Annals of Hematology (2021) 100:941–952
https://doi.org/10.1007/s00277-021-04449-4

ORIGINAL ARTICLE

Temporal trends and outcome of splenectomy in adults with immune thrombocytopenia in the USA

Antoine Finianos[1] · Hata Mujadzic[2] · Heather Peluso[3] · Tarik Mujadzic[4] · Ali Taher[1] · Marwan S. Abougergi[5,6]

Received: 24 June 2020 / Accepted: 2 February 2021 / Published online: 9 February 2021

Abstract

Splenectomy is one of the treatments of immune thrombocytopenia (ITP) with a high response rate. However, it is an irreversible procedure that can be associated with morbidity in this setting. Our aim was to study the trends of splenectomy in adults with ITP, and the factors associated with splenectomy and resource utilization during these hospitalizations. We used the National (Nationwide) Inpatient Sample (NIS) to identify hospitalizations for adult patients with a principal diagnosis of ITP between 2007 and 2017. The primary outcome was the splenectomy trend. Secondary outcomes were (1) incidence of ITP trend, (2) in-hospital mortality, length of stay, and total hospitalization costs after splenectomy trend, and (3) independent predictors of splenectomy, length of stay, and total hospitalization costs. A total of 36,141 hospitalizations for ITP were included in the study. The splenectomy rate declined over time (16% in 2007 to 8% in 2017, trend $p < 0.01$) and so did the in-hospital mortality after splenectomy. Of the independent predictors of splenectomy, the strongest was elective admissions (adjusted odds ratio [aOR]: 22.1, 95% confidence interval [CI]:17.8–27.3, $P < 0.01$), while recent hospitalization year, older age, and Black (compared to Caucasian) race were associated with lower odds of splenectomy. Splenectomy tends to occur during elective admissions in urban medical centers for patients with private insurance. Despite a stable ITP hospitalization rate over the past decade and despite listing splenectomy as a second-line option for management of ITP in major guidelines, splenectomy rates consistently declined over time.

Keywords Immune thrombocytopenia · Splenectomy · In-hospital mortality · Inpatient utilization · National inpatient sample

Introduction

Immune thrombocytopenia (ITP), previously called idiopathic thrombocytopenic purpura, is an autoimmune disease characterized by thrombocytopenia of unknown cause. Although most cases of ITP are asymptomatic, severe thrombocytopenia can cause purpura and hemorrhagic episodes. These complications are most likely to occur during interventions and procedures or also spontaneously especially when the platelet count is below 10,000 [1]. Platelet destruction due to formation of antibodies that target glycoprotein IIb/IIIa on platelets and insufficient platelet production due to impaired megakaryocyte function are both mechanisms that contribute to the development of ITP [2, 3]. According to the time from initial diagnosis, ITP can be classified into 3 phases: the first phase (acute) occurs within the first 3 months post-diagnosis. The second phase (persistent) lasts 3–12 months while the third phase (chronic) refers to symptoms that are present beyond 12 months [4]. The prevalence exceeds the incidence in patients with ITP since it is often a chronic disease in adults. Prevalence in the USA is approximately 8 per 100,000 in children and 12 per 100,000 in adults [5].

While glucocorticoids are used as a first-line therapy, multiple second-line drugs have been used with variable response rate. Those include rituximab or in refractory cases, high-dose

✉ Marwan S. Abougergi
elmarwan@gmail.com

1 Division of Hematology and Oncology, Department of Internal Medicine, American University of Beirut School of Medicine, Beirut, Lebanon

2 Department of Medicine, Prisma Health/University of South Carolina School of Medicine, Columbia, SC, USA

3 Division of Surgery, Prisma Health Upstate, Greenville, SC, USA

4 Division of Plastic Surgery, Department of Surgery, Prisma Health/University of South Carolina School of Medicine, Columbia, SC, USA

5 Division of Gastroenterology, Department of Internal Medicine, University of South Carolina School of Medicine, Columbia, SC, USA

6 Catalyst Medical Consulting, Simpsonville, SC, USA

dexamethasone, interferon, danazol, cyclosporine, and azathioprine as well as thrombopoietin-like agents such as eltrombopag or romiplostim [6]. Splenectomy can achieve the most significant long-term remission (50 to 70%) by eliminating the primary site of platelet destruction and autoantibody formation [7]. However, it is an irreversible procedure that carries the risk of morbidity and possibly mortality due to intra-operative and post-operative hemorrhage and infection with encapsulated bacteria [8, 9]. The American Society of Hematology guidelines classify splenectomy among second-line treatment options, for patients resistant to corticosteroids, but favoring rituximab based on side effect profile [6]. With the advent of medical alternatives, splenectomy rates have been declining [7].

Until this date, the decision to proceed with splenectomy is still decided on case by case basis without agreed upon patient selection criteria. In addition, predictors of treatment outcomes after splenectomy, including mortality and resource utilization among adult patients with ITP, have not been established. Thus, the aim of this study is to analyze the trends of splenectomy in adult patients with ITP using the largest publicly available national database in the USA as well as to determine the independent predictors of splenectomy and treatment outcomes.

Methods

Data source

This is a retrospective longitudinal study utilizing the Agency for Healthcare Research and Quality's Healthcare cost and Utilization Project National Inpatient Sample (NIS) for the years 2007, 2012, and 2017. The NIS is the largest publicly available all-payer in-hospital care database in the USA [10]. From 2007 to 2017, the database contained 7.1 to 8 million hospital stays from 1044 to 4585 hospitals across 40 to 48 states. It is designed as a stratified probability sample to be representative of all nonfederal acute care inpatient hospitalizations nationwide. Briefly, hospitals are stratified according to ownership/control, number of beds, teaching status, urban/rural location, and geographic region. A 20% probability sample of all hospitalizations within each stratum is then collected. Those hospital stays are recorded, and information about patients' demographics, principal and secondary diagnoses, vital status at discharge, readmission, and resource use including length of stay (LOS), procedures performed, and total hospitalization costs and charges are entered into the NIS. Each discharge is then weighted (weight = total number of discharges from all acute care hospitals in the USA divided by the number of discharges included in NIS) to make the NIS nationally representative. The NIS contains both patient- and hospital-level information. Up to 40 discharge diagnoses and 25 procedures are collected for each patient using the International Classification of Diseases, ninth or tenth Revision, Clinical Modification (ICD-9 CM and ICD-10 CM).

