American Research Journal of Hematology
ISSN: 2575-7768
Volume 3, Issue 1, pp: 1-15

AMERICAN RESEARCH JOURNALS
An Academic Publishing House

Research Article Open Access

The Epidemiology of Immune Thrombocytopenia in Taiwan: A Retrospective Analysis of Data from the National Health Database

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Abstract

Objectives: This study aimed to investigate the prevalence and current treatment status of immune thrombocytopenia (ITP) in Taiwan.

Methods: This was a retrospective study conducted using claim data collected from the Bureau of National Health Insurance (BNHI) of Taiwan from 2003 to 2007. ITP patients were identified using the ICD-9 code, 287.3 (primary thrombocytopenia), with two diagnoses separated by at least 14 days for diagnostic specificity. In addition, sensitivity analysis was based on 28 (ITP-28) and 84 (ITP-84) days.

Results: ITP prevalence ranged from 10.35 to 11.02 (per 100,000 individuals) with an annual number of 2,300 to 2,500 patients, and sensitivity analyses using ITP-28 and ITP-84 criteria showed that the prevalence were "9.52 to 10.35" and "6.87 to 8.14" in 5,445 ITP patients, respectively. The median age of ITP-14 patients was 46.5 years. In children, the female-to-male ratio was nearly equal (0.93), whereas in adults, it was 1.91. About 3.9% received splenectomy, of which 64.3% were responsive to splenectomy. Further, 92.6% were responsive to steroids. The average costs per visit were US$ 36 and US$ 1,700 for outpatients and inpatients, respectively. For steroid-responsive patients, the mean costs for clinic visits and hospitalization were US$ 35 and US$ 1,415, respectively. In contrast, the medical expense for steroid-refractory patients was approximately one and a half times the costs for responsive patients (inpatient: US$ 54; outpatient: US$ 2,349). For splenectomy-responsive inpatients, the average expenses prior to, at, and after splenectomy were US$ 1,877, 5,476, and 2,061, respectively. For splenectomy-refractory inpatients, the costs were comparable to those of responsive patients ($P > 0.05$). On the contrary, there were significant differences between the expenditure for splenectomy-responsive and -refractory outpatients. Among ITP patients in Taiwan, 7.4% and 6.4% had hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, respectively, and 1.5% had both HBV and HCV infections. Patients with HBV were significantly high in the splenectomy group (splenectomy vs. non-splenectomy 11.7% vs. 7.2%, $P = 0.01$), and those who were more responsive to splenectomy had a low HCV infection rate, i.e., 14.5% had HCV infection in splenectomy-refractory group vs. 4.38% in splenectomy-responsive group ($P = 0.02$).

Conclusions: The epidemiology of ITP in Taiwan, including the age and sex, was comparable with that in western countries, except with lower incidence of splenectomy in our patients. The status of HBV and HCV infection in splenectomized patients should be closely monitored. The medical expenditure in Taiwan was much lower than that in western countries. We suggest that novel agents or more aggressive treatment strategies should be further explored or considered in Taiwan.

Keywords: Immune thrombocytopenia (ITP), prevalence rate, medical expenditure, ITP treatment efficacy, claim database

Introduction

Immune thrombocytopenic purpura (ITP) is a common autoimmune hematological disorder characterized by abnormally low levels of platelets due to thrombocytopenia, caused by premature platelet destruction, and can affect children and adults. The prevalence rate of ITP in other countries was reported to be 9.5 to 11.2/100,000 patients (1,2); however, values over 20/100,000 patients (1) have also been reported. The incidence rate was approximately 1.6 to 3.8/100,000 patients in adults (1-8) and up to 4.8/100,000 in children <15 years (9). The female-to-male ratio was 1.9 to 1 (1).

Currently, the epidemiology data of ITP is unavailable in Taiwan. To provide epidemiology data and evaluate the current status of the treatment of ITP in this region, we conducted a retrospective analysis of the prevalence rate, age distribution, sex ratio of ITP patients, current trends in ITP treatment, treatment efficacy, and average medical expenditure for ITP treatment using data from the National Health Insurance Research Database (NHIRD) of Taiwan from 2003 to 2007.

Materials and Methods

Data Collection

Claim data were collected from Bureau of National Health Insurance (BNHI), including outpatient and inpatient records from January 1, 2003 to December 31, 2007, with an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code of 287.3. The main data evaluated in our study included ambulatory care expenditure by visits, details of ambulatory care orders, inpatient expenditure by admissions, and details of inpatient orders.

