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# Hepatobiliary laboratory abnormalities among patients with chronic or persistent immune thrombocytopenia (ITP)

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**ABSTRACT**

Therapies for immune thrombocytopenia (ITP) may be associated with abnormal hepatobiliary laboratory (HBL) values, but the epidemiology of these abnormalities is unknown in the ITP population. The study aim was to provide prevalence and incidence rates, as well as risk factors for abnormal HBL values among a cohort of patients with chronic or persistent primary ITP. Health insurance claims data from 3,244 patients with chronic or persistent ITP was examined to estimate the prevalence of abnormal HBL values: elevated levels of Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), total bilirubin, and Alkaline Phosphatase (ALP). Incidence of abnormal HBL values was estimated in a sub cohort of 2557 (79%) patients without evidence of comorbidities related to secondary thrombocytopenia, liver disease, or abnormal HBL values during the 12-month baseline period. The baseline prevalence of ALT and AST > 3x the upper limit of normal (ULN) was 4.6 and 3.7%, respectively. The baseline prevalence of total bilirubin and ALP >1.5x ULN was 4.2 and 3.2%, respectively. The incidence rate of new HBL abnormalities (HBLA) was 1.24/1,000 person-years (95% CI: 0.52-2.56) for ALT>3x ULN and 0.41/1,000 person-years (95% CI: 0.08-1.32) for AST>3x ULN. HBLAs were significantly associated with male gender, liver disease, diabetes, congestive heart failure, lupus, hematological cancers, and HIV infection. In conclusion, the prevalence of HBLA, specifically ALT>3x ULN, among the ITP population is relatively high compared with atrial fibrillation, though within the confidence interval for that estimate. HBLAs were significantly associated with male gender, liver disease, and several other comorbidities, thus, distinguishing drug-induced liver injury in this population is clinically challenging.

**Key words.** Autoimmunity. Thrombocytopenia. Retrospective cohort study. Liver function.

## INTRODUCTION

Immune thrombocytopenia (ITP), also known as idiopathic thrombocytopenia, is an autoimmune disorder characterized by low platelet count (thrombocytopenia) and increased risk of bleeding in children and adults.[1] Persistently low platelet counts of $<30 \times 10^9$/L are associated with an increased incidence of spontaneous and induced bleeding, such as bruising, mucosal bleeding, and intracranial hemorrhage.[2]

Most adults with ITP develop persistent (> 6 months of thrombocytopenia) or chronic (> 12 months) disease.[1] The incidence of ITP is estimated at 100 cases per million persons per year, with roughly half of the cases occurring in adults.[2] ITP is typically a transient illness in children. In adults, it is generally chronic, and approximately twice as many women are affected as men.[2]

Interpretation of hepatobiliary laboratory (HBL) abnormalities is a common problem for physicians.[3] Taking into account the paucity of available published epidemiological data on ITP, there is great importance in understanding the background prevalence and incidence of elevated HBL values among patients with persistent or chronic ITP in order to aid in the interpretation of any signs of liver injury observed in patients receiving a new medication. Hepatotoxicity has been the most frequent single cause of safety-related drug marketing

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withdrawals (e.g. iproniazid, ticrynafen, bromfenac, troglitazone, nefazodone). In addition, hepatotoxicity discovered after approval of a drug for marketing has limited the use of many medications, including isoniazid, labetalol, tolcapone, and felbamate.[4,5]

This database analysis contributes to the understanding of the background prevalence and incidence of elevated HBL tests in patients with ITP, and risk factors for elevated HBL tests in these patients, thus enhancing the pharmacovigilance process for drug development and future clinical trial planning.

## PATIENTS AND METHODS

### Source population

This study was a retrospective analysis using eligibility, pharmacy and medical claims from a large U.S. health insurance plan affiliated with i3 Drug Safety. The individuals covered by this health plan are geographically diverse across the United States. The plan provides fully insured coverage for the physician, hospital and prescription drug services. Total enrolment in 2006 was over 12 million patients from health plans located in the Northeast, Southeast, Midwest, and Western United States. Additionally, the database contains laboratory test results from approximately 30% of the participating laboratories. HBL values were obtained for this subset of patients in whom liver chemistry testing was performed.

