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Original Article

Outcomes of hospitalized patients with myocardial infarction and immune thrombocytopenic purpura: a cross sectional study over 15 years

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Abstract: Background: Immune Thrombocytopenic Purpura (ITP) is an autoimmune disorder characterized by low platelet counts and mucocutaneous bleeding. The outcomes of hospitalized patients with ITP and myocardial infarction (MI) have not been extensively studied and may help identify risk factors associated with adverse outcomes in this unique patient population. Methods: Patients with ITP who were admitted with MI using the National Inpatient Database for the years 2000 to 2014. Patient demographics, hospital characteristics and medical comorbidities were studied. Chi square test was used to determine associations with statistical significance and logistic regression was used to determine independent predictors of mortality. Results: A total of 753732 hospitalized patients with ITP were identified over the time period of 2000 to 2014, of which 37695 patients had both ITP and acute MI. There were more females with ITP in general (60% females vs. 40 males), but more males with ITP and acute MI (55.8% males vs. 44.2% females; P=0.0000). Caucasians were affected the most (5.5%) amongst all races and the age group of 65-79 years had the highest percentage of patients with ITP and MI (7.3%). The classical risk factors of hypertension, hyperlipidemia, and diabetes were also noted to be highly prevalent in patients with ITP and MI. 10.05% of patients with ITP and acute MI died during hospitalization, while 4% of all patients with ITP died during hospitalization (P<0.05). Multiple regression showed that stent placement, female gender, blood transfusions, platelet transfusion, 80+ age group and higher Charlson's score were independent predictors of mortality in patients with ITP which have MI. Conclusions: MI is associated with an increased rate of in-hospital death in patients with ITP. Both blood transfusions and platelet transfusions adversely affect outcomes in the management of AMI in ITP patients.

Keywords: Immune thrombocytopenic purpura, myocardial infarction, mortality, risk factor

Introduction

Idiopathic thrombocytopenic purpura (ITP) is an immune-mediated hematological disorder where autoantibodies are directed against platelets, leading to premature platelet destruction [1]. In recent years, our understanding of the pathophysiology of ITP has improved. ITP's pathogenesis has been clarified by demonstrating its autoimmune origin. The disease is largely mediated by antibodies that target glycoproteins expressed on platelets and megakaryocytes, resulting in a thrombocytopenic state [2]. The global incidence rate for ITP in adults is estimated to be 1.6-3.9/100,000 persons with over 200,000 people affected [3]. In the US, rates are fairly similar with an annual incidence of approximately 3.3 per 100,000 adults/year [4]. The incidence of ITP increases with age and is more common in patients over the age of 60.

Roughly one fourth of patients with ITP are asymptomatic without any signs of clinical presentation at the time of diagnosis [1]. However, due to decreased platelet counts, ITP may result in an increased tendency for mucocutaneous bleeding and possible spontaneous hemorrhages that may be major causes of mortality [5, 6]. The risk is greatest in the elderly, those with a history of bleeding, and those who have no response to therapy [5]. Initially, given a patient's thrombocytopenic state, ITP was only recognized to cause bleeding complications [1] and thrombotic manifestations were not even considered. It still remains unclear

how ITP paradoxically causes thrombosis, resulting in cardiovascular disease. The risk of thrombotic complications seems to be related to both the presence of abnormally enlarged immature platelets that adhere more aggressively to endothelial surfaces and increased pro-inflammatory damage that activates the coagulation cascade [7-9]. While the pathophysiology is still not well-understood, ITP has increasingly become recognized as a thrombotic disorder with studies demonstrating higher rates of thrombosis in ITP patients than non-ITP patients [1, 10-13]. Studies have concluded that rates of both arterial and venous thromboses are increased in ITP [1, 14-16]. Meta-analyses have also demonstrated that the incidence of thromboembolism was increased in ITP patients compared to non-ITP patients [17, 18]. In fact, it has become well-established that these patients have a higher mortality as a result compared to the general population [7, 14, 19]. Although there is a growing association between ITP and thrombosis, the coexistence of this hematologic disorder and complications like coronary artery disease and acute myocardial infarction (AMI) is still very rare. Management is challenging with guidelines being sparse due to the rarity of the association. Even more concerning is that treatments such as revascularization and antiplatelet therapy have their own associated risks. Thrombolytic therapy is actually contraindicated in ITP patients due to the high risk of bleeding [20]. Most data regarding AMI in patients with ITP and their management are found in case reports [20-23]. Only one study to date has specifically focused on the impact of ITP on the outcomes of myocardial ischemia, thus requiring more large-center population-based studies to further validate the findings [24]. The prevalence of AMI in ITP and the associated risk factors are still actually unknown. This study aims to explore the characteristics and outcomes of AMI in hospitalized patients with ITP. We hope to assess the prevalence of AMI in patients with ITP across the United States as well as study the impact of ITP on mortality outcomes in patients that suffer AMI.