Study Design and Eligibility

The ICD-9-CM code used to screen ITP patients was 287.3 (primary thrombocytopenia). The screened ITP patients were excluded if they were diagnosed with human immunodeficiency virus (HIV); malignancies or secondary malignancies of the lymph nodes or Hodgkin's disease; myeloma or aplastic anemia; lymphoid, myeloid, or monocytic leukemia; other specified and unspecified leukemias; or systemic lupus erythematosus in the claimed database. Patients <1 year at the first diagnosis of ITP since 2003 were also excluded due to the possibility congenital or hereditary thrombocytopenia. In addition, each ITP patient was required to have two diagnoses of ITP, separated by at least 14 days, to improve the specificity of the ITP code. To identify ITP patients, sensitivity analyses were varied by adjusting the visit interval from 14 days to 28 and 84 days.

Outcome Measures

The primary objective of this study was to estimate the prevalence rates of ITP in Taiwan from 2003 to 2007. This was defined as patients who sought medical services for ITP in a single year from ITP patients who fulfilled the inclusion and exclusion criteria divided by the total population of Taiwan for the corresponding year. The total population of Taiwan as the denominator was obtained from the Department of Household Registration Affairs, Ministry of the Interior, Taiwan.

The secondary endpoints included the following: 1.) the characteristics of ITP in Taiwan (including sex and age distribution), 2.) Current clinical treatment efficacy (analysis subgroup: non-splenectomy steroid responsive, non-splenectomy steroid refractory, splenectomy-responsive as well as splenectomy-refractory), 3.) Percentage of ITP patients with hepatitis B virus and/or hepatitis C virus infection, and 4.) The medical expenditure covered by BHNI for ITP patients in Taiwan.

Statistical Analysis

To evaluate the epidemiology in different age groups, we further subdivided our study group by age into prevalence in children (<18 years) and in adults (≥18 years).

Patients' characteristics, including age, sex, medical expenditure, frequency of visiting the outpatient clinics (OPD), splenectomy, and hepatitis B/C infection were examined. Age was calculated as the date of first diagnosis of ITP from the available data. The mean, standard deviation, median, and minimum and maximum values of age are used in this study. The expenditure and visit frequency were viewed individually for outpatients and inpatients. In addition, the length of hospitalization was analyzed for inpatient cares. Characteristics of sex, splenectomy, and hepatitis B/C infection are presented by the number of subjects and the corresponding percentage in the contingency tables.

Comparisons among patients grouped by sex, age, splenectomy, and ITP treatment were adopted. The age, medical expense, and visit frequency for ITP patients between groups were examined using the t-test. The chi-squared test was conducted to determine statistically significant differences in sex, splenectomy frequency, and hepatitis B/C infection occurrence rate between groups.

Results

Prevalence and Characteristics

The data pool obtained from NHIRD between January 1, 2003 and December 31, 2007 revealed that 14,022 unique patients were diagnosed with ITP in Taiwan. Patients with a concurrent disease that made ITP as the unlikely diagnosis, included 25 patients with HIV infection. A total of 391 children <1 year of age were excluded from this study. In addition, 2,237 patients diagnosed with alternative diseases (including malignancies or secondary malignancies of the lymph nodes or Hodgkin's disease; myeloma or aplastic anemia; lymphoid, myeloid, or monocytic leukemia; other specified and unspecified leukemias; or systemic lupus erythematosus) were excluded from this study. The remaining 11,369 patients who fulfilled all of the cohort definitions were enrolled in our study.

The enrollment criteria that there be two ITP diagnoses separated by at least 14 days further reduced the number of eligible patients to 5,445. To further improve sensitivity analysis, the number of patients with ITP diagnoses separated by 28 or 84 days was reduced to 4,659 and 3,042, respectively (Figure 1).