### Study population

- ***Entire ITP cohort.*** The population for this study included people with persistent or chronic ITP as defined by a diagnosis code of ITP (ICD-9 [International Classification of Diseases, 9th Revision] code 287.3) from an inpatient, outpatient or emergency room visit, followed by a second ITP diagnosis at least six months later (qualifying diagnosis). Eligibility required that patients have at least 12 months of continuous enrollment in the health plan prior to the qualifying diagnosis, have complete medical coverage, and be at least 18 years of age at the time of the qualifying diagnosis. The index date was defined as the date of qualifying diagnosis. Eligible patients entered the cohort from January 1, 2000 through December 31, 2006, and outcomes were identified through September 30, 2007.
- ***Sub-cohort with no evidence of HBL abnormalities (incidence sub-cohort).*** A subset of the ITP cohort was created that included patients who had no evidence of elevated HBL values during the 12-month baseline period before the index date, to evaluate the incidence of new HBL abnormalities. Patients were excluded if they met any of the following criteria during the 12-month baseline period:

a) Had a diagnosis code of systemic lupus erythematosus, malignant neoplasm of lymphatic or hematopoetic tissue or HIV infection.
b) Had a diagnosis code of liver disease.
c) Had a diagnosis code indicating other nonspecific abnormal serum.
d) Showed elevated HBL test results [Alanine Aminotransferase (ALT) > 3x the upper limit of normal (ULN) or Aspartate Aminotransferase (AST) > 3x ULN or Alkaline Phosphatase (ALP) > 1.5x ULN or total bilirubin > 1.5x ULN].

### Outcome definition and measures

The four study outcomes were elevated HBL tests based on the results obtained from the laboratory database: ALT, AST, total bilirubin, and ALP. Only those patients who had HBL tests performed at a laboratory that is part of the network in our database, and thus had test results available, were utilized for evaluation of the study outcomes. The primary outcome of elevated ALT and elevated AST was defined using 4 definitions of elevated ALT/AST: > 3x, > 5x, > 10x, > 20x ULN. Study definitions were nested. For example, if a person had ALT > 10x ULN, then they also had ALT > 5x ULN and ALT > 3x ULN. For total bilirubin and ALP, we were interested in total bilirubin or ALP values > 1.5x and > 2x ULN. These outcomes were selected based on the FDA Guidance Document for evaluating drug-induced liver injury.[5]

The normal range provided by each laboratory was used as the point of reference for the definition of ULN. If such information was missing for a particular patient's test result, ULN was estimated as the mean of the normal ranges provided for that test from all laboratories.

- ***For prevalence outcomes.*** The prevalence of each outcome during the 12-month baseline period was determined for the entire ITP cohort.
- ***For incidence outcomes.*** The incidence of each outcome during the follow-up period was determined in the incidence sub-cohort.

### Covariate definition and measures

All members of the study cohort were classified according to select covariates, including some risk factors for elevated HBL values. The following categories of covariates were evaluated:

- ***Demographics.***
- ***Comorbidities.***
- ***Outpatient medications use.***

Information regarding history of alcohol use and obesity were also evaluated, but tend to be underrepresented because they would only appear in the claims data for individuals who sought medical treatment for those conditions.

### Data analysis

Baseline characteristics were reported for the entire ITP study cohort, and separately for those with and without documented HBL test results during the baseline period.

