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Hepatotoxicity Score: A New Method to Adjust for Use of Potentially Hepatotoxic Medications by Chronic Liver Disease Status

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ABSTRACT

Background: Studies evaluating the hepatic safety of medications have been limited by the inability to control for confounding from receipt of other hepatotoxic drugs.

Objective: The objective of this study was to develop an index (Hepatotoxicity Score) to adjust for concomitant hepatotoxic medication exposure within pharmacoepidemiology studies.

Methods: We identified 193 medications with ≥ 4 reports of hepatotoxicity and created cohorts of outpatient initiators in the Veterans Health Administration (2000–2021). Exposure occurred from initiation through 30 days after discontinuation or up to 1 year. We measured age-/sex-adjusted rates of hospitalization for severe acute liver injury (ALI) by chronic liver disease (CLD), identified drugs with high rates, and used these rates as weights in the score. To demonstrate real-world use, we calculated the score for proton pump inhibitor (PPI) initiators. We summed the weights of the drugs dispensed within 90 days prior to PPI initiation. Hazard ratios (HRs) of severe ALI (95% confidence intervals) were measured with and without adjustment for Hepatotoxicity Score.

Results: Among 89 512 PPI initiators with CLD, HRs of severe ALI were higher for lansoprazole (HR = 2.17 [95% CI, 1.24–3.82]), but not pantoprazole (HR = 0.83 [95% CI, 0.61–1.13]), versus omeprazole. Adjustment for Hepatotoxicity Score attenuated HRs of lansoprazole (HR = 1.99 [95% CI, 1.13–3.50]). Among 2 462 414 PPI initiators without CLD, HRs were not significantly higher for

lansoprazole (HR = 1.66 [95% CI, 0.99–2.77]) but were significantly lower for pantoprazole (HR = 0.59 [95% CI, 0.37–0.95]), versus omeprazole. Adjustment for Hepatotoxicity Score attenuated HRs of lansoprazole (HR = 1.52 [95% CI, 0.91–2.54]).
Conclusions: The Hepatotoxicity Score provides a tool to adjust for confounding due to concomitant hepatotoxic drug exposure within hepatic safety studies.

1 | Introduction

With an ever-increasing array of medications entering the marketplace, pharmacoepidemiology studies that evaluate the risk of severe acute liver injury (ALI) or other important hepatic outcomes (e.g., hepatic decompensation) following new use of medications of interest are crucially important to the field [1–5]. For these analyses to be valid, adjustment for relevant confounding variables is important. Pharmacoepidemiology studies that have evaluated the hepatic safety of medications have assessed concomitant use of other hepatotoxic drugs by controlling for a subset that has been perceived to be at high risk of ALI [6–8] or have not controlled for the use of other hepatotoxic drugs at all, primarily because no systematic method has been developed to identify medications associated with high rates of severe ALI following initiation. If one or more concomitantly prescribed hepatotoxic drugs are associated with the use of a medication under evaluation within an hepatic safety study, those drugs may confound the relationship between the drug of interest and the liver-related outcome. The inability to control for concomitantly used hepatotoxic medications in pharmacoepidemiology studies evaluating the hepatic safety of drugs remains an important unmet need.

To address this need, in this study, we first used real-world data to measure incidence rates of hospitalization for severe ALI following the initiation of medications that had reported cases of hepatotoxicity. We stratified results by chronic liver disease (CLD) status, since preexisting CLD might affect the incidence of severe ALI [9]. Next, among the groups with and without CLD, we identified the subset of medications that had the highest rates of severe ALI and included these drugs in a novel index called the Hepatotoxicity Score. Estimates of the rates of severe ALI for these drugs in each group served as weights for the score, which can be calculated by summing the weights of the hepatotoxic drugs dispensed within a relevant period of interest. The score can be included as a variable within hepatic safety studies, allowing pharmacoepidemiologists to control for confounding due to concomitant use of drugs associated with high risk of severe ALI.

We demonstrate the application of the Hepatotoxicity Score to control for confounding due to these most hepatotoxic drugs in an example comparative hepatic safety study stratified by CLD. In our example, we evaluated the comparative rate of hospitalization for severe ALI associated with the new use of three commonly prescribed proton pump inhibitors (PPIs), each of which has reports of hepatotoxicity [10]. We created cohorts of new initiators of these PPIs with and without CLD and measured relative hazards of hospitalization for severe ALI associated with lansoprazole and pantoprazole compared with omeprazole. We evaluated how associations changed after adjustment for the Hepatotoxicity Score.

2 | Methods

2.1 | Study Design and Data Source

We conducted cohort studies of new initiators of medications within the US Veterans Health Administration (VA) between October 1, 1999 and September 30, 2021. The VA system comprises more than 1300 hospitals and community outpatient clinics nationwide. VA electronic health record data are accessible from the Corporate Data Warehouse within the VA's Informatics and Computing Infrastructure and include demographic and enrollment data as well as outpatient and hospital diagnoses (recorded by International Classification of Diseases, Ninth Revision [ICD-9] or Tenth Revision [ICD-10] diagnostic codes), laboratory results, and dispensed medications [11]. This study was approved by the Institutional Review Boards of the University of Pennsylvania, VA Connecticut Healthcare System and Yale University.

2.2 | Study Patients

2.2.1 | Medication Initiator Cohorts Evaluated to Develop Hepatotoxicity Score

We considered for inclusion in the Hepatotoxicity Score any of 220 medications that had at least four published reports of ALI on the US National Institutes of Health LiverTox website (http://livertox.nih.gov) [12]. We evaluated medications with ≥ 4 reports of hepatotoxicity to focus on the most commonly implicated products. Of these medications, 26 could not be evaluated because they were unavailable in the VA, anticoagulants, initiated in the inpatient setting via injection/intravenous route, or used for the treatment of alcohol use disorder or liver disease [13]. We also did not evaluate oral vancomycin because it is not systemically absorbed from the gastrointestinal tract [14]. We included patients who had (1) a new outpatient prescription for any of the remaining 193 medications between October 1, 2000 and September 30, 2021 and (2) ≥ 365 days in the VA system prior to the initial fill of that medication. We focused on outpatient initiators to increase the likelihood that severe ALI events would be medication-related; inclusion of medication initiators in the hospital increases the potential that severe ALI might be due to inpatient events. We examined mainly oral formulations of medications, but outpatient intravenous chemotherapy and injectable formulations of hormone therapy were included.

