ANNALS of Clinical and Translational Neurology
Open Access
AMERICAN NEUROLOGICAL ASSOCIATION

RESEARCH ARTICLE

Risk of incident autoimmune diseases in patients with thymectomy

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Funding Information
This study did not receive any funding.

Received: 26 August 2019; Revised: 8 April 2020; Accepted: 10 April 2020

Annals of Clinical and Translational Neurology **2020; 7(7): 1072–1082**

doi: 10.1002/acn3.51055

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Abstract

Objectives: The data concerning the association between Tx and ADs remain unclear and are scarce. This study was undertaken to investigate whether people with Tx are more likely to develop ADs, compared to those without Tx. **Methods**: Individuals who received Tx between 2002 and 2015 were identified and matched on age and sex with individuals without Tx. We performed multivariate and stratified analysis using the Kaplan–Meier method and Cox proportional hazards models in order to estimate the association between Tx and the risk of developing ADs. **Results**: A total of 2550 thymectomized (Txd) patients and 24,664.941 non-Txd comparison subjects were selected from NHIRD. Tx-MG (myasthenia gravis) as compared with general population (nonTx-nonMG), adjusted hazard ratio (aHR) were higher for incident Addison disease (aHR = 10.40, 95% CI 1.01–107), autoimmune hemolytic anemia (aHR = 21.54, 95% CI 2.06–14.8), Hashmoto thyroiditis (aHR = 5.52, 95% CI 1.34–34.7), ankylosing spondylitis (aHR = 2.73, 95% CI 1.09–6.84), rheumatoid arthritis (aHR = 5.25, 95% CI 1.79–15.47), primary Sjogren syndrome (pSS) (aHR = 3.77, 95% CI 1.30–11.0), and systemic lupus erythemtoasus (aHR = 10.40). Tx-nonMG as compared with general population, aHR were higher for incident autoimmune hemolytic anemia (aHR = 25.50), Hashmoto thyroiditis (aHR = 6.75) and systemic lupus erythematosus (SLE) (aHR = 13.38). NonTx-MG as compared with general population, aHR were higher for incident Hashmoto thyroiditis (aHR = 6.57), pSS (aHR = 4.50), SLE (aHR = 17.29), and systemic vasculitis (aHR = 25.86). **Interpretation**: In conclusion, based on a retrospective cohort study throughout Taiwan, patients with Tx have a higher risk of new onset ADs than patients without Tx.

Introduction

The thymus plays a crucial role in the context of cell-mediated immunity in the differentiation of T lymphocytes, not only during the embryogenesis and fetal period but also during the adulthood, even after its involution.[1] The thymus deletes self-reactive T cells with high avidity T-cell receptors for self antigens expressed in the thymus.[2] This, hence, means that thymus has a protective role against autoimmunity. It has been proved, indeed, that thymectomy (Tx) in adult rat entails a decrease in the T-lymphocyte response to mitogens and eventually its

abolition.[3] The removal of the thymus can decrease the activity of T-helper cells but in the same time it might enhance the activity of T-suppressor whose function is depressed in autoimmune diseases.[4]

The surgical removal of the thymus gland is successfully used to manage myasthenia gravis (MG).[5] The goal of Tx was not only to prevent the spread of a thymoma, a well-known associated disorder, but also to induce remission of the disease.[6] However, the precise mechanism by which Tx produces benefit in patients with MG is still unclear. This therapeutic option is indicated in young patients, usually <60 years old,[7] because there is uncertainty about the persistence of thymic tissue in elderly subjects.[8] However, it is advisable to delay Tx until puberty if possible because of the established role of the thymus in the development of the immune system.[9] Nevertheless, it is generally thought that Tx does not cause significant adverse effects.[8]

In recent years, there has been growing evidence of systemic autoimmune diseases (AIDs) occurring many years after Tx in patients with MG or other immune-mediated diseases.[10-18] The data reveled the long-term effect of Tx on T cell and on T cell–dependent B-cell activity in MG appear to be controversial. Our aim was to evaluate the role of Tx to clarify whether it may be regarded as therapeutic or a factor paving the way to the onset of ADs. No large cohort study has investigated the incidence of ADs among patients with Tx. We investigated this putative association utilizing a nationwide population-based dataset of insurance claims.

Methods

Data sources

Medical claims data were obtained from the National Health Research Institutes (NHRI). After receiving approval for this study from the NHRI, we used scrambled patient identification numbers to assess the data, including inpatient care claims and the Registry for Beneficiaries. The NHRI maintains and updates the National Health Insurance (NHI) Research Database (NHIRD). The insurance program maintains contracts with 97% of the hospitals and clinics in Taiwan.[19] The accuracy and high validity of diagnoses in the NHIRD have been evaluated.[20] The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes were used as the diagnosis codes in the present study. The claims data for all 23,740,000 insured persons were used to establish the study cohorts. The research protocol was approved by the Taipei Medical University-Joint Institutional Review Board (N201602014) and was performed in accordance with the approved guidelines. Informed consent from the study patients was not required because the dataset consisted of deidentified secondary data released for research purposes.