- ***Prevalence of elevated HBL values during 12-month baseline period in entire ITP cohort.*** The prevalence of elevated HBL for all 4 laboratory tests was determined during the 12-month baseline period for the entire ITP cohort. The outcome was considered prevalent if it occurred at any point in time during the 12-month baseline period. The prevalence was calculated in 2 ways, using different denominators for the calculation. The first prevalence calculation included all people in the ITP study cohort in the denominator, regardless of whether or not they had any HBL test results available from the 12-month baseline period. This calculation assumes that the absence of a test result means absence of liver disease, which provides a minimum estimate of the prevalence. The second prevalence calculation included only those people who had at least one HBL test result during the 12-month baseline period.
- ***Incidence of new elevated HBL values during study follow-up in the incidence sub-cohort.*** Identification of new cases of elevated HBL values during the follow-up period was restricted to the incidence sub-cohort, which included only people who had no evidence of liver disease at baseline, no history of elevated HBL values in the available laboratory data, nor history of secondary comorbidities that could affect the liver during the 12-month baseline period. Follow-up began on the index date and continued through September 30, 2007 or disenrollment from the health plan. The total person-time follow-up for each person was used to calculate the incidence rate per 1,000 person-years, and 95% confidence intervals (CI) were calculated.
- **Risk factors.** We evaluated the following among potential risk factors for abnormal HBL values: age, gender, history of hypertension, diabetes, dyslipidemia, congestive heart failure, splenectomy, liver disease, significant comorbidity related to secondary thrombocytopenia (i.e. lupus, blood cancer, HIV), alcohol use, use of systemic corticosteroids (oral, intravenous (IV) or intramuscular (IM), treatment with interferon, cyclosporine and danazol. The selected medications, particularly corticosteroids and IVIG were chosen as these represent first-line therapy for ITP and were of interest to the study team**.** As the study protocol development was completed and approved by the Protocol Review Forum (PRF) prior to approval of Romiplostim and Eltrombopag in the US, these two medications were not included in the analysis. Poisson regression was performed, and univariate risk estimates comparing the incidence of first abnormal HBL value during the follow-up period for persons with these risk factors and those without were estimated. Poisson regression modeling with univariate risk estimates was run on the entire ITP cohort. These analyses were performed separately for 2 outcome definitions of abnormal HBL: ALT > 3x ULN and total bilirubin >1.5x ULN.

All data management and statistical analysis were performed with SAS (Cary, NC, version 9.1)

### Privacy and confidentiality

All analyses and reporting were carried out using de-identified data. This study followed our internal Standard Operating Procedures, which are consistent with the Health Insurance Portability and Accountability Act guidelines for the protection of patient confidentiality and the Guidelines for Good Pharmacoepidemiology Practices.[6]

## RESULTS

We identified 3,244 patients who were eligible for the entire ITP cohort. Of these, 805 (25%) had at least one HBL test during the 12-month baseline pe-