The index date was the date that the medication was initially dispensed. The baseline period was the 365 days prior to the index date. We excluded patients who during the baseline period had (1) hospitalization for severe ALI (prevalent outcome); (2) dispensed fills for warfarin or a direct oral anticoagulant because these would prevent ascertainment of ALI-induced

Summary

- A major limitation of hepatic safety studies using real-world data has been their inability to control for confounding due to concomitant receipt of other potentially hepatotoxic medications.
- To allow pharmacoepidemiologists to adjust for concomitant hepatotoxic medication use in real-world data studies evaluating the hepatic safety of medications, we developed a novel index, called the Hepatotoxicity Score, that identifies medications with high observed rates of hospitalization for severe acute liver injury (ALI) and incorporates weights based on these medications' incidence rates of hospitalization for severe ALI.
- Among a cohort of proton pump inhibitor initiators, higher Hepatotoxicity Score was associated with higher rates of hospitalization for severe ALI among those with and without chronic liver disease (CLD).
- Among patients with CLD, lansoprazole, but not pantoprazole, was associated with a higher relative hazard of hospitalization for severe ALI compared to omeprazole. Among patients without CLD, relative hazards of severe ALI were not higher for lansoprazole, but were significantly lower for pantoprazole, compared to omeprazole. Regardless of CLD status, additional adjustment for the Hepatotoxicity Score attenuated associations of severe ALI with lansoprazole, demonstrating its utility as a confounder.

coagulopathy; or (3) pancreaticobiliary disease or other condition that might precipitate findings consistent with severe ALI (Table S1). For patients dispensed multiple courses of a medication, only the initial course was examined. Patients could be in more than one cohort if they initiated multiple hepatotoxic medications during the study period.

Within each medication initiator cohort, we defined a patient as having CLD if, during the baseline period, they had a single hospital or outpatient CLD ICD-9/-10 diagnosis (Table S2) or any positive laboratory test for hepatitis B virus infection (hepatitis B surface antigen, hepatitis B e antigen, or hepatitis B DNA) or hepatitis C virus infection (hepatitis C RNA or genotype). Among those without CLD, to minimize the likelihood of including patients with undiagnosed liver or biliary disease, we excluded those who during the baseline period had two alanine aminotransferase (ALT) results ≥ 40 U/L at least 6 months apart (validated to identify persons with metabolic dysfunction-associated steatotic liver disease in the VA system [15]), one ALT > 100 U/L, or one alkaline phosphatase > 172 mg/dL (1.5 times upper limit of normal [ULN], 115 mg/dL).

2.2.2 | PPI Initiator Cohorts to Evaluate Hepatotoxicity Score as a Confounder

We identified patients with (1) a new outpatient fill for omeprazole, lansoprazole, or pantoprazole between October 1, 2000 and September 30, 2021 and (2) ≥ 365 days in the VA prior to their initial fill. The index date was the date that the PPI was initially dispensed. The baseline period was the 365 days prior to the index date. Patients were classified by baseline CLD status, and the same exclusions described above were applied.

2.2.3 | Patient Follow-Up

Follow-up for patients in all of the above cohorts began on their index date and continued until hospitalization for severe ALI, medication discontinuation (no additional fills within 30 days after the last prescription's days' supply), incident pancreaticobiliary disease or other condition precipitating findings of ALI, dispensing of an anticoagulant, 12 months after index date (drug-induced ALI usually develops within 12 months of medication initiation [16]), last contact with the VA system, or September 30, 2021, whichever occurred first. For those without baseline CLD, follow-up was also censored at an incident liver disease diagnosis.

2.3 | Main Study Outcome

The main outcome was hospitalization for severe ALI, which was defined by either of the following definitions within the first 2 days of admission: (1) ALT > 120 U/L (3 times ULN, 40 U/L) + total bilirubin (TB) > 2.0 mg/dL (2 times ULN, 1.0 mg/dL) (definition 1) or (2) international normalized ratio (INR) ≥ 1.5 + TB > 2.0 mg/dL (definition 2). Both definitions have been used by the US Food and Drug Administration's Sentinel System to identify clinically significant drug-induced ALI in the post-marketing period [17]. Definition 1 represents Hy's Law biochemical criteria [18], which identifies hepatocellular injury severe enough to interfere with bilirubin excretion and predisposes to high risk of death [19, 20]. Definition 2 identifies hepatic dysfunction that might present in advanced acute liver failure [17]. Because ALT results were assessed across multiple VA centers using different assays with varying ULNs, we utilized a common ULN for ALT. We chose an ALT ULN of 40 U/L because this cut-off reflects a clinically meaningful level of hepatocellular injury [21]. We examined severe ALI within the first 2 days of admission to avoid capturing outcomes that developed as a consequence of the hospitalization. The event was considered to have occurred on the admission date. To increase the likelihood that severe ALI events were medication-related, patients were censored as non-events on the admission date if they had a discharge diagnosis of acute liver disease, biliary disease, or other condition precipitating findings consistent with severe ALI (Table S1). Patients without CLD were additionally censored as non-events on the date of admission if a discharge diagnosis of CLD was present.

2.4 | Covariates

For all medication cohorts, baseline data included date/route of medication administration and days' supply; age; sex; body mass index (BMI); validated diagnoses of diabetes mellitus [22, 23], hyperlipidemia [24], and heart failure [24, 25]; and inpatient or outpatient laboratory values for INR, TB, ALT, and alkaline phosphatase. Follow-up data included days' supply of

medication; oral anticoagulant use; and inpatient laboratory results for ALT, INR, and TB.

