The Presence of Idiopathic Thrombocytopenic Purpura Correlates with Lower Rate of Acute ST Elevation Myocardial Infarction

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Abstract:

Background: Platelets are important parts in the pathogenesis of myocardial infarction (MI). In order to study the role of platelet count in MI, we hypothesize that patients with acquired thrombocytopenia such as idiopathic thrombocytopenic purpura (ITP) may have lower risk of MI. Using a large database, we studied any correlation between the presence of ITP and ST Elevation Myocardial Infarction (STEMI).

Method: The Nationwide Inpatient Sample (NIS) was used for this study. Using the available NIS database from the years 2001-2011, we analyzed the correlation between STEMI and ITP utilizing International Classification of Diseases, ninth revision, and Clinical Modification (ICD-9-CM) ICD-9 codes. We used uni- and multivariate analysis adjusting for risk factors. Data was extracted from 106,653 patients with ITP and 79,636,090 patients without ITP.

Results: Between the years of 2002 and 2011, we were able to observe significant differences between the patients with ITP and those without. We found that the risk of STEMI is significantly reduced in patients with ITP in uni and multivariate analysis in every year of the 10-year period. For example, we found that in 2002 STEMI occurred in 0.09% of patients with ITP vs. 0.13% without ITP ($p<0.007$). Then in another example in 2011, the same percentage of ITP patients experienced STEMI with a prevalence of 0.09% vs. 0.15 in patients without ITP ($p<0.005$). This reduction remains significant after multivariate adjustment

Conclusion: Based on our large database, the presence of ITP appears to be associated with a lower risk of STEMI. This finding suggests that platelet counts play important role in the pathogenesis of STEMI and low platelet count may exert protective effect from STEMI.

Introduction:

Immune thrombocytopenic purpura, also known as idiopathic thrombocytopenic purpura or primary immune thrombocytopenia, is a thrombocytopenia defined by a reduction in platelet count with normal bone marrow. The disease affects "10 per 100,000 persons per year." [1] ITP may be further classified into Primary ITP or Secondary ITP if it is thought the be the consequence of a known cause of thrombocytopenia (e.g. chronic liver disease, drug-induced thrombocytopenia, bone marrow suppression).[2,3] The condition of ITP comprises heterogeneous disorders that eventuate in the production of platelet autoantibodies." [4] It is regarded as a diagnosis of exclusion. The diagnosis is considered in cases of isolated thrombocytopenia without leukopenia, anemia or an obvious cause for thrombocytopenia. [5–9]

The original suspicion that ITP was mediated by autoantibodies came from two observations. First, children born to mothers with ITP experienced transient thrombocytopenia. Second, healthy recipients of plasma, "including IgG-rich fractions" experienced transient thrombocytopenia."[10] Platelets coated with IgG autoantibodies are cleared by "tissue macrophages, predominantly in the spleen and liver."[10] Platelet production also seems to be impaired as the result of "either intramedullary destruction of antibody-coated platelets by macrophages or the inhibition of megakaryocytopoiesis." [11] The predominant theory for the mechanism of ITP involves IgG autoantibodies produced by patients' B cells with an affinity for glycoproteins such as GIIb/llla. [12]

Treatment of ITP can include treatments that either decrease antibody production, stop premature platelet clearance or increase platelet production (e.g. corticosteroids and IVIG). [13]-[14] However, treating a thrombocytopenic patient with IVIG leads to a rapid increase in platelet count and plasma viscosity and sometimes "induces thromboembolic events including myocardial infarction during or shortly after infusion."[3] Thromboembolic events such as STEMI pose a particularly challenging dilemma as efforts need to be made to both provide anticoagulation and increase platelet count[14,15].

As platelets have been found to play a significant role in the pathogenesis of myocardial infarction, antiplatelet therapy is often prescribed to at-risk patients. One class of drugs in particular, GPIIbIIIa inhibitors, has led to a reduction in thromboembolic event rates in myocardial infarction and during percutaneous coronary intervention. As GPIIbIIIa antibodies play a role in ITP and low platelet counts may reduce thrombogenicity, we hypothesize that ITP may reduce the risk of ST-elevation myocardial infarction. Using the large NIS database, we calculated the occurrence of STEMI in patients with ITP and compared it to the occurrence in patients without ITP.