**Table 1.** Descriptive characteristics of entire ITP cohort during 12-month baseline period.

| Characteristics | Total ITP cohort N = 3,244 | | HBL measurement during 12-month baseline period N = 805 | | No HBL measurement during 12-month baseline period N = 2,439 | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Age group | | | | | | |
| 18-39 | 831 | 25.6 | 193 | 24.0 | 638 | 26.2 |
| 40-49 | 578 | 17.8 | 174 | 21.6 | 404 | 16.6 |
| 50-59 | 663 | 20.4 | 187 | 23.2 | 476 | 19.5 |
| 60-69 | 538 | 16.6 | 152 | 18.9 | 386 | 15.8 |
| 70-79 | 374 | 11.5 | 68 | 8.4 | 306 | 12.5 |
| 80+ | 260 | 8.0 | 31 | 3.9 | 229 | 9.4 |
| Gender | | | | | | |
| Female | 1,916 | 59.1 | 450 | 55.9 | 1,466 | 60.1 |
| Male | 1,328 | 40.9 | 355 | 44.1 | 973 | 39.9 |
| History of hypertension | 877 | 27.0 | 245 | 30.4 | 632 | 25.9 |
| History of diabetes | 378 | 11.7 | 122 | 15.2 | 256 | 10.5 |
| History of dyslipidemia | 699 | 21.5 | 220 | 27.3 | 479 | 19.6 |
| History of metabolic syndrome | 138 | 4.3 | 57 | 7.1 | 81 | 3.3 |
| History of congestive heart failure | 206 | 6.4 | 45 | 5.6 | 161 | 6.6 |
| History of obesity | 157 | 4.8 | 52 | 6.5 | 105 | 4.3 |
| History of splenectomy | 95 | 2.9 | 20 | 2.5 | 75 | 3.1 |
| History of liver disease | 334 | 10.3 | 114 | 14.2 | 220 | 9.0 |
| History of significant comorbidity related to secondary thrombocytopenia | 334 | 10.3 | 107 | 13.3 | 227 | 9.3 |
| History of liver disease or significant comorbidity related to secondary thrombocytopenia | 632 | 19.5 | 205 | 25.5 | 427 | 17.5 |
| History of alcohol use | 71 | 2.2 | 21 | 2.6 | 50 | 2.1 |
| Number of HBL measurements in past year | | | | | | |
| 0 | 2,439 | 75.2 | 0 | 0.0 | 2,439 | 100.0 |
| 1 | 386 | 11.9 | 386 | 48.0 | 0 | 0.0 |
| 2 | 175 | 5.4 | 175 | 21.7 | 0 | 0.0 |
| 3+ | 244 | 7.5 | 244 | 30.3 | 0 | 0.0 |

**HBL:** Hepatobiliary laboratory. **ITP:** Immune thrombocytopenia.

riod performed at a laboratory that contributes test results to the database, and 2,439 had no HBL measurements. Baseline characteristics of study subjects are reported in Table 1, stratified by presence of at least one HBL value test result during the 12-month baseline period. There was a higher proportion of patients with a history of hypertension, diabetes, dyslipidemia, and liver disease among those who had at least one HBL value test result during the 12-month baseline period in comparison to those who did not (Table 1).

### Prevalence of HBLAs during 12-month baseline

During the 12-month baseline period, there were 37 patients with an ALT result > 3x ULN, with a prevalence of 1.14% (95% CI: 0.83% - 1.57%) in the entire ITP cohort (Table 2). Restricting the prevalence calculation to the 805 patients who had at least one HBL test result during the baseline period, the prevalence was 4.60% (95% CI: 3.35% - 6.27%). Thirteen patients had at least one ALT > 5x ULN during the 12-month baseline period, 1 patient had an ALT > 10x ULN, and no patients had an ALT > 20x ULN during the 12-month baseline period.

There were 30 patients with an AST result > 3x ULN during the 12-month baseline period, with a prevalence of 0.92% (95% CI: 0.65% - 1.32%) among the entire ITP cohort, and a prevalence of 3.73% (95% CI: 2.62% - 5.27%) among those who had at least one HBL test result (Table 2). There were 9 patients with AST > 5x ULN, 4 patients with AST > 10x ULN and 1 patient with AST > 20x ULN.