2.5 | Data Analysis

2.5.1 | Measurement of Incidence Rates of Hospitalization for Severe ALI

For each cohort of medication initiators, we used Poisson regression to measure age-/sex-adjusted incidence rates of hospitalization for severe ALI (events per 10000 person-years), stratified by CLD status. Each model included terms for age (continuous variable), sex, and hepatotoxic medication. To ensure that estimates of incidence rates were sufficiently precise, we required that medication cohorts had either (1) 95% confidence interval (CI) width for the rate that was < 3 times the point estimate or (2) ≥ 10000 person-years of follow-up. Moreover, to avoid inclusion of rarely used medications in our score, we required that each medication cohort had at least 1000 initiators. Medications that did not meet any of these criteria were not considered for inclusion in the score.

We organized medications into groups based on the observed rate of hospitalization for severe ALI. We created separate groupings of medications by CLD status based on different cut-offs of severe ALI rates. For patients with CLD, we organized medications into groups based on the following observed severe ALI rates: ≥ 200.0 (Group 1), 100–199 (Group 2), 50–99 (Group 3), 20–49 (Group 4), and < 20 (Group 5) events/10000 person-years. For patients without CLD, groups were based on the following severe ALI rates: ≥ 10.0 (Group 1), 5.0–9.9 (Group 2), 3.0–4.9 (Group 3), 1.0–2.9 (Group 4), and < 1.0 (Group 5) events/10000 person-years. We reported the rates of severe ALI for the Group 1–5 medications for patients without CLD in a prior analysis [13].

To assess how sensitive the rates of severe ALI were to definition 1 of our main outcome, we performed a sensitivity analysis whereby we replaced the Hy's Law biochemical criteria with an alternative definition of: ALT > 5 times ULN (40 U/L) + TB > 2 times ULN (1.0 mg/dL).

2.5.2 | Development of Hepatotoxicity Score

To ensure an adequate number of drugs for our score, all Group 1–3 medications, which had the highest rates of severe ALI, were included in our index, called the Hepatotoxicity Score. The values of the age-/sex-adjusted incidence rates of severe ALI for these drugs rounded to the nearest tenth served as weights for the score. The Hepatotoxicity Score can be calculated by identifying the hepatotoxic medications dispensed over a period of interest and then summing the weights for the drugs.

2.5.3 | Evaluation of Hepatotoxicity Score as a Confounder

To assess how adjustment for the Hepatotoxicity Score might affect associations between medications and hospitalization for severe ALI, we identified a cohort of patients who initiated a PPI. Initiators of PPIs were classified by CLD status. We calculated the Hepatotoxicity Score for each PPI initiator by ascertaining the presence of the hepatotoxic drugs that were dispensed on or within 90 days prior to PPI initiation and then summing their weights. A 90-day period prior to PPI initiation was chosen to identify hepatotoxic medications being taken at the time of PPI initiation. We felt that ascertaining hepatotoxic drug use within a period longer than 90 days prior to the index date might include a larger proportion of individuals who were no longer using these drugs at PPI initiation, which could dilute associations between the Hepatotoxicity Score and severe ALI.

We used Cox regression to determine hazard ratios (HRs) with 95% CIs of severe ALI associated with categories of Hepatotoxicity Score (patients without CLD: 0 [reference], 3.0–4.9 [low], 5.0–14.9 [medium], ≥ 15.0 [high]; patients with CLD: 0 [reference], 50.0–124.9 [low], 125.0–249.9 [medium], ≥ 250.0 [high]) among PPI initiators. We then determined HRs (with 95% CIs) of severe ALI associated with lansoprazole and pantoprazole compared to omeprazole. Analyses were adjusted for age, sex, and conditions that might affect rates of severe ALI (i.e., obesity [BMI ≥ 30 kg/m^2], diabetes, hyperlipidemia, and heart failure) [26]. The analysis was repeated additionally adjusting for category of Hepatotoxicity Score. We calculated the percent change in the point estimates of the HR. All data were analyzed using SAS Enterprise Guide 8.2 (SAS Institute, Cary, NC).

3 | Results

3.1 | Rates of Severe ALI for Hepatotoxic Drugs, by CLD Status

A total of 462734 patients with CLD were included among the 193 cohorts of initiators of medications with at least four published reports of ALI. The reasons for exclusion of patients within each cohort and the final samples are reported in Table S3. The most common reason for exclusion was < 365 days in the VA prior to initial outpatient fill. The mean age of these patients was 61 (standard deviation, 11) years and 94.5% were male.

Among the 462734 patients with CLD, we identified 933 hospitalizations for severe ALI over 324535 person-years (incidence rate, 28.7 [95% CI, 27.0–30.7] events per 10000 person-years). The median time to the outcome was 42 (interquartile range, 12–103) days. After calculation of age-/sex-adjusted incidence rates of severe ALI, 115 (59.6%) medications were not included for further consideration because the 95% CI was > 3 times the point estimate of severe ALI, there was too little person-time of follow-up, or there were fewer than 1000 initiators (Table S4). Incidence rates of severe ALI for medications in Groups 1–3 (most hepatotoxic) are given in Table 1. Rates for Group 4–5 medications are given in Table S5.

A total of 7899468 patients without CLD were included among the 193 cohorts of hepatotoxic medication initiators. Among these individuals, we identified 1739 hospitalizations for severe ALI over 10518172 person-years (incidence rate, 1.7 [95% CI, 1.6–1.7] events per 10000 person-years). The median time to the outcome was 53 days (interquartile range, 18–127 days). The reasons for exclusions, mean age, percent male, and medications

TABLE 1 | Incidence rates of severe acute liver injury and resultant Hepatotoxicity Score weights for the top three groupings of hepatotoxic medications among initiators with chronic liver disease.