Study population and design

We identified 5418 patients (case group) who received Tx (Procedure Code: 07.8) from NHIR database between 1 January 2002, and 31 December 2015. Cases with unknown age and sex, with surveyed autoimmune diseases prior to study start, and diagnosis of all cancer (except thymoma and thymic carcinoma) were excluded from the study. Then case group (n = 2550) divided to (1) thymectomized (Txd) patients (n = 1183) with MG (ICD-9-CM 358) with a catastrophic illness certificate and (2) Txd patients (n = 1367) without MG. Subjects without Tx (comparison group) were selected from among the 23 million NHI beneficiaries recorded between 2002 and 2015 using the same exclusion. The comparison group was also divided to (3) nonTx-MG group: nonTxd patients with MG and (4) nonTx-nonMG group: nonTxd patients without MG. Then we used frequency matching by sex and age to the four groups (1;1, 1;3, and 1;20, respectively).

Study endpoints

Each study patient was followed until one of the following outcomes occurred: an AD was diagnosed, the patient was lost to follow-up, the patient died, the patient withdrew from the NHI system. We identified patients with ADs using ICD-9-CM codes. ADs in this study were categorized into two broad types: systemic and organ-specific ADs. The systemic ADs included Sjögren syndrome (SS; ICD-9-CM code 710.2), psoriasis (ICD-9-CM codes 696.0 and 696.1), rheumatoid arthritis (RA; ICD-9-CM code 714.0), systemic lupus erythematosus (SLE; ICD-9-CM code 7100), scleroderma (ICD-9-CM code 710.1), polymyositis (PM; ICD-9-CM code 710.4), and systemic vasculitis (ICD-9-CM code 443.1, 446.4, 446.7). In Taiwan, patients with systemic ADs (except Ankylosing spondylitis ICD-9-CM code 712.0 and psoriasis ICD-9-CM codes 696.0, 696.1, and 694.3) are eligible for a catastrophic illness certificate after receiving the diagnosis from a rheumatology specialist based on their clinical manifestations, laboratory data, and international criteria; the certification requires the precise fulfillment of the related classification criteria.[21-29] The organ-specific ADs included Addison's disease (ICD-9-CM code 255.4), autoimmune hemolytic anemia (ICD-9-CM code 283.0), diabetes mellitus type 1 (DM; ICD-9-CM code 250.0), Graves' disease (ICD-9-CM code 242.0), Hashimoto's thyroiditis (ICD-9-CM code 245.2), Henoch–Schönlein purpura (ICD-9-CM

code 287.0), immune thrombocytopenic purpura (ICD-9-CM code 287.3), autoimmune hepatitis (ICD-9-CM code 571.49), MG (ICD-9-CM code 358.0), and inflammatory bowel disease (IBD; ICD-9-CM codes 555 and 556). A person was considered to have a new onset of an organic AD only if the condition occurred in an inpatient setting or was noted in three or more outpatient visits.

In addition, patients with the comorbidities of SLE, RA, scleroderma, PM, DM, a history of head and neck radiation treatment, hepatitis C infection, ADs, pre-existing lymphoma, sarcoidosis, graft versus host disease, and anticholinergic drug use were excluded to limit our study sample to primary SS (pSS). Therefore, the catastrophic illness patient data are highly accurate and reliable.[30]

Statistical analysis

We compared the frequency or mean of demographic status (age and sex) in the Tx-MG, Tx-nonMG, nonTx-MG, and nonTx-nonMG cohorts using the chi-squared test or *t* test. The incidence rates of any type, organ-specific and systemic ADs were estimated during the follow-up duration in the Tx-MG, Tx-nonMG, nonTx-MG, and nonTx-nonMG cohorts. The Cox proportional hazards regression model was used to estimate the corresponding hazard ratios (HRs) and 95% confidence intervals (CIs). The HRs were adjusted for sex and age in the Cox regression model. Finally, the cumulative incidences of any type, organ-specific and systemic ADs were estimated using the Kaplan–Meier estimator, known as the product limit estimator, in the Tx-MG, Tx-nonMG, nonTx-MG, and nonTx-nonMG cohorts. SAS (version 9.3, SAS Institute, Cary, NC) was used for all the data analyses, and $P < 0.05$ was considered statistically significant.

Patient and public involvement

There were no patients involved in developing the research question or the outcome measures, and no patients were involved in the design, recruitment, and conduct of the study. The data were collected from the National Health Insurance Research Database, and patients were anonymous. We were unable to disseminate the results of the research directly to study participants.

Results

Baseline characteristics of the study population

A total of 2550 Txd patients and 24,664.941 non-Txd comparison subjects were selected from NHIRD. After individual frequency matching, patients were divided in to four group: (1) 807 Txd patients with MG (Tx-MG) (2) 807 Tx patients without MG (Tx-nonMG) (3) 2421 non-Tx patients with MG (nonTx-MG) and (4) 16,140 non-Tx patients without MG (nonTx-nonMG). The flowchart of study population selection is shown in Figure 1.