Methods

Data collection:

For this study, the Nationwide Inpatient Sample (NIS) was utilized. This is a collection of hospital inpatient databases from the Healthcare Cost and Utilization Project (HCUP). The purpose of the NIS was to create a set of databases from which national trends in healthcare utilization, quality of healthcare and patient outcomes could be analyzed. From this database, we analyzed trends from the years 2002-2011. The NIS database incorporates safeguards to protect patient and physician privacy.

Description of data:

Using the available NIS database from the years 2001-2011, we analyzed correlation between STEMI and ITP utilizing International Classification of Diseases, ninth revision, and Modification (ICD-9-CM) ICD-9 codes. For this study, the following codes consistent

with STEMI were selected: true posterior wall infarction (410.61), AMI of the anterolateral wall (410.01), infarction of other anterior wall (410.11), infarction of inferolateral wall (410.21), infarction of inferoposterior wall (410.31), other inferior wall (410.41), lateral wall (410.51) infarctions. In addition, following codes were also used: immune thrombocytopenic purpura (287.31), diabetes mellitus (250.00), hypertension (401.9), hyperlipidemia (272.4). Lastly, information on variables such as age, gender and demographics were used to calculate age-adjusted occurrence of STEMI through the years of 2002-2011. The total number of ITP patients found was 106,653. The "other" group was composed of 79,636,090 patients without ITP.

Statistical analysis:

With the Statistical Package for Social Sciences (SPSS) software, uni- and multivariate analysis were performed using chi-square and adjusting for risk factors through the years 2002-2011. Following this, two separate samples form the years 2002 and 2011 were used to perform multiple regression analysis while adjusting for diabetes, hypertension, hyperlipidemia, gender, and age.

Results:

Between the years of 2002 and 2011, we were able observe significant differences between 106,653 patients with ITP and 79,636,090 patients without ITP. We found that the risk of STEMI is significantly reduced in patients with ITP in uni and multivariate analysis in every year of the study period (2002-2011). For example, we found that, in 2002, STEMI occurred in 0.64% of patients with ITP ($p<0.007$, table 1). Then in 2011, the same percentage of ITP patients experienced STEMI with a incidence of 0.30% ($p<0.005$ table 1). In the non-ITP group, 0.89% of patients experienced STEMI in 2002 and 0.30% of patients experienced STEMI in 2011. Table 1 represents the results of univariate analysis and shows odd ratios and p values of this association in each year studied. From 2002 to 2011, the odds ratio decreased from 0.71 (C.I. 0.56-0.92) to 0.63 in 2011 (C.I. 0.45-0.87) (fig. 2).After adjusting for tobacco use, diabetes, hypertension, hyperlipidemia, gender and age we found that, in 2002, the odds ratio of simultaneous diagnoses of STEMI and ITP was 0.714 (C.I. 0.557-0.915) with a p-value of 0.008. In 2011, similar values were found with an odds ratio of 0.616 (C.I. 0.446-0.850) and a p-value of 0.003. The odds ratios in the multivariate analysis show a significantly reduced risk of STEMI in patients with ITP compared to those patients without ITP.

Discussion:

Until now, the risk of myocardial infarction in patients with ITP has not been known. Theoretically, an immunologic attack against platelets in ITP causing a reduced platelet count would reduce the risk for an adverse cardiovascular event. As myocardial infarction remains one of the most significant causes of mortality, it is important that the prevalence of MI in this patient population be researched. Studying the occurrence of MI in this population will help physicians know if their ITP patients are more or less at risk of MI.

For this study we used the Nationwide Inpatient Sample (NIS) database to locate cases of patients with the diagnosis of STEMI. Statistical analysis software was then used to perform univariate and chi square analysis for 10 consecutive years (2002-2011). Next, two sample years 10 years apart (2002 and 2011) were selected for multiple regression analysis. From the uni and multivariate analysis we found that, in patients with ITP, the risk of STEMI is significantly reduced with odds ratios ranging from 0.50-0.77 in the univariate analysis and 0.616-0.714 in the multivariable analysis.

The significant reduction in STEMI risk amongst those with ITP is reflective of what is found in the existing body of research on the topic. STEMI with concurrent ITP is incredibly rare. Only a handful of case reports have been published that discuss

such cases.[16–19] These reports reveal the difficulty clinicians experience in managing such cases as standardized treatment regimens have not been agreed upon and are far from being evidence-based.