Medication	No. initiators	No. person-years	No. events	Adjusted IR[a] (95% CI), events/10000 person-years	Hepatotoxicity Score weight
Group 1 (≥200 events/10000 person-years)					
Dicloxacillin	3256	109	4	259.3 (95.7–702.5)	259.3
Erythromycin	2499	101	3	216.8 (69.1–680.8)	216.8
Ciprofloxacin	42 680	1488	44	204.9 (145.0–289.5)	204.9
Group 2 (100–199 events/10000 person-years)					
Prochlorperazine	9470	689	18	185.1 (113.0–303.1)	185.1
Metronidazole	19 472	607	15	176.8 (103.6–301.7)	176.8
Levofloxacin or ofloxacin	23 558	720	17	163.4 (98.3–271.6)	163.4
Lansoprazole or dexlansoprazole	2958	784	13	118.0 (66.7–208.9)	118.0
Estrogens or progestins[b]	5399	1070	15	113.5 (67.4–191.3)	113.5
Group 3 (50–99 events/10000 person-years)					
Sulfamethoxazole with trimethoprim	42 040	1934	22	79.6 (50.5–125.5)	79.6
Moxifloxacin	15 319	457	5	76.6 (31.3–187.3)	76.6
Clindamycin	25 434	743	8	76.5 (37.4–156.4)	76.5
Amoxicillin with clavulanate	50 395	1508	15	70.3 (41.1–120.2)	70.3
Fluconazole	11 829	717	7	69.7 (32.6–149.2)	69.7
Cephalexin	45 391	1253	12	67.4 (37.2–122.0)	67.4
Haloperidol	2039	339	3	63.4 (20.2–199.3)	63.4
Omeprazole or esomeprazole	63 280	20 589	170	57.8 (45.7–73.0)	57.8
Azithromycin	45 774	907	7	54.5 (25.4–116.8)	54.5
Levetiracetam	3822	1200	9	51.6 (26.2–101.6)	51.6

Abbreviations: CI = confidence interval; IR = incidence rate.
[a]Incidence rates adjusted for age and sex.
[b]Represents groups of medications.

not included because of lack of precision were previously published [13].

In the sensitivity analysis replacing Hy's Law criteria with an alternative definition of ALT > 5 times ULN (40 U/L) + TB > 2 times ULN (1.0 mg/dL), we observed that the rates of severe ALI were lower than in the primary analysis for patients with CLD (Table S6) and those without CLD (Table S7), but the subset of medications identified as the most hepatotoxic in the primary analysis remained with the highest rates of severe ALI, regardless of CLD status.

3.2 | Development of the Hepatotoxicity Score

The weights used to calculate the Hepatotoxicity Score are given in Table 1 for patients with CLD and in Table 2 for patients without CLD. A total of 18 hepatotoxic medications were included for patients with CLD, and 23 hepatotoxic drugs were included for those without CLD.

3.3 | Evaluation of the Hepatotoxicity Score as a Confounder Among PPI Initiators

Among 419 416 patients with CLD and 4 141 613 patients without CLD who initiated a PPI between October 1, 2000 and September 30, 2021, a total of 329 904 and 1 679 199 were excluded, respectively, leaving 89 512 PPI initiators with CLD and 2 462 414 PPI initiators without CLD (Figure 1). Select characteristics of these patients are presented in Table 3 by CLD status. A total of 2306 (2.6%) PPI initiators with CLD and 55 330 (2.2%) without CLD were dispensed ≥2 hepatotoxic medications. A higher category of Hepatotoxicity Score

TABLE 2 | Incidence rates of severe acute liver injury and resultant Hepatotoxicity Score weights for the top three groupings of hepatotoxic medications among initiators without chronic liver disease.

Medication	No. initiators	No. person-years	No. events	Adjusted IR[a] (95% CI), events/10000 person-years	Hepatotoxicity Score weight
Group 1 (≥ 10.0 events/10000 person-years)					
Erlotinib	4356	1133	4	19.7 (7.4–53.0)	19.7
Lenalidomide or thalidomide	8191	2860	7	13.7 (6.4–28.9)	13.7
Chlorpromazine	17 449	2542	4	12.0 (4.5–32.3)	12.0
Metronidazole	423 666	12 340	19	11.8 (7.4–18.7)	11.8
Prochlorperazine	167 779	11 999	20	11.6 (7.4–18.2)	11.6
Isoniazid	20 476	7642	11	10.5 (5.8–19.2)	10.5
Group 2 (5.0–9.9 events/10000 person-years)					
Moxifloxacin	376 367	11 141	16	9.3 (5.6–15.4)	9.3
Azathioprine or mercaptopurine	16 033	6305	7	7.7 (3.7–16.4)	7.7
Levofloxacin or ofloxacin	580 210	18 799	21	7.2 (4.6–11.1)	7.2
Clarithromycin	210 356	8169	8	6.7 (3.3–13.5)	6.7
Ketoconazole	29 976	2980	3	6.1 (2.0–19.0)	6.1
Fluconazole	287 646	16 008	13	6.0 (3.4–10.4)	6.0
Captopril	18 863	6859	7	5.8 (2.7–12.2)	5.8
Amoxicillin with clavulanate	1 235 143	38 233	29	5.4 (3.7–7.9)	5.4
Sulfamethoxazole with trimethoprim	1 025 123	42 145	32	5.1 (3.5–7.3)	5.1
Ciprofloxacin	1 125 460	36 803	29	5.1 (3.5–7.4)	5.1
Group 3 (3.0–4.9 events/10000 person-years)					
Cyproheptadine	65 239	14 625	10	4.96 (2.6–9.3)	5.0
Estrogens or progestins[b]	179 681	48 270	24	4.9 (3.3–7.4)	4.9
Methimazole or thiamazole	11 865	4546	3	4.4 (1.4–13.6)	4.4
Amiodarone	96 808	32 303	25	4.0 (2.6–6.0)	4.0
Azithromycin	1 303 960	24 105	14	4.0 (2.3–6.8)	4.0
Hydralazine or isosorbide dinitrate	158 674	63 745	43	3.8 (2.7–5.2)	3.8
Cephalexin	1 147 378	33 037	18	3.7 (2.3–5.9)	3.7

Abbreviations: CI = confidence interval; IR = incidence rate.
[a]Incidence rates adjusted for age and sex.
[b]Represents groups of medications.

was associated with higher incidence rates (Table 4) and HRs (Figure 2) of hospitalization for severe ALI among patients with and without CLD.