Table 1 presents the demographic characteristics and top five reason of Tx of the study cohorts. The mean ages in each group were Tx-MG: 46.79 ± 14.80, Tx-nonMG: 47.01 ± 17.78, nonTx-MG: 46.86 ± 14.83, and nonTx-nonMG: 46.75 ± 14.81, respectively, and the study population was dominated by women (58.98%). The mean follow-up duration (year) in each group were Txd-MG: 2.16 ± 1.47, Tx-nonMG: 1.83 ± 1.358, nonTx-MG: 1.56 ± 1.14, and nonTx-nonMG: 2.35 ± 1.46, respectively. The top five reasons of Tx in order were benign neoplasm of thymus, malignant neoplasm of thymus, MG, other disorders from impaired renal function, other specified diseases of thymus gland.

Incidence rates, ratio and aHRs of ADs and subgroup ADs in each cohort

Table 2 presents the incidence rates and adjusted HRs (aHRs) of ADs and subgroup AIDs in each cohorts. During the study period, 3.3% Tx-MG, 1.73% Tx-nonMG, 1.98% nonTx-MG, and 0.87% nonTx-nonMG patients, respectively, developed any type of AIDs. The incidence rate of any-type of AIDs was higher in the Txd-MG cohort (524.38 per 100,000 person years), Tx-nonMG cohort (347.02 per 100,000 person years), and nonTx-MG (463.77 per 100,000 person years) than in the nonTx-nonMG cohort (135.63 per 100,000 person-years), with an aHR of the Tx-MG cohort 3.85 (95% CI: 2.53–5.86), Tx-nonMG cohort 2.51 (95% CI: 1.44–4.39), and nonTx-MG cohort 3.32 (95% CI: 2.40–4.59) after adjustment for age and sex. For the organ-specific AIDs, the incidence rate of overall organ-specific AIDs was significantly higher in the Tx-MG, Tx-nonMG, and nonTx-MG cohort than in the nonTx-nonMG, with an aHR of the Tx-MG cohort (3.53), Tx-nonMG cohort (3.78), and nonTx-MG cohort (3.30) after adjustment for age and sex (Table 2). Furthermore, for the respective organ-specific ADs, the incidence rate of Hashmotos thyroiditis was significantly higher in the Tx-MG, Txd-non-MG, and nonTx-MG cohort than in the nonTx-nonMG control cohort, with an aHR of the Tx-MG cohort (5.52), Txd-nonMG cohort (6.75), and nonTx-MG cohort (6.57) after adjustment for age and sex. In addition, the incidence rate of autoimmune hemolytic anemia was significantly higher in the Tx-non-MG cohort than in the nonTx-nonMG control cohort, with an aHR of the Tx-MG cohort (25.50) after adjustment for age and sex.