**Table 2.** Prevalence of HBLAs in the ITP cohort during 12-month baseline period.

| Outcome* | Patients with outcome n | Total ITP cohort N = 3,244 Prevalence (%) | 95% CI | Patients with at least one HBL during 12-month baseline period N = 805 Prevalence (%) | 95% CI |
|---|---|---|---|---|---|
| ALT | | | | | |
| > 3x ULN | 37 | 1.14 | 0.83,1.57 | 4.60 | 3.35,6.27 |
| > 5x ULN | 13 | 0.40 | 0.23,0.68 | 1.61 | 0.95,2.74 |
| > 10x ULN | 1 | 0.03 | 0.00,0.11 | 0.12 | 0.00,0.46 |
| > 20x ULN | 0 | 0.00 | 0.00,0.11 | 0.00 | 0.00,0.46 |
| AST | | | | | |
| > 3x ULN | 30 | 0.92 | 0.65,1.32 | 3.73 | 2.62,5.27 |
| > 5x ULN | 9 | 0.28 | 0.15,0.53 | 1.12 | 0.59,2.11 |
| > 10x ULN | 4 | 0.12 | 0.00,0.11 | 0.50 | 0.00,0.46 |
| > 20x ULN | 1 | 0.03 | 0.00,0.11 | 0.12 | 0.00,0.46 |
| Total bilirubin | | | | | |
| > 1.5x ULN | 34 | 1.05 | 0.75,1.46 | 4.22 | 3.04,5.84 |
| > 2x ULN | 21 | 0.65 | 0.42,0.99 | 2.61 | 1.71,3.96 |
| ALP | | | | | |
| > 1.5x ULN | 26 | 0.80 | 0.55,1.17 | 3.23 | 2.21,4.69 |
| > 2x ULN | 15 | 0.46 | 0.28,0.76 | 1.86 | 1.13,3.05 |

**HBLA:** Hepatobiliary laboratory abnormalities. **ITP:** Immune thrombocytopenia. **CI:** Confidence interval. **LL:** Lower limit. **UL:** Upper limit. **ALT:** Alanine aminotransferase test. **ULN:** Upper limit of normal. **AST:** Aspartate aminiotransferase test. **ALP:** Alkaline phosphatase test. * patients can be counted in more than 1 outcome category.

**Table 3.** Incidence of newly identified HBLAs in the incidence sub-cohort during follow up period, N=2,557

| Outcome* | Patients with new HBLA, n | Person-years** | Incidence rate*** | 95% CI |
|---|---|---|---|---|
| ALT | | | | |
| > 3x ULN | 6 | 4,837 | 1.24 | 0.52,2.56 |
| > 5x ULN | 3 | 4,840 | 0.62 | 0.17,1.65 |
| > 10x ULN | 1 | 4,841 | 0.21 | 0.02,0.96 |
| > 20x ULN | 0 | 4,846 | 0.00 | 0.00,0.51 |
| AST | | | | |
| > 3x ULN | 2 | 4,841 | 0.41 | 0.08,1.32 |
| > 5x ULN | 1 | 4,841 | 0.21 | 0.02,0.96 |
| > 10x ULN | 0 | 4,846 | 0.00 | 0.00,0.51 |
| > 20x ULN | 0 | 4,846 | 0.00 | 0.00,0.51 |
| Total bilirubin | | | | |
| > 1.5x ULN | 13 | 4,829 | 2.69 | 1.51,4.47 |
| > 2x ULN | 4 | 4,838 | 0.83 | 0.28,1.97 |
| ALP | | | | |
| > 1.5x ULN | 5 | 4,845 | 1.03 | 0.39,2.26 |
| > 2x ULN | 1 | 4,845 | 0.21 | 0.02,0.96 |

**HBLA:** Hepatobiliary laboratory abnormalities. **ITP:** Immune thrombocytopenia. **CI:** Confidence interval. **LL:** Lower limit. **UL:** Upper limit. **ALT:** Alanine aminotransferase test. **ULN:** Upper limit of normal. **AST:** Aspartate aminiotransferase test. **ALP:** Alkaline phosphatase test. * patients can be counted in more than 1 outcome category. ** person-years were calculated separately for each HBLA outcome level. *** Incidence rate per 1,000 person-years.

The prevalence of elevated total bilirubin > 1.5x ULN during the 12-month baseline period was 1.05% (95% CI: 0.75% - 1.46%) in the entire ITP cohort (Table 2). Restricting to the 805 patients who had at least one HBL test result during the baseline period, the prevalence was 4.22% (95% CI: 3.04% – 5.84%). Results for the prevalence of total bilirubin > 2x ULN, ALP > 1.5x ULN, ALP > 2x ULN are also presented in Table 2.