The decreased risk of STEMI in patients with decreased numbers of platelets may perhaps be explained by the roles that platelets are thought to have in coronary heart disease. Evidence of the major role of platelets in ischemic vascular events has been resulted from the examination of pathological tissue specimens. [20,21] In addition, multiple animal models of ischemic vascular disease have shown a connection between platelets and thrombotic processes. [22–26] Platelets are believed to potentiate thrombosis via multiple mechanisms. First, platelets are believed to cause a release of "vasoactive substances that induce smooth muscle cell migration and proliferation" at the site of endothelial injury.[27] Next, platelets can stimulate foam cell formation. [28] Lastly platelets are thought to function as a "lipid source in the development of the fatty streak."[29] In addition to the role platelets play in initiating biochemical events leading to STEMI, the aggregation of platelets one with another is also believed to be necessary in the pathogenesis of ischemic damage.[30] A decrease in the number of platelets would decrease the likelihood of the biological processes occurring and leading to coronary disease.

As stated previously, we hypothesized that the reduction of platelets in ITP would lead to a reduction in STEMI events. This was hypothesized because of the effectiveness of GPIIb/IIIa inhibitors in reducing the rates of thromboembolic events in acute myocardial infarction and percutaneous coronary intervention. GPIIb/IIIa inhibitors antagonize the GPIIb/IIIa receptor. These receptors are involved in the final, common step in the formation of thrombi.[31] The GPIIbIIIa receptor binds multiple ligands such as prothrombin, Von Willebrand factor and fibrinogen with fibrinogen being most dominant protein. [31] This receptor has been found to be essential in the prevention of hemorrhage as it is the only receptor involved in cross-linking platelets.[32] In addition, platelets express a high frequency of GPIIb/IIIa receptors (80,000 per platelet). [33]

With the discovery of this essential platelet aggregating receptor, multiple GPIIb/IIIa inhibitors have been designed to antagonize the receptor and suppress platelet aggregation.[34] These drugs prevent the aggregation of platelets by blocking key binding sites necessary for the stabilization of the formed platelet aggregate.[31] In addition GPIIb/IIIa inhibitors are particularly effective because of their ability to specifically target platelets.[33] Originally approved for and used during coronary interventions, the use of GPIIb/IIIa inhibitors has expanded to include acute coronary syndrome, acute STEMI, coronary angioplasty, stenting and in peripheral vascular interventions.[35–41]

With the growing knowledge and use of GPIIb/IIIa inhibitors, came the suspicion that patients with autoantibodies against glycoproteins, e.g., ITP, would have a subsequent decreased risk for STEMI and other thromboembolic diseases. It has long been understood that platelet activation and aggregation potentiate thrombo-occlusive disease[20]. It is likely that autoantibodies involved in ITP and GPIIb/IIIa inhibitors have a similar affect the pathogenesis of STEMI in a similar way. In ITP, IgG autoantibodies coat platelets and impair platelet production via intramedullary destruction by macrophages or the inhibition of megakaryocytopoiesis. This reduction in platelet count and production seems to be sufficient to significantly lower the risk of STEMI in these patients.[11]

In conclusion:

Based on our large database, the presence of ITP appears to be associated with a lower risk of STEMI. This finding suggests that platelet counts play important role in the pathogenesis of STEMI and low platelet count may exert protective effect from STEMI.

Limitations:

This study used ICD-9 coding and was a retrospective study limiting our data that needs to be confirmed in a randomized trial. Furthermore, we cannot rule out other important factors that could be responsible for this difference in STEMI occurrence in these inpatient databases other than low platelet counts or presence of ITP only.