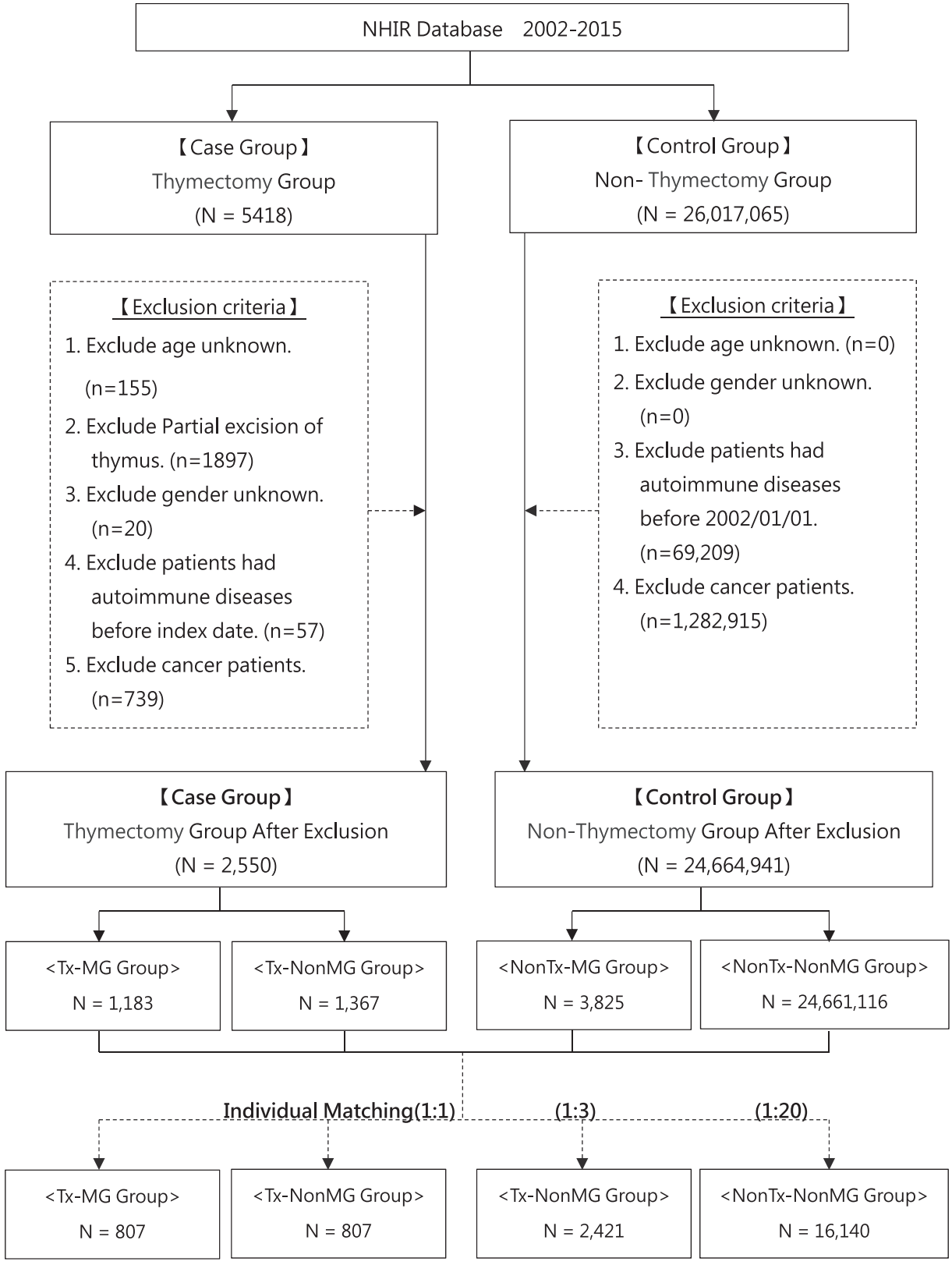

Figure 1. Flow chart for study design. MG, myasthenia gravis; Tx, thymectomy.

Table 1. Characteristic baseline of each group (Tx-MG, Tx-nonMG, nonTx-MG, and nonTx-nonMG).

Variables	Tx-MG (*N* = 807) *N* (%)	Tx-nonMG (*N* = 807) *N* (%)	NonTx-MG (*N* = 2421) *N* (%)	NonTx-nonMG (*N* = 16,140) *N* (%)	*P*-Value
Gender					1.0000
Female	476 (58.98)	476 (58.98)	1428 (58.98)	9520 (58.98)	
Male	331 (41.02)	331 (41.02)	993 (41.02)	6620 (41.02)	
Age					0.9995
≤30	122 (15.12)	118 (14.62)	346 (14.29)	2405 (14.90)	
31–40	145 (17.97)	133 (16.48)	456 (18.84)	2942 (18.23)	
41–50	201 (24.91)	212 (26.27)	605 (24.99)	4079 (25.27)	
51–60	202 (25.03)	203 (25.15)	603 (24.91)	3980 (24.66)	
61–70	87 (10.78)	94 (11.65)	264 (10.90)	1756 (10.88)	
71–80	44 (5.45)	42 (5.2)	135 (5.58)	878 (5.44)	
≥81	6 (0.74)	5 (0.62)	12 (0.50)	100 (0.62)	
Mean (SD), year	46.79 (14.80)	47.01 (14.78)	46.86 (14.83)	46.75 (14.81)	0.9525
Follow-up, year					
Mean (SD)	2,16 (1,47)	1,83 (1,35)	1,56 (1,14)	2,35 (1,46)	<0.0001
Top five reasons of Tx					
Benign neoplasm of thymus	18.77%				
Malignant neoplasm of thymus	18.48%				
Myasthenia gravis	17.78%				
Other disorders from impaired renal function	5.92%				
Other specified diseases of thymus gland	5.92%				

Tx, thymectomy; MG, myasthenia gravis.

For the systemic ADs, the incidence rate of overall systemic ADs was significantly higher in the Tx-MG and nonTx-MG cohort than in the nonTx-nonMG, with an aHR of the Tx-MG cohort (4.21) and nonTx-MG cohort (3.51) after adjustment for age and sex. Furthermore, for the respective systemic AIDs, the incidence rate of ankylosing spondylitis and RA was significantly higher in the Tx-MG than in the nonTx-nonMG control cohort, with an aHR (2.73 and 5.25, respectively). In addition, the incidence rate of pSS was significantly higher in the Tx-MG and nonTx-MG cohort than in the nonTx-nonMG control cohort, with an aHR of the Tx-MG cohort (3.77) and nonTxd-MG (4.50). The incidence rate of SLE was significantly higher in the Tx-MG, Tx-noMG, and nonTx-MG, with an aHR of 21.31, 13.38, and 17.29, respectively. The incidence rate of systemic vasculitis was significantly higher in the nonTx-MG, with an aHR of 25.86.