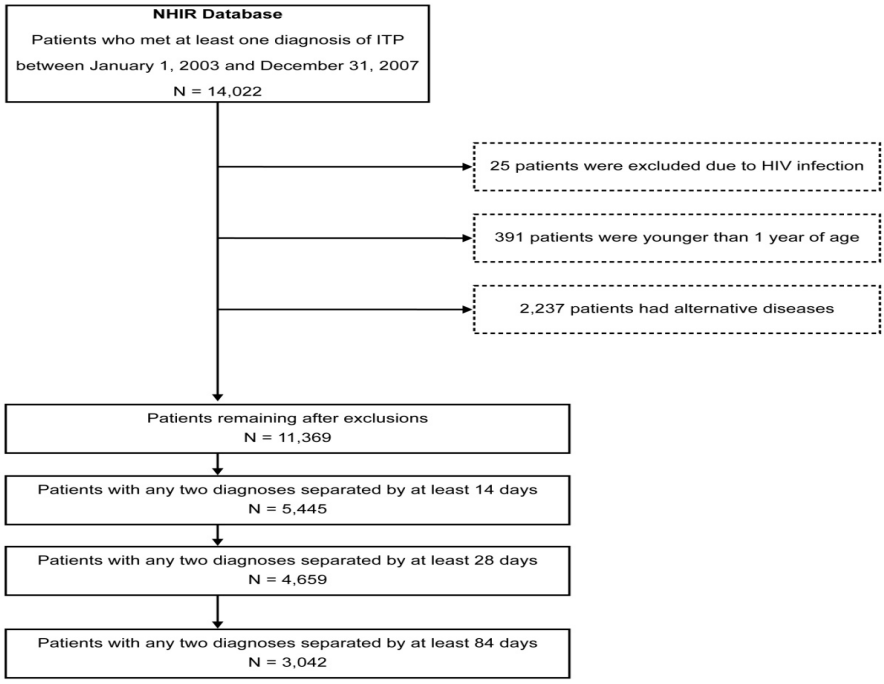

Fig1. *Patient selection flow chart*

The prevalence rate of ITP in this study was 6.87 to 11.02/100,000 patients (based on different diagnosis criteria, e.g., ITP-14, ITP-28, and ITP-84) (Table 1). ITP prevalence rate in adults and children (according to ITP-14) was conspicuously higher in adults (up to 12.09/100,000 patients) than in children (up to 8.37/100,000 patients) (Table 1).

Table1. *Number and prevalence rate of ITP patients with required visit interval in Taiwan during 2003–2007*

Years	ITP-14		ITP-28		ITP-84	
	No. of patients	Prevalence per 100,000	No. of patients	Prevalence per 100,000	No. of patients	Prevalence per 100,000
2003	2340	10.35	2152	9.52	1665	7.37
2004	2500	11.02	2348	10.35	1846	8.14
2005	2490	10.94	2343	10.29	1853	8.14
2006	2417	10.57	2266	9.91	1735	7.58
2007	2394	10.43	2186	9.52	1578	6.87
Adults (≥18 years old)						
2003	1966	11.45	1812	10.55	1395	8.12
2004	2097	12.09	1969	11.35	1550	8.96
2005	2051	11.7	1943	11.09	1543	8.8
2006	2045	11.51	1914	10.77	1469	8.27
2007	2024	11.27	1856	10.34	1365	7.6
Children (<18 years old)						
2003	374	6.89	340	6.26	270	4.97
2004	403	7.54	379	7.09	296	5.54
2005	439	8.37	400	7.63	310	5.91
2006	372	7.28	352	6.89	266	5.21
2007	370	7.4	330	6.6	213	4.26

ITP-14, patients with any two diagnoses separated by at least 14 days

ITP-28, patients with any two diagnoses separated by at least 28 days

ITP-84, patients with any two diagnoses separated by at least 84 days

Sex distribution with female-to-male ratio was 1.67 and the median age of patients was46.5 years (Table 2). The age distribution of ITP-14 patients by sex is presented in Figure 2. Of 961 children <18 years, the sex ratio was comparable (male-to-female: 499 : 462) in contrast to the ratio of female-to-male of 1.91 among 4,484 adults.