Methods

Study design

A retrospective analysis of in-hospital data from the years 2000-2014 was conducted. The data was obtained from the National Inpatient Sample (NIS) database, the largest all-payer inpatient care database maintained by the Agency for Healthcare Research and Quality as part of the Healthcare Cost and Utilization Project [25]. It represents approximately 20% sampling of inpatient admissions to acute care hospitals. It is stratified by parameters such as geographic region, urban/rural location, teaching status, and hospital bed size to minimize sampling bias. Each admission is weighted to make NIS representative of nationwide hospital systems. Patient's demographics, primary and secondary diagnoses, Clinical Modification (ICD-9-CM) diagnosis and procedure codes, resource utilization and clinical outcomes are reported in the database. The data within the NIS is publicly available and does not contain any identifying information, making this retrospective study exempt from review by the Institutional Review Board. The retrospective nature of studying de-identified patient data, lack of direct patient contact or intervention also makes this study exempt for ethics committee and from the requirement of patient consent.

Study population

Records of any admissions with a principal diagnosis of ITP were obtained. The current procedural terminology code (CPT) for ITP was utilized to ensure inclusion of all patients with ITP. Amongst these patients, all patients who had a secondary diagnosis of AMI during the hospitalization were identified. Demographic information consisting of age, gender, race, comorbidities was extracted from patients that met this criterion. Other details related to their hospitalization, hospital disposition, hospital size, location, region and teaching status were also determined. The presence of common medical comorbidities such as hypertension, hyperlipidemia, diabetes, chronic kidney disease atrial fibrillation, coronary artery disease, congestive heart failure, malignancy, and smoking was collected in this patient population. Comorbidities were itemized and assessed using the Charlson Comorbidity Index (CCI) [26, 27]. CCI is a composite measure of the patient's health status based on chronic conditions. Also, information regarding receipt of blood product transfusions (platelet, RBC) and medical interventions like stent placements and coronary artery bypass grafting (CABG) were collected. The primary outcome of interest was in-hospital mor-

Table 1. Demographic distribution of ITP patients with and without MI between the years 2000-2014

Hospitalized patients with ITP	Gender		Race						Age Group				
	Male	Female	White	Black	Hispanic	Asian	Native American	Unknown	18-34	35-49	50-64	65-79	80+
No MI	57843	87373	85890	14956	12958	2971	3961	24670	24493	22324	29741	39308	29541
MI	4275	3384	5069	469	398	132	206	1385	63	416	1622	3130	2428

tality. We investigated the impact of demographics, hospital characteristics, blood product transfusions, medical interventions, and CCI on mortality outcomes in this patient population.

Statistical analysis

Descriptive statistics were used to estimate the national rate of AMI among patients with ITP. We assessed the distribution of sociodemographic, behavioral, hospital characteristics, and selected clinical conditions to explore differences in baseline characteristics. We categorized age in years into five clinically consequential categories: 18-34, 35-49, 50-64, 65-79, ≥80. Race was determined by self-reported ethnicity. The primary payer for each hospitalization was classified into private (commercial carriers and private HMOs and PPOs), Medicare, Medicaid, self-pay, and other. Hospital characteristics assessed included US geographic region (Northeast, Midwest, South, or West) and size dependent on hospital occupancy. Categoric group comparisons were made using Pearson χ^2 tests. Survey logistic regression analyses were used to estimate odds ratios and 95% confidence intervals for the association between patients with ITP who suffered an AMI and each outcome of interest. This was used to determine independent predictors of mortality. Covariates were picked based on a review of the literature and included year, age, race, sex, comorbidities, CCI, hospital characteristics, insurance, and medical treatment interventions. Statistical significance was defined as a *P* value of <0.05. All statistical analysis was performed using STATA software version 14.2 (College Station, TX).