The NIS maintains internal validity in its database by annual data quality assessments, while the external validity of the NIS is supported by comparisons against the following data sources: The American Hospital Association Annual Survey Database, the National Hospital Discharge Survey from the National Center for Health Statistics, and the MedPAR (Medicare Provider and Analysis Review) inpatient data from the Centers for Medicare and Medicaid Services. The NIS has been previously used to provide reliable estimates of the burden of hematological diseases [11].

Study population

Patients were included in the study if they had a principal diagnosis of immune thrombocytopenia. The ICD-9 CM and ICD-10 CM codes used to identify patients with immune thrombocytopenia are listed in the Appendix. Patients were excluded if they were younger than 18 years. The institutional review board of Prisma Health deemed the research project exempt from approval because it is a retrospective review of already collected, de-identified data.

Study outcomes

The primary outcome was the annual incidence of splenectomy. The secondary outcomes were (a) annual incidence of hospitalization for ITP, (b) in-hospital mortality, (c) resource utilization: length of stay and total hospitalization costs and charges, and (d) predictors of splenectomy, length of stay, and total hospitalization charges.

Definition of variables

We used NIS variables to identify each patient's age (in years), sex, median household income for patient's zip code ((1) $1–$42,999; (2) $43,000–$53,999; (3) $54,000–$70,999; and (4) $71,000 or more), primary expected payer (Medicare, Medicaid, private insurance, and uninsured), median income in the patient's zipcode divided into quartiles ((1) $1–$43,999; (2) $44,000–$55,999; (3) $56,000–73,999; and (4) $74,000 or more), hospital size based on number of beds (small, medium, and large), urban location, and teaching status. Overall comorbidity burden was calculated utilizing the Deyo modification of the Charlson comorbidity index [12]. For the in-hospital mortality rate, the patient vital status at discharge, which is directly coded in the NIS, was used. Length of hospital stay and total hospitalization charges are variables directly coded in the NIS. Total hospital charges represent the amount that the hospitals billed for the entire hospital stay but do not

reflect the actual cost of care. The Healthcare Cost and Utilization Project provides data that contain hospital-specific cost-to-charge ratios based on all-payer inpatient cost. This cost information is obtained from the hospital accounting reports collected by the Centers for Medicare and Medicaid Services [13]. Using this information, total hospitalization costs were calculated by multiplying total hospital charges by the corresponding cost-to-charge ratio. Both total hospitalization charges and costs were adjusted for inflation using the consumer price index [14]. The prevalence of ITP was calculated by dividing the number of ITP hospitalizations by the total number of persons in the USA for each study year, which was obtained from the Census Bureau website [15]. The ICD-9 CM and ICD-10 CM codes used to identify patients with splenectomy, thrombosis, sepsis, traumatic intracranial hemorrhage (ICH), nontraumatic intracranial hemorrhage, upper gastrointestinal (GI) hemorrhage, lower gastrointestinal bleed, non-specified GI bleeding, and non-GI bleeding are listed in the Appendix. Those diagnoses were secondary diagnoses, which means that they occurred either before admission or during the hospital stay, but were not the reason for admission to the hospital.

Statistical analyses

All data analyses were conducted using STATA, version 13.0 (StataCorp, College Station, TX). NIS is based on a complex sampling design that includes stratification, clustering, and weighting. This software facilitates analysis to produce nationally representative unbiased results, variance estimates, and *P* values. Weighting of patient-level observations was implemented to obtain estimates for the entire population in the USA of hospitalized patients with immune thrombocytopenia. Proportions were compared with the Fisher exact test while continuous variables were compared using the Student *t* test. Univariable linear (continuous outcomes) or logistic (dichotomous outcomes) regression analysis was used to calculate unadjusted odds ratios for the primary and secondary outcomes. Subsequently, multivariable regression analysis was used to adjust the results for potential confounders. Multivariable regression models were built by including all confounders that were significantly associated with the outcome on univariable analysis with a cutoff *P* value of 0.2. All statistical analyses were two-sided, with cutoff *P* value of 0.05.

Results

Patients' characteristics

From a total of 111,825,247 patient encounters in the USA during the three study years, 36,141 encounters with ITP were included in the study. Figure 1 shows the flow diagram of patient encounter selection. Table 1 details the patients' demographic and hospital characteristics. Compared with 2007, a higher proportion of patients were insured by Medicaid and a lower proportion had a private insurance in 2017. In addition, comorbidities such as thrombosis were less prevalent while nontraumatic ICH and nonspecific as well as upper GI bleed were more prevalent in 2017 compared with 2007. A larger proportion of admissions were treated at small hospitals and urban teaching hospitals in 2017 compared with 2007. Patients' age, sex, race distribution, median household income, hospital region, and elective admissions as well as comorbidities such as traumatic ICH, lower GI bleed, and sepsis were similar in all 3 years studied (2007, 2012, 2017).

Trend of hospitalization and splenectomy rates over the years

The number of hospitalizations due to ITP was constant over time: it was 12,441, 11,710 and 11,990 in 2007, 2012, and 2017, respectively (trend $p = 0.58$). The corresponding ITP incidence was also constant over time: 47, 36, and 37 per million persons in 2007, 2012, and 2017, respectively (trend $p = 0.39$). On the other hand, the splenectomy rate showed steady decline from 16% in year 2007 to 13% in 2012 to 8% in year 2017 (trend $p < 0.01$).