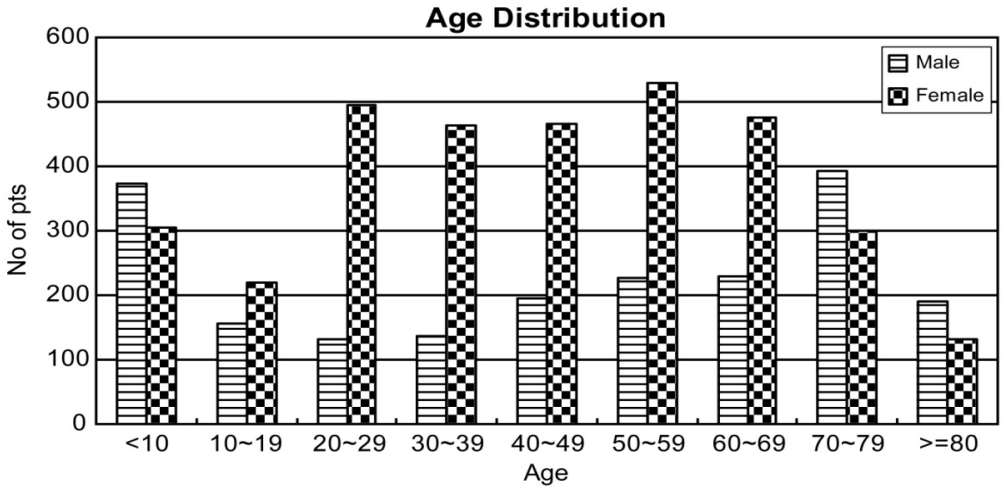

Fig2. *Age distribution of ITP-14 patients*

Table2. *Sexand Age Distribution of ITP patients in Taiwan*

Characteristics	**ITP-14 patients**
Age	
Number of patients	5445
Mean ± sd (years)	44.5 ± 24.5
median age	46.5
Sex	
Male	2028 (37.3%)
Female	3389 (62.2%)
Unknown	28 (0.5%)
Female to Male ratio	1.67
Children (age of year <18)	
Male	499 (51.9%)
Female	462 (48.1%)
Female to Male ratio	0.93
Adults (age of year ≥18)	
Male	1529 (34.1%)
Female	2927 (65.3%)
Unknown	28 (0.6%)
Female to Male ratio	1.91
Mean medical expenditure for outpatients per visit (USD)	36.2 ± 87.3
Mean medical expenditure for inpatients per visit (USD)	1700.0 ± 2137.2

Current Treatment Efficacy

Of 5,445 ITP-14 patients, 3.9% underwent splenectomy. Splenectomy was only performed in 1.7% children, but this value was conspicuously higher in adults (4.4%, 197/4,484 patients, $P<0.0001$). Of 213 ITP patients who received splenectomy, 64.3% (137/213) responded to the surgery. The median age of patients receiving splenectomy with response was 41.3 years, and that of refractory to splenectomy patients was45.4 years (Table 3).

Majority of ITP patients who did not receive splenectomy were responsive to corticosteroids (92.6%, 4,844/5,232 patients), and were first diagnosed with ITP at a young age (steroid-refractory vs. steroid-responsive = 49.0 vs. 44.3, $P = 0.0003$) (Table 3).

Table3. *Current Treatment Efficacy*

Characteristics	Splenectomy	Non-splenectomy
Age †		
Number of patients	213/5445 (3.9%)	5232/5445 (96.1%)
Mean ± sd (years)	42.1 ± 18.4	44.6 ± 24.7
P value	0.14	
Sex§		
Male	55/213 (25.8%)	1973/5232 (37.7%)
Female	157/213 (73.7%)	3232/5232 (61.8%)
Unknown	1/213 (0.5%)	27/5232 (0.5%)
P value	0.004*	
Children (<18 years old)§	16/961 (1.7%)	945/961 (98.3%)
Adults (≥18 years old) §	197/4484 (4.4%)	4287/4484 (95.6%)
P value	0.0001*	
Responsive to splenectomy	137/213 (64.3%)	
Mean age at first diagnosis †	41.3 ± 18.7	
Refractory to splenectomy	76/213 (35.7%)	
Mean age at first diagnosis †	45.4 ± 17.3	
P value, by age	0.05	
Responsive to steroid		4844/5232 (92.6%)
Mean age at first diagnosis †		44.3 ± 24.6
Refractory to steroid		388/5232 (7.4%)
Mean age at first diagnosis †		49.0 ± 26.1
P value, by age		0.0003*

†, T-test; §, Chi-square test

Hepatitis B Virus and Hepatitis C Virus Infection

The prevalence rate of HBV and HCV infections in ITP-14 patients was 7.4% (404/5,445) and 6.4% (348/5,445), respectively. Approximately, 1.5% (82/5,445) of ITP patients had both HBV and HCV infection (Table 4). We observed that more patients were diagnosed with HBV infection in the splenectomy group than in

the non-splenectomy group (11.7% vs. 7.2%, *P* = 0.01). Another interesting finding was that patients who were more responsive to the splenectomy had a low HCV infection rate, i.e., 14.5% had HCV infection in the splenectomy-refractory group vs. 4.4% in the splenectomy-responsive group (*P* = 0.02). However, there was no significant difference in HBV infection between splenectomy and non-splenectomy patients (*P*> 0.99).