Higher incidence of incident autoimmune diseases among Txd patients than non-Txd controls

For respective ADs, the incidence rate of any type ADs (aHR 2.65, 95% CI: 1.880–3.728, $P < 0.001$), organ specific ADs (aHR 3.00, 95% CI: 1.761–5.099, $P < 0.001$) and systemic ADs (aHR 2.56, 95% CI: 1.648–3.982, $P < 0.001$) were significantly higher in the Txd cohort than in the non-Txd control cohort, as shown in Table 3. Kaplan–Meier analyses also revealed that patients with Tx had a higher risk for development of ADs (log-rank test, $P < 0.001$, Fig. 2).

Kaplan–Meier survival of ADs and subgroup ADs in each cohort

Analysis of Kaplan–Meier survival of any type ADs, organ specific ADs and systemic ADs showed that the survival rate of Tx-MG, Tx-nonMG, and nonTx-MG cohort was significantly lower than that of nonTx-nonMG cohort ($P < 0.0001$; Fig. 3).

Discussion

According to our review of the relevant literature, this study is the first nationwide population-based work to evaluate the relationship between Tx and ADs. In this study, the overall incidence rate of any type ADs was 2.68 times higher in the Txd cohort than in the non-Txd cohort, with an aHR of 2.65 after adjustment for age and sex. Furthermore, we found that patients underwent Tx also had an increased risk of organ-specific and systemic ADs, respectively.

In this study, we found that patients underwent Tx had an increased risk of any type ADs. Tx may exert

Table 2. Incidence rate and hazard rate of Autoimmune diseases and subgroup in each cohort.

	Tx-MG				Tx-nonMG				NonTx-MG				NonTx-nonMG			
Type of ADs	Event (%)	IR	IRR	Adjusted-HR (95% CI)	Event (%)	IR	IRR	Adjusted-HR (95% CI)	Event (%)	IR	IRR	Adjusted-HR (95% CI)	Event (%)	IR	IRR	Adjusted-HR
Organ specific-AIDs																
Addison disease	0.12	20.45	10.70	10.40* (1.01–107)	0.00	–	–	–	0.00	–	–	–	0.01	1.91	Ref	Ref
AHA	0.12	20.44	21.40	21.54* (1.34–347)	0.12	24.42	25.55	25.50* (1.59-410)	0.04	9.53	9.97	9.01 (0.54–150)	0.01	0.96	Ref	Ref
DM (type 1)	0.12	20.45	0.82	0.81 (0.11–6.01)	0.12	24.8	0.98	0.95 (0.13–7.03)	0.21	47.69	1.92	1.86 (0.69–4.97)	0.16	24.89	Ref	Ref
Hashmoto thyroiditis	0.62	102.64	5.65	5.52** (2.06–14.8)	0.62	122.62	6.75	6.75** (2.54-17.9)	0.50	114.69	6.31	6.57*** (3.20–13.48)	0.12	18.18	Ref	Ref
HSP	0.12	20.47	5.35	5.57 (0.62–50.4)	0.12	24.43	6.39	6.28 (0.70–56.3)	0.00	–	–	–	0.02	3.82	Ref	Ref
Systemic ADs																
AS	0.62	102.78	2.75	2.73* (1.09–6.84)	0.12	48.87	1.31	1.23 (0.29–5.14)	0.25	57.31	1.53	1.37 (0.58–3.28)	0.24	37.35	Ref	Ref
RA	0.50	82.19	5.05	5.25** (1.79–15.4)	0.00	–	–	–	0.04	19.07	1.17	1.20 (0.29–5.03)	0.11	16.26	Ref	Ref
PSS	0.50	82.19	3.74	3.77* (1.30–11.0)	0.12	24.40	1.11	1.07 (0.14–8.06)	0.45	105.35	4.79	4.50*** (2.34–8.69)	0.14	22.01	Ref	Ref
SLE	0.74	123.47	21.52	21.31*** (6.26–72.5)	0.37	73.42	12.78	13.38** (3.10–57.8)	0.37%	85.95	14.98	17.29*** (6.23–48.0)	0.04	5.74	Ref	Ref
SSc	0.00	–	–	–	0.00	–	–	–	0.04	9.53	9.97	8.80 (0.74–105)	0.01	0.96	Ref	Ref
Systemc vasculitis	0.00	–	–	–	0.00	–	–	–	0.12	28.59	29.91	25.86** (3.70-181)	0.01	0.96	Ref	Ref

IR, incidence rate: per 100,000 person year; IRR, incidence rate ratio; adjusted-HR, adjusted hazards ratio was adjusted by gender, age group; AID, autoimmue disease; AHA, autoimmune hemolytic anemia; AS, ankylosing spondylitis; DM, diabetes mellitus; HSP, Henoch Scholen purpura; PSS, primary Sjogren syndrome; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; Tx, thymectomy; MG, myasthenia gravis.