### Incidence Sub-Cohort

Six hundred eighty-seven patients (21%) in the entire ITP cohort had a significant comorbidity rela-

ted to secondary thrombocytopenia, liver disease diagnosis, or elevated HBL values during the 12-month baseline period, and thus were excluded from the incidence sub-cohort, leaving 2,557 (79%) patients eligible for the incidence sub-cohort. Of these, 560 (22%) had at least one HBL test during the 12-month baseline period performed at a laboratory that contributes test results to the database. During the follow-up period, 624 (24%) of the 2,557 patients had at least one HBL test performed at a participating laboratory.

### Incidence of new HBLAs during follow-up among the incidence sub-cohort

Table 3 reports the incidence of newly identified elevated HBL values during the follow-up period among this sub-cohort. There were 6 patients with ALT > 3x ULN during the follow-up period, for an incidence rate of 1.24 per 1,000 person-years (95% CI: 0.52-2.56 per 1,000 person-years). Three patients had ALT > 5x ULN, 1 patient had ALT > 10x ULN, and no patients had an ALT > 20x ULN.

There were 2 patients with AST > 3x ULN during the follow-up period and 1 patient with AST > 5x ULN during the follow-up period. No patients had AST > 10x during the follow-up period (Table 3). The incidence rate of AST > 3x ULN was 0.41/1,000 person-years (95% CI: 0.08-1.32 per 1,000 person-years).

The incidence rates for total bilirubin > 1.5x ULN, total bilirubin > 2x ULN, ALP > 1.5x ULN and ALP > 2x ULN are shown in Table 3. Thirteen patients had a total bilirubin > 1.5x ULN during

**Table 4.** Rate ratios for new or recurrent elevated ALT or total bilirubin value in the entire ITP cohort (N = 3,244) during follow-up period.

| Characteristics | ALT > 3x ULN* | | Total Bilirubin > 1.5x ULN** | |
|---|---|---|---|---|
| | RR | 95% CI | RR | 95% CI |
| Age groups: | | | | |
| 18-39 | 1.00 | Referent | 1.00 | Referent |
| 40-49 | 1.97 | 0.63 - 6.21 | 4.91 | 1.62 - 14.92 |
| 50-59 | 2.20 | 0.75 - 6.42 | 3.84 | 1.26 - 11.67 |
| 60-69 | 0.65 | 0.13 - 3.35 | 2.04 | 0.55 - 7.61 |
| 70-79 | 0.00 | NC | 3.01 | 0.85 - 10.67 |
| 80+ | 0.69 | 0.08 - 5.91 | 4.35 | 1.17 - 16.21 |
| Male Gender | 2.69 | 1.19 - 6.09 | 2.11 | 1.19 - 3.75 |
| History of hypertension | 0.76 | 0.28 - 2.01 | 1.38 | 0.75 - 2.54 |
| History of diabetes | 2.70 | 1.08 - 6.75 | 1.44 | 0.65 - 3.21 |
| History of dyslipidemia | 0.53 | 0.16 - 1.77 | 0.66 | 0.30 - 1.48 |
| History of congestive heart failure | 1.71 | 0.40 - 7.24 | 3.98 | 1.86 - 8.50 |
| History of splenectomy | 1.52 | 0.21 - 11.25 | 1.57 | 0.38 - 6.48 |
| History of liver disease | 13.65 | 6.20 - 30.06 | 10.46 | 5.94 - 18.43 |
| History of significant comorbidity related to secondary thrombocytopenia (i.e. lupus, blood cancers, HIV) | 3.95 | 1.65 - 9.46 | 2.02 | 0.94 - 4.31 |
| History of liver disease or significant comorbidity related to secondary thrombocytopenia (i.e. lupus, blood cancers, HIV) | 10.72 | 4.63 - 24.84 | 7.59 | 4.26 - 13.54 |
| History of alcohol use | 7.81 | 2.34 - 26.08 | 9.51 | 4.26 - 21.19 |
| High use of oral corticosteroids | 3.01 | 1.33 - 6.82 | 1.32 | 0.66 - 2.66 |
| High use of IV/IM corticosteroids | 6.07 | 1.80 - 20.50 | 0.88 | 0.12 - 6.40 |
| High use of systemic corticosteroids | 4.25 | 1.33 - 13.55 | 1.67 | 0.58 - 4.78 |
| Treatment with interferon | 39.83 | 11.92 - 133.07 | 12.18 | 2.96 - 50.19 |
| Treatment with IVIG | 1.97 | 0.67 - 5.73 | 1.76 | 0.79 - 3.93 |
| Treatment with cyclosporine | 6.89 | 1.62 - 29.21 | 3.43 | 0.83 - 14.13 |
| Treatment with statins | 0.27 | 0.04 - 2.01 | 0.44 | 0.14 - 1.40 |
| Past year use of danazol | 2.53 | 0.60 - 10.71 | 1.26 | 0.31 - 5.21 |