Table4. *Hepatitis B Virus and/or Hepatitis C Virus Infection*

Characteristics	Hepatitis B Virus Infection	Hepatitis C Virus Infection
ITP-14	404/5445 (7.4%)	348/5445 (6.4%)
Both HBV and HCV Infection	82/5445 (1.5%)	
ITP-14 (Age <18 years old) ※	5/961 (0.5%)	398/4484 (8.9%)
ITP-14 (Age ≥18 years old) ※	2/961 (0.2%)	346/4484 (7.7%)
P value, by age	<0.0001*	<0.0001*
Male§	201/2028 (9.9%)	115/2028 (5.7%)
Female§	203/3389 (6.0%)	233/3389 (6.9%)
P value, by sex	0.0002*	0.08
Splenectomy§	25/213 (11.7%)	17/213 (8.0%)
Non-Splenectomy§	379/5232 (7.2%)	331/5232 (6.3%)
P value, by type of treatment	0.01*	0.33
Splenectomy Responsive§	16/137 (11.7%)	6/137 (4.4)
Splenectomy Refractory§	9/76 (11.8%)	11/76 (14.5%)
P value, by results	>0.99	0.02*
Steroid Responsive§	346/4844 (7.1%)	299/4844 (6.2%)
Steroid Refractory§	33/388 (8.5%)	32/388 (8.3%)
P value, by results	0.32	0.11

※, Fisher's exact test; §, Chi-square test

ITP-14, patients with any two diagnoses separated by at least 14 days

Medical Expenditure of ITP Patients in Taiwan

Although the clinical visit frequency was higher in female patients than in male patients (*P*<0.0001), the average expenditure for outpatientsshowed no difference between male and female patients [Table 5 (A)]. This situation was almost the same for our inpatients both with respect to medical expenditure and visit frequency. Medical expenditure was higher in adult patients than in children, despite the treatment being conducted at a clinic or hospital (*P*< 0.0001)[Table 5 (A)].

On comparing medical reimbursement in patients with or without splenectomy, we observed that the inpatient cost was approximately two times higher in the splenectomy group than in the non-splenectomy group (US$3,270 vs. US$ 1,524) (*P*< 0.0001) [Table 5 (A)]. This was probably related to the expenditure of the surgical procedure and other novel treatments (i.e., intravenous immunoglobulin, antithymocyte globulin, among others).For outpatients, the mean cost per clinic visit was approximately equal in patients with or without spleen removal surgery; however, the visit frequency was conspicuously high, as expected, in the splenectomy group (*P*<0.0001) [Table 5 (A)].

Table5 (A). *Required Medical Expenditure for ITP patients in Taiwan (by sex and by age)*

Characteristics (USD)	**Male**	**Female**
Mean expenditure of outpatients per visit (USD) †	38.4 ± 92.0	35.0 ± 84.7
P value	0.17	
Visit frequency of outpatients†	16.6 ± 22.3	19.3 ± 25.0
P value	<0.0001*	
Mean expenditure of inpatients per visit (USD) †	1782.1 ± 2305.2	1648.3 ± 2026.8
P value	0.18	
Visit frequency of inpatients†	2.0 ± 2.1	1.9 ± 1.7
P value	0.06	
	Children (Age < 18 years)	**Adults (Age ≥ 18 years)**
Mean expenditure of outpatients per visit (USD) †	24.4 ± 58.7	38.7 ± 92.1
P value	<0.0001*	
Visit frequency of outpatients†	18.0 ± 24.3	18.3 ± 24.0
	0.79	
Mean expenditure of inpatients per visit (USD) †	1105.8 ± 1179.6	1922.2 ± 2362.6
P value	<0.0001*	
Visit frequency of inpatients†	2.1 ± 2.6	1.8 ± 1.5
P value	0.002*	
	Splenectomy	**Non-Splenectomy**
Mean expenditure of outpatients per visit (USD) †	42.1 ± 43.2	35.9 ± 88.6
P value	0.32	
Visit frequency of outpatients†	31.2 ± 29.6	17.7 ± 23.6
P value	<0.0001*	
Mean expenditure of inpatients per visit (USD) †	3270.0 ± 3056.5	1524.2 ± 1935.2
P value	<0.0001*	
Visit frequency of inpatients†	2.2 ± 1.5	1.9 ± 1.9
	0.01*	