*$P < 0.01$.

**$P < 0.001$.

***$P < 0.0001$.

Table 3. Incidence rate ratio and hazard rate of autoimmune diseases in patient with and without thymectomy.

	Event (*n*/%) (any type ADs)	Person Year	IR[1]	IRR	Adjusted HR[2]		
					HR	95% CI	*P*-Value
Thymectomy							
Yes	39 (17.1)	8803	443.04	2.68	2.65	1.880–3.728	<0.0001
No	189 (82.9)	114,306	165.35	Ref.	Ref.		
	Event (*n*/%) (organ specifc ADs)	Person Year	IR[1]	IRR	Adjusted. HR[2]		
					HR	95% CI	*P*-Value
Thymectomy							
Yes	17 (7.4)	8919	190.60	3.04	3.00	1.761–5.099	<0.0001
No	72 (31.6)	114,815	62.71	Ref.	Ref.		
	Event (*n*/%) (systemic ADs)	Person Year	IR[1]	IRR	Adjusted HR[2]		
					HR	95% CI	*P*-Value
Thymectomy							
Yes	24 (10.5)	8866	270.69	2.59	2.56	1.648–3.982	<0.0001
No	120 (52.6)	114,578	104.73	Ref.	Ref.		

IR, incidence rate; IRR, incidence rate ratio; HR, hazard ratio.
[1]Per 100,000 person year.
[2]Adjusted HR was adjusted by gender, age group.

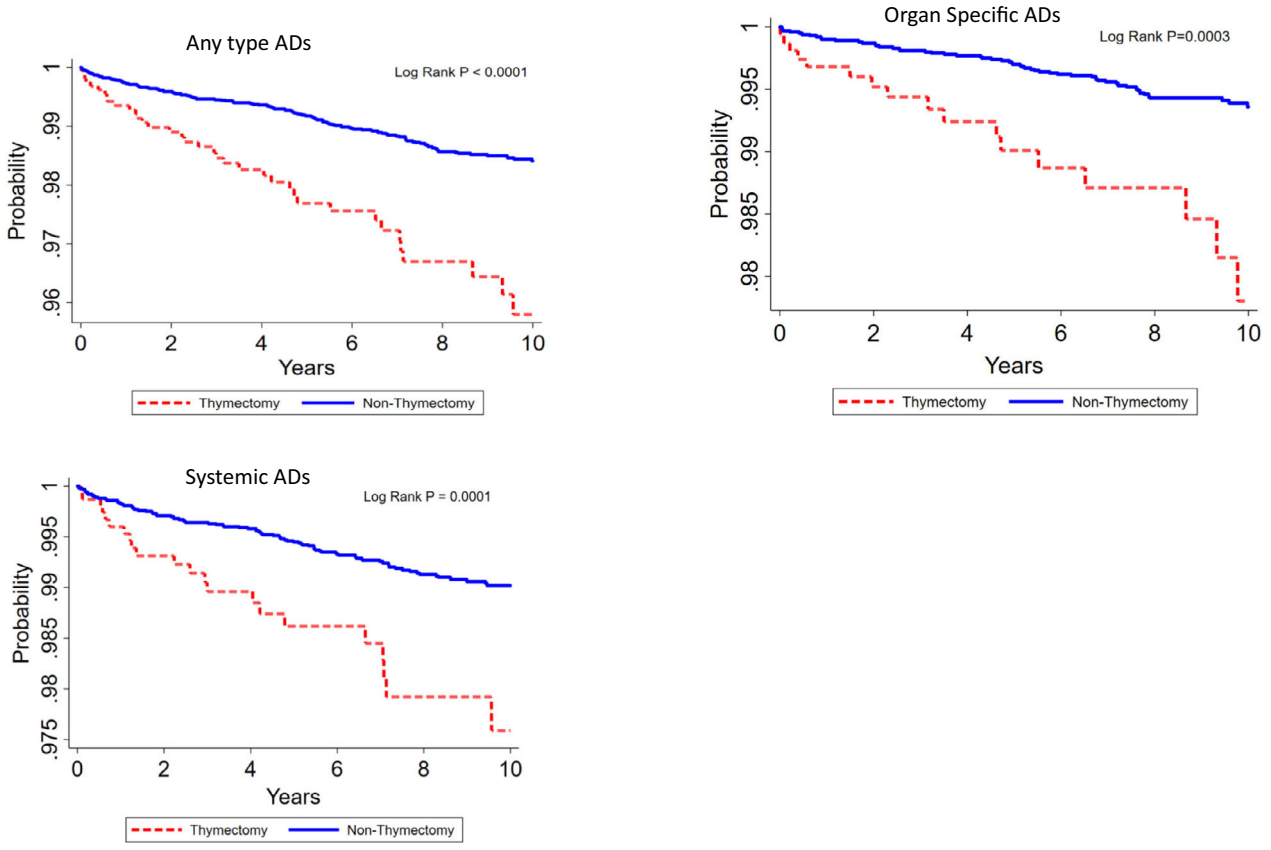

Figure 2. The overall survival of ADs outcomes in Thymectomy and non-Thymectomy cohorts.