Trend of splenectomy outcomes over time

The outcomes of patients with ITP who had a splenectomy are summarized in Fig. 2. The all-cause mortality rate (case fatality rate) declined from 3.8% in 2007 to 2.6% in 2012 to 1.1% in 2017 (trend $p < 0.01$). The mean length of stay did not change significantly during those 3 years and was 7.1, 6.1, and 6.2 days in 2007, 2012, and 2017, respectively (trend $p = 0.22$). The inflation-adjusted mean total hospitalization costs also did not show a linear trend over time: $25,516 ($21,805–$29,228) in 2007, $23, 613 ($20,349–$26,877) in 2012, and $28,759 ($23,064–$34,454) in 2017, trend $p = 0.50$.

Independent predictors of splenectomy

The strength of association of splenectomy with multiple variables was tested individually using univariate logistic regression analysis. Multiple patient and hospital-level variables were tested as detailed in the "Methods" section. Those were the following: (1) patient level: sex, age, race, insurance carrier, median income in the patient's zip code, comorbidities, including thrombosis; sepsis; nontraumatic ICH; and upper, lower, and nonspecific GI bleed, and steroid use; (2) hospital level: hospital location, teaching status, and hospital bed size. The final model is presented in Table 2. The factors found to

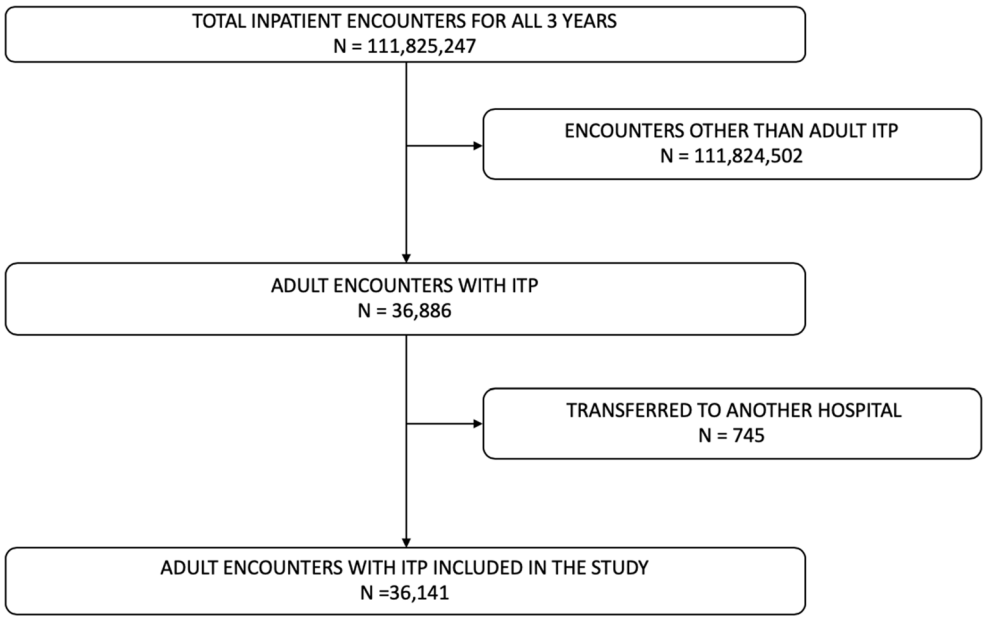

Fig. 1 Flow diagram for study inclusion

be independent predictors of splenectomy were as follows: elective admission, private insurance, urban hospitals, sepsis, and steroid use. In contrast, recent year of hospitalization (declining trend from 2007 to 2017), older age, and Black (compared to Caucasian) race were associated with lower odds of splenectomy. The rest of the variables tested had no influence on splenectomy.

Independent predictors of length of stay

The same process above was applied to identify independent predictors of prolonged length of stay. As is shown in Table 3, variables that were found to be independent predictors of longer LOS were the following: older age, large hospital bed size, urban teaching and non-teaching hospitals, and any of the following comorbidities: thrombosis, nontraumatic ICH, lower, and nonspecific GI hemorrhage. On the other hand, recent year of hospitalization, private insurance, and high median household income were found to be associated with shorter LOS. The other studied variables were found to have no influence on LOS.

Independent predictors of total hospitalization costs

Table 4 shows the final model of the independent predictors of total hospitalization costs: older age, higher median household income, comorbidities including thrombosis, sepsis, nontraumatic ICH, and nonspecific GI bleed, and urban teaching hospitals were associated with higher total hospitalization costs. In contrast, female sex, Asian or Pacific Islander race, and upper GI hemorrhage were associated with lower hospitalization cost. The rest of variables that were included in the study have not shown to predict total hospitalization cost.

Discussion

Using a national representative database, we analyzed the trends of splenectomy in adult patients with ITP as well as the factors associated with splenectomy, its outcomes, and associated resource utilization over a span of a decade (2007–2017). We showed that splenectomy rates among patients with ITP declined by more than 50% (from 16 to 7.6%) from 2007 to 2017 despite a relatively constant hospitalization incidence. In the same time period, splenectomy-associated in-hospital mortality rate also dropped sharply by more than 75% (from 3.8 to 1.1%). For patients who had a splenectomy, there was a very modest change in the mean length of stay over the years (7.1 to 6.2 days), but the inflation-adjusted mean total hospitalization costs increased by almost 33% (from $21,624 to $28,759). Independent predictors of splenectomy were elective admission, private insurance, younger age, Caucasian race, and urban hospitals.