Among PPI initiators with CLD, after adjusting for age, sex, obesity, diabetes, hyperlipidemia, and heart failure, HRs of severe ALI were higher for lansoprazole (HR = 2.17 [95% CI, 1.24–3.82]), but not pantoprazole (HR = 0.83 [95% CI, 0.61–1.13]), compared to omeprazole (Table 5). Additional adjustment for the Hepatotoxicity Score category attenuated the HR of lansoprazole (HR = 1.99 [95% CI, 1.13–3.50]; 8.3% decrease in HR) but not pantoprazole (HR = 0.83 [95% CI, 0.61–1.12]; 0.0% decrease in HR).

Among PPI initiators without CLD, after adjusting for age, sex, obesity, diabetes, hyperlipidemia, and heart failure, HRs of severe ALI were not significantly higher for lansoprazole (HR = 1.66 [95% CI, 0.99–2.77]), but were significantly lower for pantoprazole (HR = 0.59 [95% CI, 0.37–0.95]), compared to omeprazole (Table 5). Further adjustment for the Hepatotoxicity Score category attenuated the HR of lansoprazole (HR = 1.52 [95% CI, 0.91–2.54]; 8.4% decrease in HR) but only minimally

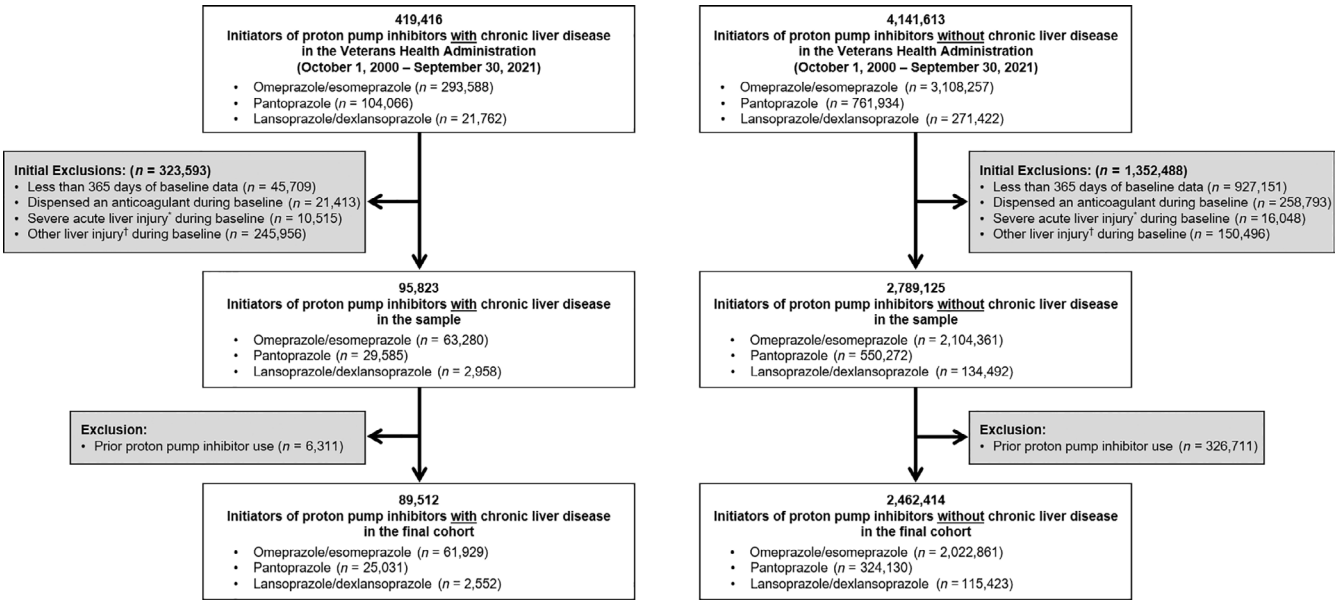

FIGURE 1 | Selection flow for the evaluation of the Hepatotoxicity Score as a confounder among initiators of proton pump inhibitors. *Baseline severe acute liver injury defined by either of the following definitions within the first two days of hospital admission: 1) alanine aminotransferase > 120 U/L (3 times upper limit of normal, 40 U/L) + total bilirubin > 2.0 mg/dL (2 times upper limit of normal, 1.0 mg/dL) (definition 1), or 2) international normalized ratio ≥ 1.5 + total bilirubin > 2.0 mg/dL (definition 2). †Other baseline evidence of liver injury defined as any of the following during the baseline period: (1) one alanine aminotransferase > 100 U/L, (2) two alanine aminotransferases ≥ 40 U/L separated by at least 6 months, or (3) or one alkaline phosphatase > 172 mg/dL (1.5 times the upper limit of normal).

affected the HR of pantoprazole (HR = 0.58 [95% CI, 0.36–0.94]; 1.7% decrease in HR).