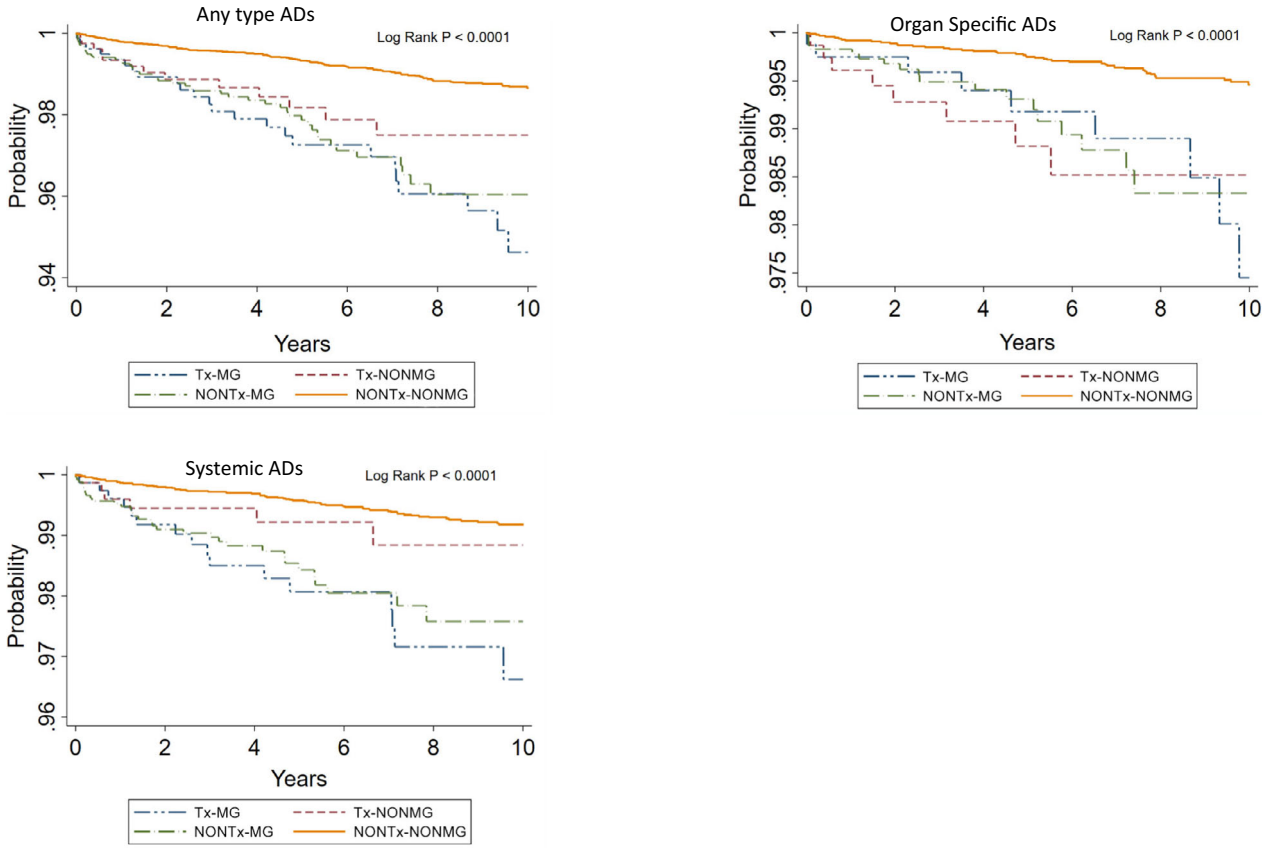

Figure 3. The overall survival of subgroup AIDs outcomes in each cohorts.

contrasting effects on the course of distinct autoimmune diseases in humans.[31] Tx may induce clinical deterioration or even create a new disease, suggesting a protective role of the thymus against autoimmunity.

Although the results of Tx vary considerably from one species to another. Experimental animal models may help in understanding the effect of Tx in humans. For example, the extent of T-cell depletion that follows neonatal Tx can range from moderate reduction of total T-cell number in sheep to dramatic T-cell depletion in mice.[32] In addition, the immunologic perturbation after Tx may be dependent on the time in which the gland is surgically removed. Recent studies show that autoreactive T cells, which are able to elicit organ-specific autoimmune diseases, develop in both the neonatal and adult thymuses, and they persist in the normal peripheral immune system.[33] In adult mice these autoreactive T cells are under the control of suppressor T cells, which maintain peripheral tolerance.[33,34] When the clonal balance of these T cells is tipped in favor of pathogenic T cells, autoimmune disease could ensue. Thus autoimmunity may be induced by Tx in adults as a result of a T-cell imbalance of autoreactive and regulatory T cells. In animal models of autoimmune disorder, surgical removal of the thymus can be associated with prevention or improvement of the autoimmune diseases.[31,35] More often, however, Tx is associated with induction or acceleration of the autoimmune process.[36]