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	ITP	Non-ITP	P-value	Odds Ratio (C.I)
2002	0.64%	0.89%	0.007	0.71 (0.56-0.92)
2003	0.64%	0.83%	0.032	0.77 (0.61-0.98)
2004	0.51%	0.70%	0.019	0.73 (0.56-0.95)
2005	0.47%	0.64%	0.031	0.74 (0.56-0.97)
2006	0.39%	0.65%	<0.005	0.59 (0.43-0.82)
2007	0.34%	0.56%	<0.005	0.61 (0.44-0.85)
2008	0.29%	0.56%	<0.005	0.53 (0.37-0.75)
2009	0.32%	0.52%	<0.005	0.63 (0.45-0.87)
2010	0.24%	0.49%	<0.005	0.50 (0.34-0.72)
2011	0.30%	0.48%	<0.005	0.63 (0.45-0.87)

Table 1. Incidence of STEMI in patients with ITP compared with general population over a 10-year period

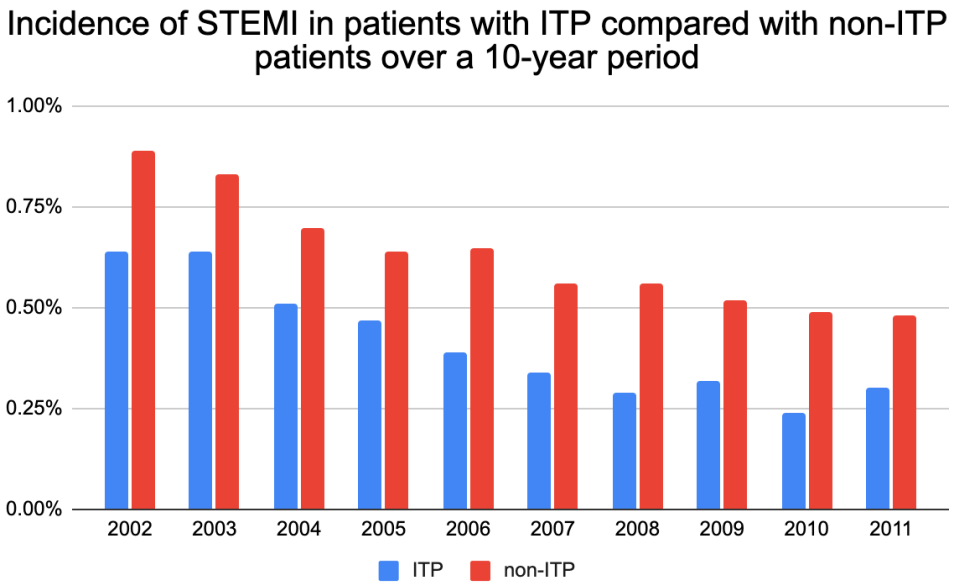

Figure 1. Incidence of STEMI over a 10-year period in patients with ITP vs without ITP

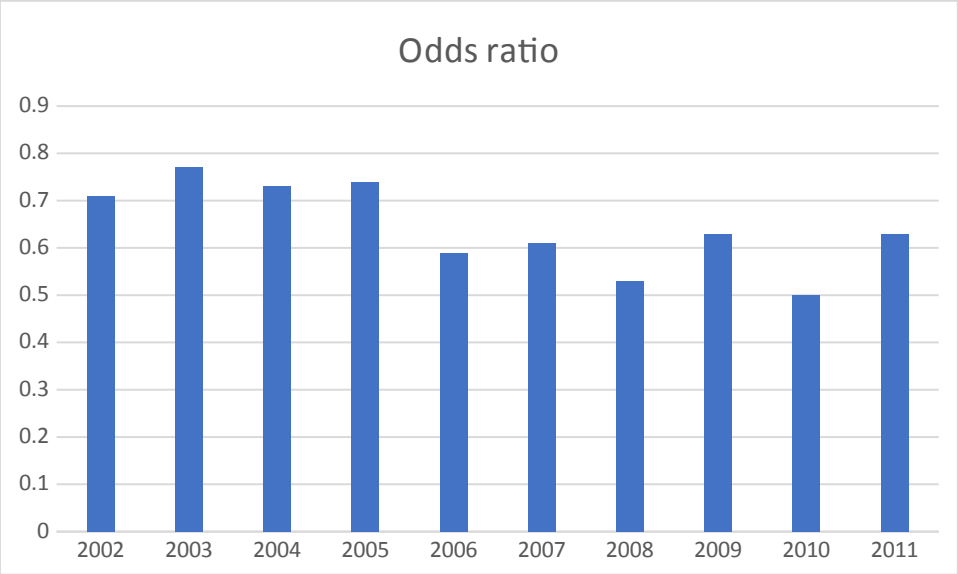

Figure 2. Odds ratio of STEMI with ITP compared with patients without ITP over a 10-year period