†, T-test; §, Chi-square test

USD: US Dollar

Exchange rate, United States Dollar: New Taiwan Dollar = 1: 33

On further analyzing the cost-effectiveness of the treatment, we observed that the visit frequency of inpatients and outpatients as well as the length of hospitalization were equal between responsive and refractory patients before splenectomy ($P > 0.05$) [Table 5 (B)]. However, the mean cost and visit frequency for outpatients was significantly low in responsive patients after splenectomy ($P < 0.05$). In contrast, the visit frequency and the length of hospitalization in inpatients was equivalent in the responsive and refractory groups ($P > 0.05$).

The inpatient/outpatient expenditure and visit frequency were lower in steroid-responsive patients than in steroid-refractory patients ($P < 0.0001$) [Table 5 (B)].

Table5 (B). *Detailed Information and Required Medical Expenditure for ITP patients in Taiwan*

Characteristics	Splenectomy Responsive	Splenectomy Refractory	Steroid Responsive	Steroid Refractory
Age†	40.2 ± 18.8	45.4 ± 17.3	44.3 ± 24.6	49.0 ± 26.1
P value	0.05		0.0003*	
Age at splenectomy†	41.3 ± 18.7	46.3 ± 17.2	NA	NA
Time (year) to splenectomy†	1.0 ± 1.1	0.9 ± 1.1	NA	NA
Number of visits of outpatients†			17.2 ± 23.0	24.2 ± 30.0
before splenectomy	15.3 ± 16.8	17.6 ± 17.1	<0.0001*	
	0.38			
after splenectomy	16.5 ± 17.0	23.5 ± 23.1		
P value	0.02*			
Number of visits of inpatients† (USD)			1.8 ± 73.5	2.9 ± 3.3
before splenectomy	1.7 ± 1.01	1.5 ± 1.0	*P*<0.0001*	
P value	0.43			
after splenectomy	1.9 ± 1.3	1.6 ± 0.8		
P value	0.38			
Length of hospitalization (Days) †			7.3 ± 6.7	9.6 ± 9.0
before splenectomy	7.9 ± 7.7	8.0 ± 6.9	*P*<0.0001*	
P value	0.94			
after splenectomy	10.0 ± 8.67	8.7 ± 7.7		
P value	0.58			
Mean expenditure of outpatients per visit (USD) †			34.6 ± 2424.2	53.8 ± 202.4
before splenectomy	60.6 ± 103.6	34.3 ± 26.7	*p* < 0.0001*	
	0.04*			
after splenectomy	27.1 ± 24.3	41.6 ± 57.9		
P value	0.02*			
Mean expenditure of inpatients per visit (USD) †			1415.4 ± 1660.7	2349.1 ± 3241.3
before splenectomy	1877.1 ± 2786.5	2290.3 ± 4082.7	*P*<0.0001*	
P value	0.54			
at splenectomy	5476.3 ± 7186.8	4103.5 ± 3720.3		
P value	0.96			
after splenectomy	2060.5 ± 2433.2	2273.8 ± 2352.6		
P value	0.77			

†,T-test

USD: US Dollar

Exchange rate, United States Dollar: New Taiwan Dollar = 1: 33

Discussion

Terrell et al. (2), reported that the annual prevalence of ITP was11.2/100,000 patients (2).Another report by Feudjo-Tepie et al. (3) demonstrated a prevalence rate up to 23.6 in USA (3). Landgren et al. (10), recently estimated a prevalence rate of 176/10,000 patients (10). Our study showed that the prevalence rate of ITP between 2003 and 2007 ranged from 10.35 to 11.02/100,000 patients per year. In addition, we demonstrated that the prevalence rate of ITP in adults was higher than that in children. These results are comparable with those of Terrell et al. (2). However, the prevalence rate of ITP in our study was higher than that in The Netherlands (prevalence rate of ITP, 2.64) (11) and lower than that in Kuwait, with an annual incidence rate of 12.5 (12). Sensitivity analysis demonstrated that the prevalence rate of ITP was 10.35/100,000 patients for ITP-28 (or 8.14/100,000 patients for ITP-84). If this is the case, further studies on the impact of environmental, social, ethical, and genetic factors that contributeto the occurrence of ITP in Taiwan should be conducted in the near future.