4 | Discussion

Given the prevalence of polypharmacy [27], lack of adjustment for concomitant use of other hepatotoxic medications may lead to inaccurate measures of association between drugs of interest and relevant liver outcomes. We developed the Hepatotoxicity Score to allow pharmacoepidemiologists to adjust for concomitant hepatotoxic medication use in hepatic safety studies. We measured rates of hospitalization for severe ALI following initiation of 193 hepatotoxic drugs in groups with and without CLD, identified the subset of drugs that had high rates of outcomes in each group, and used the estimates of the rates as weights for the score, which could be calculated by summing the weights of the drugs used over a relevant period. To assess the ability of the score to control for confounding in comparative hepatic safety studies, we created cohorts of initiators of PPIs, a drug class that includes medications with reports of hepatotoxicity [10], stratified by CLD status. Higher Hepatotoxicity Score was associated with higher rates of severe ALI among those with and without CLD. For patients with CLD, lansoprazole, but not pantoprazole, was associated with significantly higher relative hazard of hospitalization for severe ALI compared to omeprazole. Among patients without CLD, relative hazards of severe ALI were not significantly higher for lansoprazole but were significantly lower for pantoprazole, compared to omeprazole. Regardless of CLD status, additional adjustment for the Hepatotoxicity Score attenuated associations of severe ALI with lansoprazole, demonstrating its utility as a confounder.

The Hepatotoxicity Score provides a systematic method to control for concomitant hepatotoxic medications. The score is easy to calculate and could be utilized by researchers examining a variety of liver-related outcomes associated with medications of interest within real-world data. For example, if a patient without CLD had dispensed fills for hepatotoxic medications included within the Hepatotoxicity Score such as isoniazid (Hepatotoxicity Score weight = 10.5), moxifloxacin (Hepatotoxicity Score weight = 9.3), and amiodarone (Hepatotoxicity Score weight = 4.0) within 90 days prior to initiation of a candidate medication being evaluated for its risk of severe ALI, the Hepatotoxicity Score for that patient would be the sum of these drugs' weights, calculated to be 23.8.

Our example comparative hepatic safety study found that lansoprazole, but not pantoprazole, was associated with a higher rate of hospitalization for severe ALI compared to omeprazole. Case studies have reported hepatocellular and cholestatic injury after PPI use [10], but no cohort studies have compared rates of severe ALI following outpatient PPI initiation stratified by CLD status while adjusting for important confounding variables, including concomitant receipt of hepatotoxic medications. Our analyses demonstrate how real-world data can be used to examine the comparative hepatic safety of medications within a commonly used drug class. Future studies should confirm whether lansoprazole is associated with a higher rate of severe ALI compared to other PPIs among persons with and without CLD.

We evaluated hospitalizations for severe ALI following medication initiation because these events reflect symptomatic drug-induced liver injury (DILI), which we considered a clinically relevant outcome. Symptomatic DILI is uncommon and rare, affecting ~1:10,000 patients without CLD receiving a medication

TABLE 3 | Select baseline characteristics of proton pump inhibitor initiators, stratified by chronic liver disease status.

Characteristic[a]	With chronic liver disease			Without chronic liver disease		
	Omeprazole and esomeprazole ($n = 61\,929$)	Lansoprazole and dexlansoprazole ($n = 2552$)	Pantoprazole ($n = 25\,031$)	Omeprazole and esomeprazole ($n = 2\,022\,861$)	Lansoprazole and dexlansoprazole ($n = 115\,423$)	Pantoprazole ($n = 324\,130$)
Age (median, IQR)	59.4 (53.4–65.6)	57.6 (51.0–67.2)	63.1 (56.5–68.4)	63.7 (52.7–73.8)	66.4 (54.5–75.2)	64.5 (51.7–72.6)
Male sex	59 091 (95.4%)	2418 (94.7%)	23 415 (93.5%)	1 866 585 (92.3%)	108 568 (94.1%)	291 607 (90.0%)
BMI ≥ 30 kg/m^2	22 813 (36.8%)	926 (36.3%)	10 490 (41.9%)	793 216 (39.2%)	39 211 (34.0%)	139 593 (43.1%)
Diabetes mellitus	18 892 (30.5%)	807 (31.6%)	10 125 (40.4%)	524 061 (25.9%)	28 597 (24.8%)	101 788 (31.4%)
Hyperlipidemia	22 364 (36.1%)	823 (32.2%)	11 997 (47.9%)	1 057 769 (52.3%)	49 546 (42.9%)	177 449 (54.7%)
Heart failure	681 (1.1%)	22 (0.9%)	854 (3.4%)	8607 (0.4%)	299 (0.3%)	5802 (1.8%)
Hepatotoxicity score category						
0	53 496 (86.4%)	2022 (79.2%)	21 436 (85.6%)	1 760 253 (87.0%)	90 399 (78.3%)	280 019 (86.4%)
Low[b]	4877 (7.9%)	254 (10.0%)	1992 (8.0%)	84 818 (4.2%)	5527 (4.8%)	16 081 (5.0%)
Medium[c]	2948 (4.8%)	232 (9.1%)	1280 (5.1%)	159 428 (7.9%)	17 173 (14.9%)	24 736 (7.6%)
High[d]	608 (1.0%)	44 (1.7%)	323 (1.3%)	18 362 (0.9%)	2324 (2.0%)	3294 (1.0%)
Dispensed ≥ 2 drugs included in Hepatotoxicity Score[e]	1474 (2.4%)	112 (4.4%)	720 (2.9%)	42 625 (2.1%)	5055 (4.4%)	7650 (2.4%)

Note: The category of Hepatotoxicity Score was classified by chronic liver disease status (patients without chronic liver disease: 0 [reference], 3.0–4.9, 5.0–14.9, ≥ 15.0; patients with chronic liver disease: 0 [reference], 50.0–124.9, 125.0–249.9, ≥ 250.0).

Abbreviations: BMI, body mass index; IQR, interquartile range.

[a]Presented as number (percent) unless otherwise noted.

[b]Low score defined as 50.0–124.9 among initiators with chronic liver disease and 3.0–4.9 among initiators without chronic liver disease.

[c]Medium score defined as 125.0–249.9 among initiators with chronic liver disease and 5.0–14.9 among initiators without chronic liver disease.

[d]High score defined as ≥ 250.0 among initiators with chronic liver disease and ≥ 15.0 among initiators without chronic liver disease.

[e]Represents hepatotoxic medications included in Hepatotoxicity Score that were dispensed within 90 days prior to proton pump inhibitor initiation.