Results

Patient demographics

In the 15-year period from 2000-2014, a total of 753732 hospitalized patients with ITP were identified, of which 37695 patients had both ITP and acute MI. There were more females with ITP in general (60% females vs. 40 males), but more males with ITP and AMI (55.8% males vs. 44.2% females; P=0.0000). Caucasians were affected the most (5.5%) amongst all races and the age group of 65-79 years had the highest percentage of patients with ITP and MI (7.3%). While hospitals located in the Northeast region of the country had the highest prevalence of MI in ITP, there was no statistical difference between prevalence in hospitals of different sizes (small vs. medium vs. large). The gender, age and race distribution is shown in **Table 1**. A majority of patients with MI and ITP were covered by Medicare and were discharged home. For medical intervention, 5572 patients received a stent and 3353 patients underwent coronary artery bypass grafting. The classical risk factors of hypertension, hyperlipidemia, diabetes were also noted to be highly prevalent in patients with ITP and MI. 10.05% of patients with ITP and acute MI died during hospitalization, while 4% of all patients with ITP died during hospitalization (P<0.05).

Multivariate analysis

Multiple regression showed that stent placement, female gender, blood transfusions, platelet transfusion, 80+ age group and higher Charlson's score were independent predictors of mortality in patients with ITP which have MI. **Table 2** enlists some of the predictors analyzed in this study.

Discussion

ITP is a hematological disease mediated by the autoimmune destruction of platelets resulting in low platelet counts. While ITP is associated primarily with thrombocytopenia and mucocutaneous bleeding, there are increased risks for thrombosis and coronary artery disease like AMI in this patient population. The objective of our investigation was to evaluate using a nationwide population-based study the characteristics and outcomes of AMI in patients

Table 2. Independent predictors of in-hospital mortality

Predictor	Odds ratio (95% confidence interval)	*P* Value
Age group	1.40 (1.28-1.53)	0.0001
Sex	0.86 (0.74-1.01)	0.07
Comorbidities		
Atrial fibrillation	0.95 (0.79-1.14)	0.62
Hypertension	1.04 (0.88-1.22)	0.59
Diabetes	0.81 (0.66-0.99)	0.04
Hyperlipidemia	1.05 (0.81-1.36)	0.66
Chronic renal failure	0.73 (0.57-0.95)	0.09
Smoking	0.73 (0.50-1.07)	0.11
Charlson comorbidity score	1.76 (1.58-1.96)	0.000
Insurance	0.87 (0.77-0.99)	0.03
Hospital region	0.97 (1.02-1.29)	0.01

with ITP. Our study noted that ITP has a predilection for female patients, supporting past reports [28]. However, patients with AMI and ITP were more likely to be Caucasian male with the majority of individuals being affected between 65-79 years of age.

The results of this study also corroborate current literature accentuating a link between ITP and AMI. Individuals with ITP may show an increased thrombotic and atherosclerotic risk that worsens health outcomes [7, 29, 30]. In-hospital mortality rates were higher in ITP patients that present with AMI than the general population of patients with ITP in this study. This may be related to the added risks of other comorbid conditions and higher CCI that are often associated with these clinical diseases and which can exacerbate medical problems. Similar to Chehab et al. [8], hypertension, hyperlipidemia, and diabetes were highly prevalent in patients with ITP who suffered AMI. Patients with persistent or chronic ITP are at increased risk for several of these comorbidities [14]. This combined with the similar comorbid risks associated with AMI underscore the high prevalence seen in our patient population. In one study assessing over 15000 patients, ≥90% of myocardial infarctions were attributable to comorbidities such as smoking, hyperlipidemia, hypertension, abdominal obesity, and diabetes in men and women [31]. Many patients with AMI often present with multiple comorbidities and the presence of comorbid cardiovascular disease itself is associated with increased mortality in the general population without ITP [32]. Thus, the increased rate of mortality in patients with both ITP and AMI seen in our study is expected.