To our knowledge, the current study is among the first to report the trends of splenectomy in adult patients with ITP. The downward trend in splenectomy rates we present is in line with previous publications that studied pediatric ITP hospitalization and splenectomy rates in the USA [11, 16]. While glucocorticoids still are the first-line therapy for ITP, second-line drugs usually include rituximab, high-dose dexamethasone, interferon, danazol, cyclosporine, and azathioprine as well as thrombopoietin-like agents such as eltrombopag or romiplostim. The declining splenectomy rate

Table 1 Baseline characteristics of hospital encounters with immune thrombocytopenia during years 2007, 2012, and 2017

Patient characteristics	Observation			*P* value
	2007	2012	2017	
Number of ITP encounters	12,441	11,710	11,990	Reference
Number of encounters with splenectomy	2054	1530	915	Reference
Mean age, (95% CI)	52.8 (50.9–54.8)	51.9 (49.8–54.1)	50.9 (48.3–53.5)	0.38
Female	1273 (62%)	918 (60%)	567 (62%)	0.12
Race (%)				
White	1479 (72%)	1040 (68%)	595 (65%)	0.48
Black	185 (9%)	138 (9%)	110 (12%)	
Hispanic	308 (15%)	245 (16%)	119 (13%)	
Asian or Pacific Islander	41 (2%)	31 (2%)	37 (4%)	
Native American	21 (1%)	15 (1%)	9 (1%)	
Other	21 (1%)	61 (4%)	46 (5%)	
Median household income category in patient's zip code (%)				
$1–$38,999	472 (23%)	428 (28%)	229 (25%)	0.85
$39–$47,999	512 (25%)	413 (27%)	275 (30%)	
$48,000–$62,999	555 (27%)	337 (22%)	229 (25%)	
> $63,000	512 (25%)	352 (23%)	183 (20%)	
Hospital region (%)				
Northeast	288 (14%)	214 (14%)	137 (15%)	0.95
Midwest	493 (24%)	367 (24%)	156 (17%)	
South	719 (35%)	581 (38%)	393 (43%)	
West	555 (27%)	367 (24%)	229 (25%)	
Hospital bed size (%)				
Small	185 (9%)	168 (11%)	146 (16%)	<0.01
Medium	452 (22%)	413 (27%)	247 (27%)	
Large	1417 (69%)	949 (62%)	522 (57%)	
Hospital location and teaching status (%)				
Rural	103 (5%)	92 (6%)	27 (3%)	<0.01
Urban non-teaching	863 (42%)	520 (34%)	174 (19%)	
Urban teaching	1089 (53%)	918 (60%)	714 (78%)	
Elective admission (%)	575 (28%)	428 (28%)	247 (27%)	<0.01

Table 1 (continued)

Patient characteristics	Observation			*P* value
Insurance type (%)				
Medicare	678 (33%)	490 (32%)	284 (31%)	<0.01
Medicaid	144 (7%)	168 (11%)	156 (17%)	
Private	1130 (55%)	83 (55%)	448 (49%)	
None	103 (5%)	31 (2%)	27 (3%)	
Thrombosis (%)	62 (3%)	77 (5%)	0	<0.01
Sepsis (%)	62 (3%)	61 (4%)	5 (0.5%)	0.07
Bleeding events (%)				
Traumatic ICH	0	0	0	0.41
Nontraumatic ICH	10 (0.5%)	15 (1%)	9 (1%)	0.03
Upper GI bleed	10 (0.5%)	0	92 (10%)	<0.01
Lower GI bleed	0	8 (0.5%)	0	<0.01
Nonspecific GI bleed	123 (6%)	153 (10%)	92 (10%)	<0.01

from 2007 to 2017 may be a result of the increasing availability of multiple medical alternatives, some of which associated with better response rates, despite the fact that major guidelines still consider splenectomy as a second-line option. Given this information and the fact that the presented data is from the national inpatient database, the clinical practice trend in many nonfederal hospitals is to sway away from splenectomy and probably using effective alternative second-line pharmacologic agents. Additionally, although, as we present, short-term post-splenectomy mortality and morbidity have declined due to advances in surgical techniques and equipment, the avoidance of this procedure might be due to its risk of longer-term complications, including that of thrombosis and infection with encapsulated bacteria [8, 9].

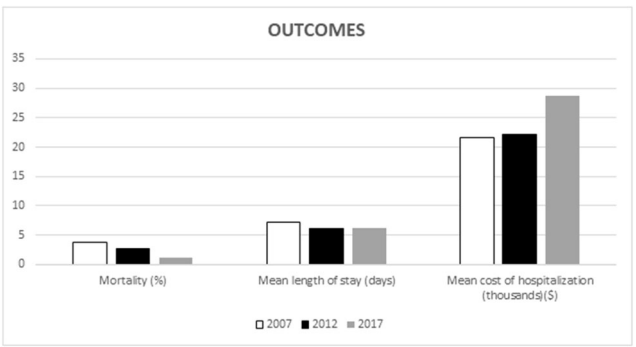

Fig. 2 Outcomes of ITP patients with splenectomy

Furthermore, our nationwide analysis provides insights into factors associated with splenectomy among patients with ITP. Older age and Black race (compared to Caucasian) were associated with lower likelihood of splenectomy. Although older patients are in general less suitable for a surgical procedure like splenectomy, previous research shows that careful patient selection can increase the splenectomy response rate among older adults to around 67% at 60 months [17]. Nevertheless, medical treatment is currently preferred over surgical intervention [18] among both younger and older adults. On the other hand, the etiology underlying lower splenectomy rates among Black compared with Caucasian patients is unclear. Lower socioeconomic status, lack of adequate insurance, decreased access to care in general, and advanced specialty care, in particular poor post-surgical follow-up and possibly patient preference, have all been previously reported as possible mechanisms behind this association in other medical and surgical conditions [19–21]. Similar mechanisms might be at play in this setting. This finding is even more interesting in the setting of higher prevalence of ITP among Black compared with White patients (43.4 versus 33.2/million persons, p value: <0.01). Further research is needed to clarify this association. Race was also included in all regression models in the present study as a result. Private insurance has also been shown to be a predictor of complex expensive intervention similar to splenectomy [19–21] presumably due to better coverage and easier access to care. It is evident from our analysis that most splenectomies are

Table 2 Factors associated as predictors of splenectomy among patient hospitalizations with ITP in years 2007, 2012, and 2017