TABLE 4 | Incidence rates of hospitalization for severe acute liver injury for according to category of Hepatotoxicity Score among initiators of proton pump inhibitors, stratified by chronic liver disease status.

Score	No. patients	No. person-years	No. Events	Adjusted IR[a] (95% CI), events per 10 000 person-years
Initiators of proton pump inhibitors with chronic liver disease				
Hepatotoxicity Score = 0	76 954	26076.24	179	68.6 (59.3–79.5)
Hepatotoxicity Score = 50.0–124.9 (Low)	7123	2163.13	26	120.2 (81.8–176.5)
Hepatotoxicity Score = 125.0–249.9 (Medium)	4460	1066.77	24	225.0 (150.8–335.7)
Hepatotoxicity Score ≥ 250.0 (High)	975	242.14	6	247.8 (111.3–551.6)
Initiators of proton pump inhibitors without chronic liver disease				
Hepatotoxicity Score = 0	2 130 671	907849.92	173	1.9 (1.6–2.2)
Hepatotoxicity Score = 3.0–4.9 (Low)	106 426	41938.94	18	4.3 (2.7–6.8)
Hepatotoxicity Score = 5.0–14.9 (Medium)	201 337	64752.70	33	5.1 (3.6–7.2)
Hepatotoxicity Score ≥ 15.0 (High)	23 980	5666.84	6	10.6 (4.8–23.6)

Note: The category of hepatotoxicity score was classified by chronic liver disease status (patients without chronic liver disease: 0 [reference], 3.0–4.9, 5.0–14.9, ≥ 15.0; patients with chronic liver disease: 0 [reference], 50.0–124.9, 125.0–249.9, ≥ 250.0).
Abbreviations: CI = confidence interval; IR = incidence rate.
[a]Incidence rates adjusted for age and sex.

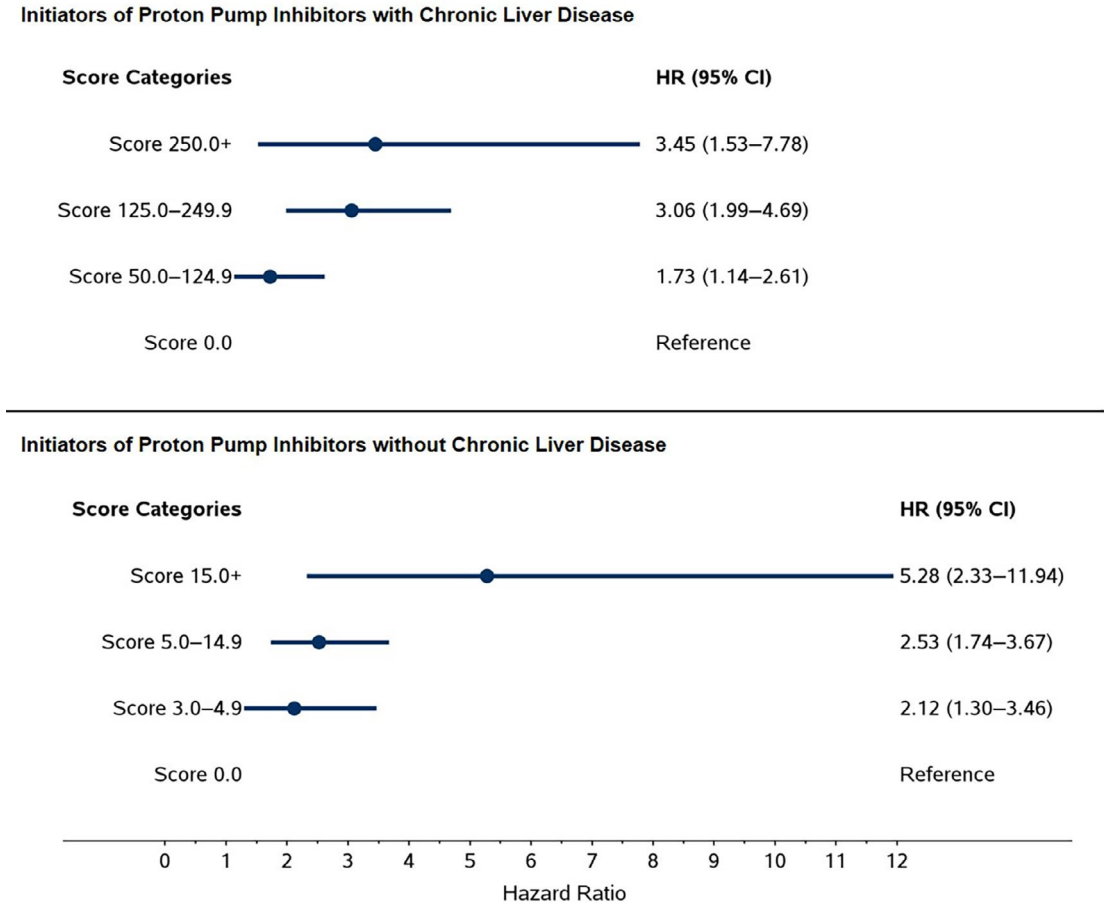

FIGURE 2 | Hazard ratios with 95% confidence intervals of severe acute liver injury for category of Hepatotoxicity Score among initiators of proton pump inhibitors, adjusted for age, sex, obesity (body mass index ≥ 30 kg/m^2), diabetes mellitus, hyperlipidemia, and heart failure. CI = confidence interval; HR = hazard ratio.

TABLE 5 | Impact on the hazard ratio of severe acute liver injury when controlling for the Hepatotoxicity Score.