Although some studies demonstrated that ITP was more common in boys than in girls (13, 14), our data did not reveal and differences in sex among our pediatric patients (<18 years old, 499 male ITP patients vs. 462 female ITP patients). This situation is similar to that in the report by Segal and Powe (1). However, a trend of an increase in the incidence of ITP cases was observed in boys. Further investigation on whether this is due to triggering mechanisms related to sex and age should be conducted.

The percentage of splenectomy was 45.9% in France (15), 35.5% in United Kingdom (16), 22.7% in northern Turkey (17), and 29% in Denmark (18). However, only 3.9% of our ITP patients underwent splenectomy. This was probably related to the following possibilities: 1.) higher response rate to steroids in most of our ITP patients (92.6%) compared with a previously reported response rate of 14–65% (19-25) and 44–100% (26-29) to regular and high doses of steroids, respectively; 2.) the population was more culturally conservative to splenectomy; 3.) less severe ITP symptoms in our patients, especially the risk related to bleeding. The risk of infections throughout a patient's lifetime after splenectomy may be another concerning factor explaining the low splenectomy rate in our study (although the risk is small, with an estimated mortality rate of 0.73/1,000 patients per year) (30).

In Taiwan, splenectomy was not performed very often in children (1.7%), but this value was considerably higher in adults (4.4%, $P< 0.0001$). Previous research reviewed the long-term follow-up of 184 chronic ITP patients who underwent splenectomy, and revealed that approximately two-thirds of patients responded to splenectomy (17, 31). Our data exhibited a similar trend, where 64.3% ITP patients responded to splenectomy. The median age to receive splenectomy with response and refractory in our patients was 41.3 and 45.4, respectively. This appeared to indicate that splenectomy performed at a younger age is more beneficial than that performed in older ITP patients. Furthermore, our findings were compatible with those of Naouri et al. (32) and Avinashet al. (33).

A higher incidence of remission was reported in one-third of children with ITP (34). This could be one of the reasons for the less numbers of splenectomy procedures in children. Therefore, splenectomy is usually deferred in pediatric patients for as long as possible (6). The maturation of the immune system in pediatric patients is another aspect considered while postponing the surgery.

The medical expenditure of ITP, irrespective of inpatient/outpatients or steroid/splenectomy, in Taiwan was much lower than that in western countries. Danese et al. (35), reported that the expenditure for their inpatients was US$ 16,476, with a 6.4-day hospitalization in United States (35). Kumar et al.(36), reported that the medical cost of steroids for non-splenectomy ITP in children was approximately US$ 1,815 (36). If we compare the costs for ITP between USA and Taiwan by GDP adjustment based on the data published by the International Monetary

Fund, the GDP (nominal) per capita for 2009 in the USA was 2.8 times more than that in Taiwan (US$ 46,381 of USA vs. US$16,392 of Taiwan). The expenditure for inpatients per visit was approximately US$1,700 in Taiwan (Table 2), which was approximately one-tenth of that in the US. This difference may be due to the following factors: 1.) the reimbursement system of NHI controlled the prices of health care in Taiwan; 2.) the percentage of patients receiving more biological or novel agents as treatments, i.e., IVIG therapy, was low in Taiwan (1.83% in children and 2.81% in adults), 3.) currently, some novel therapies for ITP (such as anti-D and rituximab) are not reimbursed via our NHI reimbursement system.

Our study also demonstrated a correlation between HCV infection and the refractory status after splenectomy (14.5% had HCV infection in the splenectomy-refractory group vs. 4.4% in the splenectomy responsive group, $P = 0.02$). In contrast, HBV was not the contributing factor affecting the responsiveness to splenectomy in this study.