	Univariate odds ratio (OR) (95% CI)	*P* value	Multivariate odds ratio (OR) (95% CI)	*P* value
Year of hospitalization	0.66 (0.61–0.72)	<0.01	0.79 (0.68–0.90)	<0.01
Sex				
Female	1.07 (0.92–1.22)	0.38		
Age	0.99 (0.98–0.99)	< 0.01	0.99 (0.97–0.99)	0.02
Comorbidities				
Thrombosis	1.22 (0.83–1.81)	0.3		
Sepsis	2.13 (1.35–3.35)	<0.01	3.88 (1.69–8.86)	<0.01
Nontraumatic ICH	0.69 (0.32–1.50)	0.36		
Upper GI hemorrhage	0.59 (0.37–0.92)	0.02	1.40 (0.80–2.54)	0.26
Lower GI hemorrhage	0.08 (0.01–0.61)	0.01	0.17 (0.02–1.45)	0.11
Nonspecific GI hemorrhage	0.96 (0.75–1.23)	0.74		
Type of admission				
Elective	21.4 (17.82–25.76)	<0.01	21.7 (17.5–26.9)	<0.01
Insurance type				
Medicare	Reference	Reference	Reference	Reference
Medicaid	1.04 (0.82–1.32)	0.76	1.22 (0.81–1.84)	0.34
Private	1.87 (1.59–2.18)	<0.01	1.39 (1.03–1.87)	0.03
None	0.84 (0.58–1.21)	0.33	0.95 (0.52–1.72)	0.86
Median income				
$1–$38,999	Reference	Reference	Reference	Reference
$39–$47,999	1.27 (1.05–1.53)	0.01	1.46 (1.10–1.94)	0.01
$48,000–$62,999	1.13 0.93–1.38)	0.22	1.21 (0.90–1.61)	0.20
> $63,000	1.09 (0.89–1.34)	0.42	1.13 (0.83–1.54)	0.43
Race				
White	Reference	Reference	Reference	Reference
Black	0.59 (0.46–0.77)	<0.01	0.63 (0.45–0.88)	<0.01
Hispanic	0.91 (0.75–1.12)	0.38	0.94 (0.70–1.27)	>0.70
Asian or Pacific Islander	0.71 (0.44–1.16)	0.18	0.80 (0.45–1.43)	0.45
Native American	1.07 0.31–3.71)	0.92	0.69 (0.05–8.75)	0.77
Other	1.00 (0.67–1.48)	0.99	1.22 (0.68–2.19)	0.51
Hospital location and teaching status (%)				
Rural	Reference	Reference	Reference	Reference
Urban non-teaching	2.21 (1.04–2.0)	<0.01	2.22 (1.37–3.59)	<0.01
Urban teaching	2.37 (1.04–1.97)	<0.01	2.29 (1.42–3.71)	<0.01
Hospital bed size (%)				
Small	Reference	Reference		
Medium	1.00 (0.79–1.27)	0.99		
Large	1.13 (0.92–1.41)	0.24		
Steroids use	2.85 (2.30–3.54)	<0.01	2.60 (1.96–3.46)	<0.01

Table 3 Factors associated as predictors of length of stay among patient hospitalizations with ITP in years 2007, 2012, and 2017

	Univariate mean difference in days (95% CI)	*P* value	Multivariate-adjusted mean difference in days (95% CI)	*P* value
Year of hospitalization	−0.32 (−0.51–− 0.14)	<0.01	−0.45 (−0.64–− 0.26)	<0.01
Sex				
Female	−0.43 (−0.70–− 0.15)	<0.01	−0.18 (−0.44–0.09)	0.19
Age	0.04 (0.04–0.05)	<0.01	0.04 (0.03–0.04)	<0.01
Comorbidities				
Thrombosis	3.43 (1.99–4.86)	<0.01	1.72 (0.62–0.04)	<0.01
Sepsis	2.13 (11.60–18.80)	<0.01	12.70 (9.19–16.20)	<0.01
Traumatic ICH	3.61 (−3.50–10.72)	0.32		
Nontraumatic ICH	5.45 (3.62–7.29)	<0.01	4.21 (2.29–6.12)	<0.01
Upper GI hemorrhage	2.85 (1.94–3.75)	<0.01	−0.35 (−1.49–0.79)	0.54
Lower GI hemorrhage	2.94 (1.36–4.51)	<0.01	1.62 (0.22–3.01)	0.02
Nonspecific GI hemorrhage	3.68 (3.04–4.33)	<0.01	2.77 (1.94–3.60)	<0.01
Type of admission				
Elective	−0.74 (−1.07–− 0.41)	<0.01	−0.26 (−0.63–0.11)	0.16
Insurance type				
Medicare	Reference	Reference	Reference	Reference
Medicaid	−0.69 (−1.21–− 0.16)	0.01	0.35 (−0.22–0.92)	0.23
Private	−1.84 (−2.12–− 1.56)	<0.01	−0.39 (−0.77–− 0.03)	0.04
None	−1.18 (−1.71–− 0.65)	<0.01	0.08 (−0.56–0.71)	0.82
Median income				
$1–$38,999	Reference	Reference	Reference	Reference
$39–$47,999	−0.02 (−0.43–0.38)	0.91	0.12 (−0.28–0.52)	0.54
$48,000–$62,999	−0.23 (−0.43–0.38)	0.18	0.02 (−3.56–0.39)	0.92
> $63,000	−0.62 (−1.00–− 0.25)	<0.01	−0.48 (−0.85–− 0.11)	0.01
Race				
White	Reference	Reference	Reference	Reference
Black	0.12 (−0.25–0.59)	0.61	0.33 (−0.07–0.74)	0.11
Hispanic	−0.18 (−0.61–0.24)	0.40	0.28 (−0.15–0.71)	0.21
Asian or Pacific Islander	−0.09 (−1.01–0.84)	0.86	−0.01 (−0.84–0.83)	0.99
Native American	4.98 (−0.49–10.4)	0.08	4.58 (−0.27–9.42)	0.06
Other	−0.23 (−0.83–0.36)	0.44	0.31 (−0.30–0.92)	0.32
Hospital location and teaching status (%)				
Rural	Reference	Reference	Reference	Reference
Urban non-teaching	0.48 (0.06–0.89)	0.02	0.81 (0.34–1.29)	<0.01
Urban teaching	0.79 (0.37–1.20)	<0.01	1.26 (0.76–1.76)	<0.01
Hospital bed size (%)				
Small	Reference	Reference	Reference	Reference
Medium	0.22 (−0.23–0.67)	0.34	0.25 (−0.22–0.72)	0.29
Large	0.55 (0.11–0.98)	0.01	0.48 (0.51–0.93)	0.03

