	0.174	210 (3.08%)	209 (3.07%)	0.000
HIV	24 (0.04%)	44 (0.64%)	0.102	19 (0.28%)	24 (0.35%)	0.013
Tuberculosis	244 (0.45%)	156 (2.28%)	0.158	131 (1.92%)	142 (2.08%)	0.011
CCI score			4.291			3.260
0–2	49,050 (89.56%)	0 (0%)		5697 (83.64%)	0 (0%)	
3–5	4734 (8.64%)	4939 (72.14%)		887 (13.02%)	4933 (72.43%)	
6–8	710 (1.3%)	837 (12.23%)		167 (2.45%)	832 (12.22%)	
≥9	274 (0.5%)	1070 (15.63%)		60 (0.88%)	1046 (15.36%)	

AMI = acute myocardial infarction, ASD = absolute standardized difference, CAD = coronary artery disease, HIV = human immunodeficiency virus, PSM = propensity score matching, SD = standard deviation.

incidence rate was around 0.79 per 10,000 people per month, which is still lower than our present study.[26,27] Several reasons may explain the difference. First, access to health care is extremely convenient in Taiwan. Patients in this population with uveitis may be more likely to seek an ophthalmologist's evaluation than patients in other populations studied. Second, since patients with systemic lymphoma regularly follow up in the health care system, we speculate that health awareness and willingness to accept referral with the presentation of ocular symptoms may be higher among these patients than the general population.

A previous NHIRD study in Taiwan which reported average uveitis incidence was 0.93 cases per 10,000 person-months from 2003 to 2008 with the 95% CI ranged between 0.90 cases and 0.95 cases per 10,000 person-months.[28] The incidence was comparable to our study results when a similar aged group was selected. In the age group from 56 to 65 and older than 66-year-old, the incidence was 1.24 and 1.62 cases per 10,000 person-months which served as another evidence to the validity of the present study.

Several limitations remain in the current study. First, most of the biases came from the retrospective nature of this study. The usage of insurance claim database, rather than real medical documents, inevitably renders some important information unavailable, such as the severity of uveitis, the etiology of uveitis, and the disease status of systemic lymphoma. Nevertheless, the PSM process and multivariable analysis were used for further verification. Also, the sample size might also influence the results. Although NHIRD covered more than 99% of the cases in our population, a cross-national database could provide a more comparative observation and confirm the relationship of lymphoma and uveitis. Finally, only patients of uveitis suspected

Table 2

Incidence rate for the uveitis.

	Before PSM		After PSM	
	Non-systemic lymphoma	Systemic lymphoma	Non-systemic lymphoma	Systemic lymphoma
N	54,768	6846	6811	6811
Follow up person months	5,302,788	545,111	645,434	543,220
New diagnosed uveitis	808	106	115	106
Incidence rate (95% CI)	1.52 (1.42–1.63)	1.94 (1.60–2.35)	1.78 (1.48–2.13)	1.95 (1.61–2.36)
Crude relative risk (95% CI)	Reference	1.27 (1.04–1.56)	Reference	1.09 (0.83–1.41)
Model 1: adjusted hazard ratio (95% CI)	Reference	1.34 (1.10–1.65)	Reference	1.16 (0.89–1.51)
Model 2: adjusted hazard ratio (95% CI)	Reference	1.28 (1.05- 1.58)	Reference	1.17 (0.89–1.52)
Model 3: adjusted hazard ratio (95% CI)	Reference	1.24 (1.00–1.52)	Reference	1.17 (0.90–1.53)

Incidence rate, per 10,000 person-months.

Model 1: including age, sex, marital status, and education.

Model 2: including age, sex, marital status, education, hypertension, diabetes mellitus, and hyperlipidemia.

Model 3: including age, sex, marital status, education, and co-morbidities (hypertension, diabetes mellitus, stable coronary artery disease, hyperlipidemia, congestive heart failure, acute myocardial infarction, rheumatic disease, liver disease, liver cirrhosis, HIV, and tuberculosis.

CI = confidence interval, PSM=propensity score matching.

by ophthalmologists were enrolled in the current study to gain the incidence of the diagnosis. Other patients who did not seek medical care may have contributed to an underestimation of the incidence of uveitis.

Table 3

Multiple Cox proportional hazard regression.

	Adjusted hazard ratio (95% CI)	
Variable	**Before PSM**	**After PSM**
Study		
Uveitis without systemic lymphoma	Reference	Reference
Uveitis with systemic lymphoma	1.24 (1.00–1.52)	1.17 (0.90–1.53)
Sex		
Male	1.10 (0.96–1.26)	1.21 (0.91–1.60)
Female	Reference	Reference
Age at index		
≤20	Reference	Reference
21–40	1.33 (0.91–1.94)	1.45 (0.63–3.30)
41–65	2.07 (1.42–3.04)	3.05 (1.32–7.03)
>65	2.44 (1.64–3.62)	3.31 (1.39–7.85)
Marital status		
Unmarried	Reference	Reference
Married	1.25 (0.98–1.61)	1.07 (0.64–1.80)
Divorced	1.14 (0.79–1.65)	0.82 (0.37–1.81)
Widowed	1.13 (0.80–1.58)	0.82 (0.39–1.72)
Education		
Elementary school or below	Reference	Reference
Junior high school	0.76 (0.62–0.94)	0.62 (0.39–0.99)
Senior high school	0.89 (0.74–1.06)	0.93 (0.65–1.32)
University/college or above	0.85 (0.68–1.06)	1.04 (0.69–1.57)
Co-morbidities		
Hypertension	1.18 (1.00–1.40)	1.31 (0.95–1.80)
Diabetes mellitus	1.30 (1.07–1.57)	1.08 (0.76–1.55)
Stable coronary artery disease	1.37 (1.13–1.64)	1.24 (0.87–1.76)
Hyperlipidemia	1.25 (1.01–1.54)	1.13 (0.76–1.68)
Congestive heart failure	0.97 (0.67–1.42)	1.05 (0.58–1.90)
Acute myocardial infarction	0.79 (0.25–2.49)	1.44 (0.34–5.97)
Rheumatic disease	2.01 (1.33–3.06)	1.85 (1.03–3.32)
Liver disease	1.07 (0.86–1.34)	1.17 (0.84–1.64)
Cirrhosis	0.89 (0.41–1.94)	1.02 (0.43–2.42)
Human immunodeficiency virus	1.68 (0.23–12.0)	2.06 (0.28–14.9)
Tuberculosis	1.51 (0.78–2.93)	1.92 (0.94–3.93)

CI = confidence interval, PSM=propensity score matching.

In conclusion, despite the fact that systemic lymphoma with intraocular involvement may present as uveitis, this 18-year nationwide population-based cohort study showed that the incidence of uveitis after systemic lymphoma was not significantly higher than the PSM group in Taiwan. Nevertheless, the incidence of uveitis is higher than epidemiological data from western countries. In elderly and rheumatic patients with intraocular inflammation, it is important to first exclude uveitis masquerade syndrome, which could be a harbinger of intraocular involvement from systemic lymphoma. An earlier diagnosis is essential to prescribe appropriate treatment and to improve the outcome. Further large-scale prospective clinical studies to investigate whether systemic lymphoma influences the incidence of uveitis are warranted.

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Author contributions

The authors have no proprietary or commercial interest in any materials mentioned in this article. The authors were involved in design and conduct of study; data collection; analysis, management, and interpretation of data; and preparation, review, and approval of the manuscript.

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