PPI drug	No. patients	No. person-years	No. events	Adjusted IR[a] (95% CI), events per 10000 person-years	Hazard ratio (95% CI)		% Change in hazard ratio
					Adjusted without score	Adjusted with score[b]	
Initiators of proton pump inhibitors with chronic liver disease							
Lansoprazole or dexlansoprazole	2552	664.71	13	195.6 (113.6–336.8)	2.17 (1.24–3.82)	1.99 (1.13–3.50)	−8.3%
Pantoprazole	25031	8745.00	56	64.0 (49.3–83.2)	0.83 (0.61–1.13)	0.83 (0.61–1.12)	0.0%
Omeprazole or esomeprazole	61929	20138.56	166	82.4 (70.8–96.0)	Reference	Reference	—
Initiators of proton pump inhibitors without chronic liver disease							
Lansoprazole or dexlansoprazole	115423	37964.83	16	4.2 (2.6–6.9)	1.66 (0.99–2.77)	1.52 (0.91–2.54)	−8.4%
Pantoprazole	324130	130073.98	19	1.5 (0.9–2.3)	0.59 (0.37–0.95)	0.58 (0.36–0.94)	−1.7%
Omeprazole or esomeprazole	2022861	852169.59	195	2.3 (2.0–2.6)	Reference	Reference	—

Note: Incidence rates and hazard ratios for initiators of proton pump inhibitors, stratified by chronic liver disease status.
Abbreviations: CI = confidence interval; IR = incidence rate.
[a]Incidence rates adjusted for age and sex.
[b]Analyses adjusted for categories of Hepatotoxicity Score (patients without CLD: 0 [reference], 3.0–4.9, 5.0–14.9, ≥15.0; patients with CLD: 0 [reference], 50.0–124.9, 125.0–249.9, ≥250.0).

within population-based cohort studies [28, 29]. Notably, the overall rate of hospitalization for severe ALI following new use of the medications evaluated among the patients without CLD in our study was 1.7 events per 10000 person-years, which aligns closely with previously published results and supports our methods. No population-based studies have examined rates of hospitalization for severe ALI (or hepatologist-confirmed DILI) following new use of drugs in patients with CLD, so the true rate of symptomatic DILI in this group is unknown. Additional studies are needed to assess rates of severe ALI in patients with CLD.

Our study had several limitations. First, we did not perform a causality assessment of all outcomes, and there is the potential that some severe ALI events may have been misclassified due to undiagnosed liver/biliary diseases. A prior analysis showed that 76% of the hospitalizations for severe ALI among patients without CLD were classified as medication-related by hepatologist review [13], but patients with CLD were not included. Furthermore, some outcomes might have been caused by herbal or dietary supplements, over-the-counter products (e.g., acetaminophen), or hepatotoxic medications other than one of the drugs under study. Second, our Hepatotoxicity Score did not include medications that had 1–3 published reports of hepatotoxicity or those only recently released into the market. Third, medications that were rarely used in the VA formulary were not included in the Hepatotoxicity Score, but those medications might be used more frequently within other healthcare systems. Fourth, it is possible that concomitantly used hepatotoxic medications might have additive effects on rates of liver outcomes, but it was beyond the scope of our analyses to examine rates of severe ALI with specific combinations of medications. Fifth, the Hepatotoxicity Score cannot account for potentially hepatotoxic herbal or dietary supplements, since such products do not require a prescription in the United States and dispensed fills for them are not routinely recorded in electronic medical record databases. Finally, as our study predominantly included male patients, the results may not be generalizable to females. However, the total sample of women in care in the VA system (~500000 women) is as large as in many major cohort studies [30, 31], permitting evaluation of rates of severe ALI following new use of many medications used by women.

In conclusion, we developed the Hepatotoxicity Score based on incidence rates of severe ALI for medications with at least four reports of hepatotoxicity and separately developed scores according to CLD status. Among a cohort of PPI initiators, higher Hepatotoxicity Score was associated with higher rates of hospitalization for severe ALI among patients with and without CLD. Regardless of CLD status, additional adjustment for the Hepatotoxicity Score attenuated associations of severe ALI with lansoprazole, demonstrating its utility as a confounder. The Hepatotoxicity Score represents a valuable tool to adjust for potential confounding due to hepatotoxic drugs within hepatic safety studies.

4.1 | Plain Language Summary

Studies evaluating the liver safety of medications using real-world data have been limited by their inability to control for the effect of other hepatotoxic medications. To address this

limitation, we developed a novel index, called the Hepatotoxicity Score, to adjust for concurrent use of hepatotoxic medications within pharmacoepidemiology studies. The Hepatotoxicity Score consists of weights based on the incidence rates of hospitalization for severe acute liver injury (ALI) for medications with at least four published reports of hepatotoxicity. Because chronic liver disease (CLD) might affect rates of severe ALI after medication initiation, we developed separate scores by CLD status. To demonstrate the use of the Hepatotoxicity Score, we selected three commonly used proton pump inhibitors (lansoprazole, pantoprazole, and omeprazole) that had reports of hepatotoxicity and created groups of new users with and without CLD. Higher Hepatotoxicity Score was associated with higher rates of hospitalization for severe ALI among patients with and without CLD. Regardless of CLD status, additional adjustment for the Hepatotoxicity Score attenuated associations of severe ALI with lansoprazole, demonstrating its utility as a confounder. The Hepatotoxicity Score provides a tool to adjust for the use of multiple hepatotoxic medications in real-world data studies evaluating the hepatic safety of medications.

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Ethics Statement

This study was approved by the Institutional Review Boards of the University of Pennsylvania, Yale University, and VA Connecticut Healthcare System.

Conflicts of Interest

S.H. has consulted for Balance Opthalmics Inc.; Lycos Therapeutics Inc.; Applied Therapeutics Inc.; The Medullary Thyroid Cancer Registry Consortium (Novo Nordisk Inc.; AstraZeneca Pharmaceuticals LP, Eli Lilly and Company), Urvant Sciences, i20 Therapeutics, Basilea, Bluebird bio Inc.; Amylyx Pharmaceuticals; Ipsen Bioscience Inc.; Covis Pharma GmbH. V.L.R. has received consulting fees from Entasis, Takeda, and Urovant Sciences.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.