Table 4 Factors associated as predictors of total hospitalization costs among patient hospitalizations with ITP in years 2007, 2012, and 2017

	Univariate mean difference (95% CI)	*P* value	Multivariate-adjusted mean difference (95% CI)	*P* value
Year of hospitalization	$861 ($136–$1587)	0.02	$573 (−$232–$1379)	0.16
Sex				
Female	−$4158 (−$5289–(−$3027))	<0.01	−$3432 (−$4551–(−$2314))	<0.01
Age	$79 ($5–$102)	<0.01	$54 ($18–$89)	<0.01
Comorbidities				
Thrombosis	$11,051 ($5309–$16,794)	<0.01	$5552 ($1995–$9110)	<0.01
Sepsis	$51,217 ($38,030–$64,404)	<0.01	$40,591 ($28,976–$52,207)	<0.01
Traumatic ICH	$5478 (−$1763–$12,720)	0.14		
Nontraumatic ICH	$24,744 ($16,742–$32,746)	<0.01	$21,868 ($13,102–$30,634)	<0.01
Upper GI hemorrhage	$10,576 ($6612–$14,539)	<0.01	−$4342 (−$8507–(−$177))	0.04
Lower GI hemorrhage	$10,974 ($4686–$17,262)	<0.01	$4995 (−$116–$10,106)	0.06
Nonspecific GI hemorrhage	$12,689 ($10,107–$15,271)	<0.01	$10,250 ($7056–$13,444)	<0.01
Type of admission				
Elective	−$3213 (−$4372–(−$2053))	<0.01	−$1475 (−$2696–(−$254)	0.09
Insurance type				
Medicare	Reference	Reference	Reference	Reference
Medicaid	-$966 (−$2862–$930)	0.32	$1834 (−$416–$4084)	0.11
Private	−$3195 (−$4302–(−$2088)	<0.01	$114 (−$1428–$1656)	0.89
None	−$3330 (−$5318–(−$1342))	<0.01	−$451 (−$2908–$2007)	0.72
Median income				
$1–$38,999	Reference	Reference	Reference	Reference
$39–$47,999	$964 (−$519–$2446)	0.20	$1477 ($125–$2941)	0.05
$48,000–$62,999	$1344 (−$170–$2860)	0.08	$2320 ($819–$3821)	<0.01
> $63,000	$1060 (−$423–$2542)	0.16	$1722 ($256–$3189)	0.02
Race				
White	Reference	Reference	Reference	Reference
Black	$147 (−$1840-$2134)	0.89	$1052 (−$471–$2576)	0.18
Hispanic	−$1305 (−$2894–$282)	0.11	$133 (−$1539–$1806)	0.88
Asian or Pacific Islander	−$1618 (-$4095–$859)	0.20	−$2399 (−$4679–(−$119)	0.04
Native American	$8029 (−$7531–$23,589)	0.31	$7657 (−$6853–$22,168)	0.30
Other	$841 (−$2219–$3902)	0.59	$2606 (−$629–$5841)	0.11
Hospital location and teaching status (%)				
Rural	Reference	Reference	Reference	Reference
Urban non-teaching	$1348 (−$883-$3579)	0.24	$1599 (−$1169–$4367)	0.26
Urban teaching	$3219 ($1023–$5416)	<0.01	$2841 ($83–$5599)	0.04
Hospital bed size (%)				
Small	Reference	Reference	Reference	Reference
Medium	−$21 (−$1858–$1816)	0.98		
Large	$1062 (−$697–$2821)	0.01		

performed on a non-emergent basis, since elective admission was a predictor of splenectomy. This finding is similar to splenectomy in the pediatric ITP population [11].

Likewise, in this study, we report that older age, thrombosis, sepsis, nontraumatic ICH, GI hemorrhage, higher median household income, and large, urban teaching and non-teaching hospitals were associated with prolonged length of stay (LOS), higher costs of hospitalization, or both among patients who had a splenectomy. Since secondary diagnoses can be either new diagnoses or elements of the past medical history, it is unclear whether the comorbidities listed above are complications of splenectomy or pre-existing conditions. Based on clinical practice, it seems that they would be post-surgical complications with the exception of nontraumatic ICH and GI hemorrhage. Irrespective, careful patient selection can decrease resource utilization in addition to improving mortality. These findings are comparable to other previously published papers that described ITP-related hospitalization in children or adults [11, 12, 22–25]. Across diagnosis-related groups, septicemia was the most contributing factor for longer LOS (12.7 (9.19–16.2) days, $P < 0.01$) and highest costs of hospitalization ($40,591 ($28,976–$52,207) $P < 0.01$).

Our study has certain limitations. First, it is a retrospective analysis using NIS, a national representative database, which has previously been used for the study of ITP [11]. However, NIS captures only inpatient encounters and therefore misses outpatient medical management. Second, it has been documented that claims-based databases are vulnerable to imprecisely entered or missing codes [26]. However, the positive predictive value for the ICD-9 code CM code for ITP was shown to be high [27]. Third, we were unable to identify and exclude readmission, because NIS is a discharge-level database. Thus, the incidence of ITP we report might be an overestimation while that of splenectomy we report an underestimation. Fourth, NIS does not include medications nor laboratory or radiology data and thus cannot be used to study the association between prior treatment and splenectomy including platelet count and medical treatment the patient has received.