**ALT:** Alanine aminotransferase test. **ITP:** Immune thrombocytopenia. **ULN:** Upper limit of normal. **RR:** Rate ratio. **CI:** Confidence interval. **NC:** Not calculated due to 0 cases. * Incidence rate for ALT > 3x ULN = 4.23 per 1,000 person-years (95% CI: 2.81 - 6.15 per 1,000 person-years). ** Incidence rate for total bilirubin > 1.5x ULN = 8.13 per 1,000 person-years (95% CI: 6.06 - 10.68 per 1,000 person-years).

the follow-up period, for an incidence rate of 2.69 per 1,000 person-years (95% CI: 1.51 – 4.47 per 1,000 person-years). The incidence rate for ALP > 1.5x ULN was 1.03/1,000 person-years (95% CI: 0.39-2.26 per 1,000 person-years).

### Rate ratios for new or recurrent abnormal HBL values in entire ITP cohort

Univariate rate ratios for new or recurrent ALT > 3x ULN and new or recurrent total bilirubin > 1.5x ULN in the entire ITP cohort are reported in Table 4. The incidence rate for ALT > 3x ULN was 4.23 per 1,000 person-years (95% CI: 2.81 – 6.15 per 1,000 person-years). Factors that were significantly associated with ALT > 3x ULN were male gender, history of diabetes, history of liver disease, history of one of the significant comorbidities, history of alcohol use, high use of systemic, oral, and IV/IM corticosteroids, treatment with interferon, and treatment with cyclosporine. The incidence rate for total bilirubin > 1.5x ULN was 8.13 per 1,000 person-years (95% CI: 6.06 – 10.68 per 1,000 person-years). Factors significantly associated with total bilirubin > 1.5x ULN were age, male gender, history of congestive heart failure, history of liver disease, history of alcohol use, and treatment with interferon.

## DISCUSSION

In this study we evaluated HBL values among a cohort of patients with persistent or chronic ITP. The prevalence of abnormal HBL values during the 12-month baseline period was 4.6% for elevated ALT >3x ULN and 4.2% for elevated total bilirubin >1.5x ULN, among those with available laboratory values. We found that 687 patients (21%) had some evidence of liver disease, abnormal liver tests, or other diagnoses that were related to secondary thrombocytopenia during the 12-month baseline period. These estimates are somewhat higher than what has been reported in the published literature for other diseases, in particular atrial fibrillation, though within the confidence interval for that estimate. For example, in a study conducted by Makar GA, *et al*.[7] in patients with atrial fibrillation, the ALT >3x ULN prevalence was 3.7% (95% CI: 2.9%-4.8%) in comparison to the 4.60% (95% CI: 3.35%-6.27%) among the persistent or chronic ITP patients in our study.