In humans, long-term Txd MG patients display mild T-cell lymphopenia, which is associated with hypergammaglobulinemia and evidence of B-cell hyperreactivity. In addition, many of these patients have high titers of a variety of autoantibodies, including anti-dsDNA and anti-cardiolipin antibodies.[1]

Our previous study revealed an association between MG and incident autoimmune rheumatic diseases. The MG cohort who underwent Tx had an increased risk of RA, pSS, and SLE.[23] The present study further confirmed such cohort increased more spectrum ADs. ADs mainly develops after the onset of MG, whereas occurrence of MG after SLE has been described only sporadically.[16] These observations seem to support the concept that MG, as an organ-specific autoimmune disease, may predispose to the development of systemic autoimmunity. However, this study showed higher risk of ADs in Txd patients with MG compared with non-Txd patients with MG.

Furthermore, the Tx-nonMG cohort also had higher risk compared to nonTx-nonMG. These observation suggest an important role of the Tx, rather than the MG.

The therapeutic role of Tx is proved in MG even if the exact mechanism underlying its effect remains largely unknown. However, in recent years, evidences emerged of systemic autoimmune disorders including SLE, Hashimoto's thyroiditis, cutaneous vasculitis, and antiphospholipid syndrome occurring many years after Tx in patients with MG or other immunological diseases[1] seem to be consistent with this hypothesis.

This study showed that Tx in patients with MG or without MG both increase the risk of SLE. The proof that Tx can facilitate the development of SLE can be traced in the cases reported by the literature.[37] Txd patients revealed T-helper subset and T-helper/T-suppressor ratio decreased. Suppressor cell function was also low. The authors proposed that Tx decreases the number and function of some lymphocyte subpopulations. Tx may be followed by the development of autoimmune diseases such as SLE. The possibility of secondary autoimmune pathologies following Tx should be highly considered.

In addition, in animal models, the thymus has been demonstrated to be necessary for development of regulatory T cells (Tregs) and continued postnatal production is required to prevent autoimmunity.[38] The impact of incidental Tx and maintenance of functional Treg is unknown. Halnon et al,[39] found that there are long-term immune effects after cardiothoracic surgeries and incidental Tx. While total Treg number is maintained, homeostasis of this population is affected with unclear affects on autoimmunity. Treg cells are a subset of CD4+ T cells that maintain self-tolerance by suppressing autoreactive lymphocytes; Defects in Treg cells, or a lack of Treg cells, are therefore thought to contribute to SLE pathogenesis.[40]

The strengths of the present study include large sample size, a large validation cohort, and the long-term ascertainment of concurrent autoimmune diseases. However, the present study has some limitations. First, although the Bureau of NHI routinely and randomly checks patient charts to ensure the quality of claims from all medical institutions, the possibility of miscoding or misclassification cannot be completely ruled out. However, such bias would apply to both Tx and control cohorts, and therefore the present findings are expected to underestimate, rather than overestimate, the magnitude of the association between Tx and AIDs. Second, the relationship between disease activity and the severity of AIDs and Tx could not be analyzed. Third, although we employed many methods to prevent potential confounders, there is still a likelihood of unmeasurable bias due to the observational nature of our study design. Fourth, some important information regarding laboratory or clinical data was not readily available in the administrative database, namely ADs subtype data. Additional studies are warranted to explore this association. Finally, all thymomas are malignant. Although the ICD codes with "benign Tumors" of the thymus and some of this is a hangover from old terminology.

In conclusion, although Tx as a treatment of autoimmune diseases other than MG may be effective, our findings support the view that this surgical option may be a precipitating factor for other autoimmune diseases, such as SLE. Further investigations will need to elucidate the effects of Tx on the immune system in humans. Nonetheless, the possibility that novel autoimmune diseases emerge following Tx cannot be ignored.

Author Contributions

Tzu-Min Lin and Jin-Hua Chen contributed to study conception and design, article drafting, critical article revision for crucial intellectual content, and the final approval of the submitted version. Sheng-Hung, Lin and Yu-Sheng Chang contributed to data interpretation, critical article revision for crucial intellectual content, and the final approval of the submitted version. Wei-Sheng Chen, Pei-i Kuo, Tsung-Yun Hou, and Hui-Ching Hsu contributed to data analysis, critical article revision for crucial intellectual content, and the final approval of the submitted version. Yi-Chun Lin contributed to data analysis, article drafting, and the final approval of the submitted version. Chi-Ching Chang was responsible for study conception and design, complete data analysis, critical article revision for crucial intellectual content, and correspondence for the final approval of the submitted version.

Conflict of Interests

All authors declare no conflicts of interest.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Causes of thymectomy.