However, our study has advantages. It uses the largest publicly available all-payer inpatient database in the USA, minimizing the likelihood of a beta error. NIS is nationally representative and includes patients from hospitals that are small, medium, and large; teaching and non-teaching; rural and urban; and privately or publicly owned across 48 states. This makes the study results likely generalizable to patients admitted with ITP across the USA. Additionally, the unique variables in the database permitted us to study factors such as hospitalization costs, household income estimates, and hospital factors, which are not commonly available in single-center studies. Lastly, a change in NIS' sampling frame occurred in 2012 [28]. New weights, called trend weights, are provided for NIS years before 2012 to make the NIS sampling frame and design homogeneous throughout the years, allowing for accurate trend calculation over time [29].

In conclusion, to our knowledge, this is the first analysis to report the yearly incidence of ITP over time at the national level as well as the trends of splenectomy among adult patients with ITP along with the predictors of splenectomy, length of stay, and hospitalization costs. Our analysis showed that, despite a stable ITP hospitalization rate over the past decade, and despite considering splenectomy as a second-line option by many guidelines, splenectomy rates among patients with ITP had steady declined from 16% in year 2007 to 7.6% in year 2017. Post-splenectomy in-hospital mortality rate dropped from 3.8% in 2007 to 1.1% in 2017. Despite an essentially constant mean length of stay, the mean inflation–adjusted total hospitalization costs significantly increased over the study period.

Appendix

ICD-9 CM codes:

Immune thrombocytopenia:

287.31

Splenectomy:

Procedural ICD-9 CM code: 41.5

Thrombosis:

Clinical Classifications Software (CCS) diagnosis codes 116 and 118

Sepsis:

CCS diagnosis code: 2

Steroid use:

V58.65

Traumatic intracranial hemorrhage:

800.2x, 800.3x, 800.7x, 800.8x, 801.2x, 801.3x, 801.7x, 801.8x, 803.2x, 803.3x,803.7, 803.8x, 804.2x, 804.3x, 804.7x, 804.8x, 852.00-06, 852.09, 852.10-16, 852.19, 852.20-26, 852.29, 852.30-36, 852.39, 852.40-46, 852.49, 852.50-56, 852.59, 853.00- 06, 853.09, 853.10-16, 853.19

Nontraumatic intracranial hemorrhage:

430, 431, 432.0, 432.1, 432.9

Upper gastrointestinal hemorrhage:

530.7, 531.0, 531.00, 531.01, 531.2, 531.20, 531.21, 531.4, 531.40, 531.41, 531.6, 531.60 ,531.61, 532.0, 532.00, 532.01, 532.2, 532.20, 532.21, 532.4, 532.40, 532.41, 532.6, 532.60, 532.61, 533.0,533.00, 533.01, 533.2, 533.20, 533.21, 533.4, 533.40, 533.41, 533.6, 533.60, 533.61, 534.0, 534,00, 534.01, 534.2, 534.20, 534.21, 534.4, 534.40, 534.41, 534.6, 534.60, 534.61, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.71, 537.83, 530.82, 537.84, 578.0, 530.21, 578.9, 285.1, 578.1

Lower GI bleed:
569.85, 455.2, 455.5, 455.8
Non-specified GI bleeding:
578.1, 578.9, 285.1
Non-GI bleeding:
078.6, 246.3, 360.43, 362.43, 362.81, 363.6, 363.61, 363.62, 363.72, 372.72, 374.81, 376.32, 377.42, 379.23, 380.31, 423.0, 459.0, 596.7, 608.82, 665.7, 665.70, 665.71, 665.72, 665.74, 767.11, 782.7, 784.7, 784.8, 786.3, 864.01, 864.11, 865.01, 865.11, 866.01, 866.11, 997.02, 998.1, 998.11, 998.12
ICD-10 CM codes:
Immune thrombocytopenia:
D69.3
Splenectomy:
Procedural ICD-10 CM code: 07TP0ZZ and 07TP4ZZ
Thrombosis:
I51.3, I63.0, I63.3, I63.6, I67.6, K64.5, I74.xxxx. I82.xxxx except "82.0 and I82.1
Sepsis:
A40.xxxx, A41.xxxx, A02.1, A22.7, A26.7, A32.7, A42.7, A54.86, B37.7, R65.2
Steroid use:
Z79.52
Traumatic intracranial hemorrhage:
S06.5xxx, S06.6xxx, S06.34xx, S06.35xx, S06.36xx
Nontraumatic intracranial hemorrhage:
I60.xxxx, I61.xxxx, I62.xxxx
Upper gastrointestinal hemorrhage:
`K22.11, K22.6, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.01, K29.21, K29.31, K29.41, K29.51, K29.61, K29.71, K29.81, K29.91, K31.811, K31.82, K92.1, K92.2, D62, K92.0
Lower GI bleed:
K57.11, K57.31, K57.51, K57.91, K62.5, K55.21, K64.xxxx
Non-specified GI bleeding:
K92.1, K92.2, D62
Non-GI bleeding:
A98.5, I31.2, R58, R36.1, O71.7, S36.112, S36.029A, S36.021A, S36.020A, H44.81xx, H35.73xx, H35.6xxx, H31.30xx, H31.31xx, H31.41xx, H11.3xxx, H47.02xx, H05.23xx, H43.1xxx, H61.12xx, R04.xxxx, S37.01xx, S37.02xx, I97.4xxx, I97.6xxx

Author contribution Antoine Finianos and Ali Taher contributed to the study conception and design. Data collection and analysis were performed by Marwan S. Abougergi. The first draft of the manuscript was written by Antoine Finianos, Hata Mujadzic, Tarik Mujadzic, Heather Peluso, and Marwan S. Abougergi. All authors commented on previous versions of the manuscript, read and approved the final manuscript.