The incidence rate of new cases of elevated HBL values during the follow-up period in the incidence ITP sub-cohort was 1.24 per 1,000 person-years, while the incidence rate of new or repeat cases of elevated ALT during the follow-up period was higher at 4.23 per 1,000 person-years among the entire ITP cohort, which includes prevalent cases of liver disease and patients with other significant comorbidities. Similarly, the incidence rates for elevated total bilirubin were higher in the entire ITP cohort (8.13 per 1,000 person-years), which includes prevalent cases of liver disease and other significant comorbidities, than in the incidence sub-cohort (2.69 per 1,000 person-years).

Several factors were associated with elevated HBL value results during the follow-up period, including male gender, history of diabetes and treatment with systemic corticosteroids. These results suggest that underlying liver disease may be underdiagnosed in this population. Because the number of new events in the incidence sub-cohort was small, the analyses were conducted on the number of new or recurrent events during the follow-up period in the entire cohort.

While claims data are valuable for examination of health care outcomes and treatment patterns, these data are collected for the purpose of payment rather than research. Therefore, there are certain limitations associated with the use of these data. Diagnosis codes on claims do not necessarily mean that a definitive diagnosis was made, as a patient may be evaluated for a disease, but the diagnosis is then ruled-out. Certain information is not readily available in claims data that could have an effect on study outcomes, such as certain clinical and disease-specific parameters. This cohort of patients with persistent or chronic ITP had varying and unknown durations of ITP; thus, they may have been identified for the study cohort shortly after ITP had been diagnosed, or ITP may have been long-standing and these patients received various treatments for ITP.

Although the population under study is large, the group over the age of 65 years may not be representative of the US population, as about 2% of the i3 Drug Safety database are aged 65 years or older, compared with about 12% of the US 2000 census population. The main reason for this is that primarily employed people and their families were insured by the health plan.

The laboratory data are available for only a subset of the health plan members, depending on which laboratory did the testing. The proportion of patients with repeat HBL results during the study period was small with 560 patients having at least one measurement during the 12-month baseline period

and at least one measurement during the follow-up period. Among those with at least one HBL measurement during the 12-month baseline period, approximately half had only a single measurement, and the median number of tests during the follow-up period was 1 for this subgroup. Thus, we have the definitive status of HBL values on just this subset, which must be considered when interpreting the results of this study. However, the availability of the laboratory data is unrelated to disease or treatment status. The laboratory data are not available from inpatient stays, which limits the ability to assess the status during a clinically relevant period of time, although this would be a relatively short period of time relative to the entire follow-up period. Finally, there is the possibility of surveillance bias, as the likelihood of having HBL values performed is not the same for all patients. It is possible that patients at higher risk may be tested more frequently, and thus be more likely to have an abnormal HBL, which could affect the interpretation of the findings.

## CONCLUSION

The prevalence of HBLA, specifically ALT >3x ULN (4.60%), among the ITP population in this study is relatively high compared with other disease populations, in particular atrial fibrillation, though within the confidence interval for that estimate. Abnormal hepatobiliary laboratory test results were significantly associated with male gender, liver disease, diabetes, congestive heart failure, lupus, hematological cancers, and HIV infection, thus making identifying drug-induced liver injury in this population challenging.

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## AUTHOR CONTRIBUTIONS

All listed authors meet the criteria for authorship set forth by the International Committee for Medical Journal Editors. C.E., D.B., and A.M. designed the study protocol; C.E. and A.M. performed the statistical analyses; C.E., D.B., K.D., M.A., D.T., and A.M. analyzed the results and helped draft the manuscript.

## ABBREVIATIONS

- **ALT:** Alanine aminotransferase.
- **ALP:** Alkaline phosphatase.
- **AST:** Aspartate aminotransferase.
- **CI:** Confidence intervals.
- **HBL:** Hepatobiliary laboratory.
- **HBLA:** Hepatobiliary laboratory abnormalities.
- **IM:** Intramuscular.
- **ITP:** Immune thrombocytopenia.
- **IV:** Intravenous.
- **IVIG:** Intravenous immunoglobulin.
- **PRF:** Protocol Review Forum.
- **ULN:** Upper limit of normal.

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