Moreover, management of AMI in this patient population may further provide support for the poor outcomes. Given the rarity of AMI in patients with ITP, literature regarding the clinical management of ITP patients who develop AMI, including the use of revascularization and antiplatelet/anticoagulant therapy, is nonexistent. This is a dilemma in this patient population considering the fact that revascularization and particularly antiplatelet therapy are essential parts of management in coronary artery disease, but the inherent inhibition of platelet function can paradoxically compound bleeding tendencies in ITP patients [21, 25, 33]. In this study, more patients with ITP underwent PCI and stenting procedures compared to CABG for the management of their AMIs. Stenting was also found to be an independent predictor of mortality in these patients. Our finding supports the study by Yadav et al. which assessed the implications of baseline thrombocytopenia on clinical outcomes in 10,603 patients who underwent PCI and stenting for non-ST-elevation acute coronary syndrome or ST-elevation myocardial infarction. They found that the presence of thrombocytopenia in patients undergoing these procedures had worse health outcomes and adverse cardiac events [34]. Ayoub et al. utilized a population-based study and concluded that PCI in chronic thrombocytopenic patients was associated with a higher risk of bleeding complications, ischemic cerebrovascular accidents, and mortality after PCI [35]. A review by Russo et al. further illustrated that while both PCI and CABG can successfully be performed in patients with ITP, there is an increased bleeding risk compared to the general population [30]. These studies show the increased risks associated with both procedures and support the increased mortality rates seen in this study. Additionally, without standard guidelines to guide clinicians through this conundrum and direct specific management for certain circumstances, the likelihood of morbidity and mortality in ITP patients suffering from AMI will continue to be higher.

This lack of clinical guidance may also contribute to our finding that transfusions adversely

affect clinical outcomes. There already appears to be substantial utilization of platelet transfusion in the management of hospitalized patients with ITP [36]. Undoubtedly, transfusions are likely to be utilized even more in ITP patients with AMI to manage bleeding risks [21]. Other studies have also found similar results [35, 37]. However, both blood and platelet transfusions have their own risks as well. They can cause complications including febrile non-hemolytic reactions, allergic reactions, transfusion-related acute lung injury, and bacterial sepsis, thus contributing to increased rates of adverse outcomes in this patient population [36]. The use of blood transfusions in AMI patients specifically was found to increase the risk of mortality by 12% independent of hemoglobin level [38]. As our study demonstrates, blood product transfusions are an independent predictor of mortality. Patients in need of blood product transfusions often already have worse prognoses and are at higher risk of complications, likely contributing to worse health outcomes [39]. To our knowledge, this is the first study to find such an association. Such findings were assessed by Chehab et al. [8], but not found to be significant; notably Chehab et al. found that patients with AML had the same mortality but had higher complications and longer length of stay. Our study encompasses a larger sample size over a longer time frame and thus may add to the significance of this finding. Thus, while necessary, our study underscores the prudent and judicious utilization of transfusions. We also hope our findings encourage future studies to risk stratify the utilization of blood products in patients with ITP and cardiovascular outcomes.

Strengths & limitations

This retrospective study has several important strengths and weaknesses. A major strength of this study is the utilization of the large nationwide NIS database, which is representative of most hospitalizations across the US. Limitations include the possible erroneous entry of ICD-9-CM diagnostic and procedural codes by hospital systems and clinicians, insufficient coding of medical conditions, and the inability to assess follow-up data after a patient is discharged from her respective hospital. The NIS unfortunately limits the amount of detailed clinical data that can be obtained about outcomes and increases the likelihood of potential coding errors that can skew data results [40]. These results cannot be validated as the info is de-identified. Moreover, because the study is restricted to the data provided by the NIS, it is difficult to assess prognostic implications since the data does not provide information regarding ITP severity, length of medical condition, and therapeutic management, both outpatient and inpatient. Also, there is a bias associated with using the NIS. The management of ITP in an inpatient hospital setting may reflect a sicker patient population warranting the utilization of more intense interventions that increase the chances of mortality further skewing results. Moreover, as our study indicated, many of these patients were discharged home after hospitalization. However, due to the limitations of the database, we were unable to follow-up with post-hospitalization outcomes which could have added further support for the conclusions drawn in this study.

Conclusions

This study is one of the first population-based investigations to examine the trends and outcomes of AMI in hospitalized patients with ITP. Our study found that AMI in ITP patients is rare but associated with worse overall health outcomes and an increased rate of in-hospital deaths. ITP patients with AMI were more likely noted to have medical comorbidities, many of which are risk factors found in the general population with AMI. As a result, higher Charlson comorbidity scores were found to be an independent predictor of mortality in this patient population. Revascularization via stenting was more likely to be utilized to manage these patients, but it was also found to adversely affect outcomes. Similarly, patients who required blood product transfusions were noted to have worse health outcomes. However, they still need to be considered in the management of AMI in ITP patients especially given the present bleeding risks. The findings in this study advocate the need for concrete guidelines for the therapeutic and medical management of patients with ITP who develop AMIs. We not only identify trends and modifiable risk factors that can possibly provide guidance in the complex management of these patients but also provide evidence for better strategies in regard to risk stratification and interventions to

improve patient outcomes and minimize morbidity and mortality.

Disclosure of conflict of interest

None.

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