Funding Funding was provided by the American University of Beirut, Naef K. Basile Cancer Institute.

Declarations

Ethics approval This retrospective review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of Prisma Health-Upstate, Greenville South Carolina.

Consent to participate This study is a retrospective review of already collected and de-identified data, thus, informed consent was not obtained

Conflict of interest The authors declare no competing interests.

References

1. Kayal L, Jayachandran S, Singh K (2014) Idiopathic thrombocytopenic purpura. Contemp Clin Dent 5(3):410–414. https://doi.org/10.4103/0976-237X.137976
2. Godeau B (2014) Immune thrombocytopenic purpura: major progress in knowledge of the pathophysiology and the therapeutic strategy, but still a lot of issues. Presse Med 43(4 pt 2):e47–e48
3. Tripathi AK, Mishra S, Kumar A, Yadav D, Shukla A, Yadav Y (2014) Megakaryocyte morphology and its impact in predicting response to steroid in immune thrombocytopenia. Platelets. 25(7): 526–531
4. Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Arnold DM, Bussel JB, Cines DB, Chong BH, Cooper N, Godeau B, Lechner K, Mazzucconi MG, McMillan R, Sanz MA, Imbach P, Blanchette V, Kühne T, Ruggeri M, George JN (2009) Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: Report from an international working group. Blood. 113:2386–2393
5. Terrell DR, Beebe LA, Neas BR, Vesely SK, Segal JB, George JN (2012) Immune thrombocytopenia (ITP) in adults: clinical manifestations and diagnosis. Am J Hematol 87(9):848–852
6. Neunert C, Terrell DR, Arnold DM, Buchanan G, Cines DB, Cooper N, Cuker A, Despotovic JM, George JN, Grace RF, Kühne T (2019) American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv 3(23):3829–3866
7. Chaturvedi S, Arnold DM, McCrae KR (2018) Splenectomy for immune thrombocytopenia: down but not out. Blood. 131:1172–1182
8. Rodeghiero F (2007) First-line therapies for immune thrombocytopenic purpura. Blood 110:2924–2930
9. Thomsen RW, Schoonen WM, Farkas, Riis A, Jakobsen J, Fryzek JP et al (2009) Risk for hospital contact with infection in patients with splenectom; a population-based cohort study. Ann Intern Med 151(8):546–555
10. https://www.hcupus.ahrq.gov/db/nation/nis/NISIntroduction2017.pdf, accessed on May 11, 2020
11. Bhatt NS, Bhatt P, Donda K, Dapaah-Siakwan F, Chaudhari R, Linga VG, Patel B, Lekshminarayanan A, Bhaskaran S, Zaid-Kaylani S, Badawy SM (2018) Temporal trends of splenectomy in pediatric hospitalizations with immune thrombocytopenia. Pediatr Blood Cancer 65(7):e27072

12. Deyo RA, Cherkin DC, Ciol MA (1992) Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 45(6):613–619
13. US Agency for Healthcare Research and quality cost-to-charge ratio files. https://www.hcup-us.ahrq.gov/db/state/costtocharge.jsp. Accessed May 11, 2020
14. https://www.bls.gov/cpi/. Accessed April 15, 2020
15. https://www.census.gov/. Accessed December 22, 2020
16. Tarantino MD, Danese M, Klaassen RJ, Duryea J, Eisen M, Bussel J (2016) Hospitalizations in pediatric patients with immune thrombocytopenia in the United States. Platelets. 27:472–478
17. Giudice V, Rosamilio R, Serio B, di Crescenzo RM, Rossi F, de Paulis A, Pilone V, Selleri C (2016) Role of laparoscopic splenectomy in elderly immune thrombocytopenia. Open Med (Wars) 11(1):361–368
18. Mahévas M, Michel M, Godeau B (2016) How we manage immune thrombocytopenia in the elderly. Br J Haematol 173:844–856
19. Abougergi MS, Avila P, Saltzman JR (2019) Impact of insurance status and race on outcomes in nonvariceal upper gastrointestinal hemorrhage: a nationwide analysis. J Clin Gastroenterol 53(1):e12–e18
20. Molina Y, Silva A, Rauscher GH (2015) Racial/ethnic disparities in time to a breast cancer diagnosis: the mediating effects of health care facility factors. Med Care 53:872–878
21. Haider AH, Chang DC, Efron DT, Haut ER, Crandall M, Cornwell EE 3rd (2008) Race and insurance status as risk factors for trauma mortality. Arch Surg 143:945–949
22. Okubo Y, Handa A (2018) Nationwide trend analysis of pediatric inpatients with immune thrombocytopenia in the United States. J Pediatr Hematol Oncol 40(3):e140–e144
23. An R, Wang PP (2017) Length of stay, hospitalization cost, and in-hospital mortality in US adult inpatients with immune thrombocytopenic purpura, 2006-2012. Vasc Health Risk Manag 13:15–21. Published 2017 Jan 20. https://doi.org/10.2147/VHRM.S123631
24. Danese MD, Lindquist K, Gleeson M, Deuson R, Mikhael J (2009) Cost and mortality associated with hospitalizations in patients with immune thrombocytopenic purpura. Am J Hematol 84:631–635
25. Bansal D, Bhamare TA, Trehan A, Ahluwalia J, Varma N, Marwaha R (2010) Outcome of chronic idiopathic thrombocytopenic purpura in children. Pediatr Blood Cancer 54:403–407
26. Klabunde CN, Warren JL, Legler JM (2002) Assessing comorbidity using claims data: an overview. Med Care 40(Suppl):IV-26–IV-35
27. (2012) Determining a definite diagnosis of primary immune thrombocytopenia by medical record review. Am J Hematol 87(9):843–847. https://doi.org/10.1002/ajh.23226
28. https://www.hcup-us.ahrq.gov/reports/methods/2014-04.pdf. Accessed May 11, 2020
29. https://www.hcup-us.ahrq.gov/db/nation/nis/trendwghts.jsp. Accessed May 11, 2020