In our study, of 5,445 ITP patients, 35.7% and 36.2% of ITP patients had received HBV and HCV assay-guided therapy, respectively. Our data showed that 7.4% and 6.4% of ITP-14 patients had HBV and HCV infections, respectively, and 1.5% of ITP patients had HBV and comorbid HCV infections. In Taiwan, the seroprevalence of HBV and HCV infections were 17.3% and 4.4%, respectively (37). However, the ratio of ITP patients with HBC to HCV infections was almost equal in our data. Therefore, we can assume that ITP is highly correlated with HCV infection not only according to our data, but it is also supported by previous research that showed a significantly higher proportion of thrombocytopenia in 41.0% patients with HCV than that in patients with chronic HBV infections (18.9%, $P< 0.01$) (38). A large-scale survey involving 11,239 residences in Taiwan also proved that HCV infection affects platelet counts (39). In addition, HCV infection had been proposed to play a potential role in the pathogenesis of chronic ITP. The mechanism of HCV related to thrombocytopenia is as follows: 1.) HCV infections may induce immune abnormalities and stimulate the autoimmune process (40), 2.) immuno-mediated platelet destruction may be due to the immune complex and/or viral antigen attachment onto platelet membranes (41), and 3.) a change in the antigenicity of platelets due to HCV infection may induce cross-reactivities between platelets and HCV (13). The receptor for HCV infection was identified on B lymphocytes (CD81) (42), and was reported to bind to activate B lymphocytes (43). The HCV RNA was detected via RT-PCR in the platelets of most chronic ITP patients (30). These data suggest HCV infection as an alternative factor in patients who are initially suspected with ITP (44-47). In contrast, there is no strong evidence correlating HBV infection to ITP diagnosis, which is clinically important for management.

In this data analysis, we report two interesting findings: 1.) the number of patient with HBV was significantly higher in the splenectomy group than in the non-splenectomy group, and 2.) those who were more responsive to splenectomy had a low HCV infection rate, which is the same as that reported by Sakyraya M. et al.(48). Additional experiments, including virological studies (e.g., examination of the viral RNA or anti-HCV antibody) and biochemistry studies (e.g., examination of the platelet antibody, PAIgG), are suggested to be performed to establish the correlation between HCV/HBV infection and treatment efficacy in ITP patients.

Although current treatment options are more effective than those from previous years, there remains substantial room for improvement. Future research should focus on examining the platelet count response rates following treatment for HBV and HCV infections, and consequently confirm that the detection and treatment of HBV and HCV infections should be a part of the routine evaluation and management of ITP patients. It is essential that patients newly diagnosed with ITP should be screened for HBV/HCV infections at diagnosis itself, because the treatment regimen for such patients could be modified accordingly to the viral infection. Several current articles have recommended alternative therapies for patients with confirmed viral infections (49,50).

This study was based on retrospectively claimed data from the BNHI database. However, there were some limitations and pitfalls in the interpretation our data. First, examinations for diagnosis of certain diseases

requires the corresponding ICD-9 code in Taiwan. Although examinations demonstrated negative test results, the patient's medical history may still have record of their diseases. Therefore, we excluded patients who did not have any of the excluded diseases but underwent some examinations such diseases (e.g., HIV infection and Hodgkin's disease). Second, the actual total medical expenditure for ITP treatment in Taiwan may be higher than that reported in our study, because the cost of certain therapies (e.g., anti-D and IVIG) is not routinely covered by NHI. Therefore, future prospective studies should be conducted to evaluate the characteristics, treatment status, and the medical expenditure of ITP.

Conclusion

In conclusion, to the best of our knowledge, our study was the first to evaluate the status of ITP treatment in Taiwan on a national scale, including the total ITP population, prevalence rates, sex ratios, treatment modality, the distribution of HBV/HCV infection in ITP patients, response of ITP to splenectomy, and average medical expenditure. Steroids remain as the initial therapy for ITP and is effective in most of our patients. The percentage of splenectomy for ITP treatment was only 3.9% in our patients. To improve the quality of care in ITP patients, we should focus on providing education to ITP patients and continuous education to primary care physicians about the potential benefits and disadvantages of long-term use of steroids and splenectomy procedures in the treatment of chronic ITPs.

Acknowledgements

This study got partial grant support from LIHPAO Life Science R12004, MOST105-2314-B-075-MY2, V106C-179 and V107C-018.

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Citation: **Tzeon-Jye Chiou, Liang-Tsai. Hsiao, Wang-Fang Tzeng. "***The Epidemiology of Immune Thrombocytopenia in Taiwan: A Retrospective Analysis of Data from the National Health Database". American Research Journal of Hematology; 3(1): 1-15.*