Validation of Acute Liver Injury Cases in a Population-Based Cohort Study of Oral Antimicrobial Users

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Abstract: We conducted a cohort study of acute, noninfectious liver injury among oral antimicrobial users. Potential cases were identified in the HealthCore Integrated Research Database (HIRD^{SM}) population between July 1, 2001, and March 31, 2009, using ICD-9-CM codes primarily for acute and subacute necrosis of the liver, hepatic coma, and unspecified hepatitis.

Liver test results were used to confirm case status according to published criteria. Two physician reviewers experienced in studying acute liver injury (blinded to study drug exposures) evaluated data abstracted from hospital and emergency department records to validate potential cases. Of 715 potential cases having claims associated with any of the primary screening codes, 312 (44%) were valid cases, 108 (15%) were not cases, and 295 (41%) were of uncertain status (records inadequate for validation). Among potential cases with adequate medical records, the PPV for presence of any of the primary codes was 74% (95% CI, 70%-78%). The highest PPV for a single code was for acute and subacute necrosis of the liver (84%; 95% CI, 77%-90%).

Evaluation of cases of noninfectious liver injury using hospital and emergency department medical records continues to represent the preferred approach in studies using insurance claims data.

Keywords: Antimicrobials, cohort, liver injury, nested case-control, validation.

BACKGROUND

Noninfectious acute liver injury (ALI) is uncommon in the general population, with estimated incidence rates ranging from 2.4 to 14.8 cases per 100,000 person-years [1-7]. Nonetheless, serious hepatotoxicity is reported to be the leading cause of drug withdrawals from the market [8], and many prescription drugs, including antimicrobials [9,10], have been implicated as causes of potentially life-threatening liver injury.

Clinical criteria for the assessment of liver injury are well established [8,11,12]. However, detecting cases of liver injury in insurance claims databases requires the initial use of criteria based on relatively nonspecific diagnostic codes. Because the diagnosis of liver injury ultimately depends on liver test results, which are not recorded in claims databases, it is necessary to validate code-identified ("potential") cases using additional information from hospital or other medical records.

We assessed the risk of hospitalization or emergency department (ED) visits for noninfectious liver injury associated with the use of 8 antimicrobials in the population of the HealthCore Integrated Research Database (HIRD^{SM}) [13]. Herein we describe the claims screening and validation procedures used to identify cases of noninfectious ALI and present the positive predictive values (PPVs) of the full screening algorithm and of the individual diagnostic codes used to detect clinically important liver injury.

METHODS

Study Design and Data Source

We conducted a retrospective cohort and nested case-control study of liver injury among adult antimicrobial users

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identified from the HIRD[SM] from July 1, 2001, to March 31, 2009 [13].

The HIRD[SM] includes data from WellPoint, Inc., one of the largest health benefits companies in the United States and an independent licensee of the Blue Cross and Blue Shield Association, covering members in 14 states. In 2009, it contained fully adjudicated paid claims for approximately 30 million covered lives, with dates of service for all noncapitated ambulatory, ED, inpatient, and outpatient encounters. Patient enrollment data, medical care, prescription drug use, laboratory test results, and health care utilization can be tracked for each patient in the database. Diagnoses and procedures are identified by International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), Current Procedural Terminology (CPT), and Healthcare Common Procedure Coding System codes; drug claims are captured by National Drug Codes and Generic Product Identifiers.

Inclusion and Exclusion Criteria

Eligible new users of the study antimicrobials included those aged ≥18 years with continuous health plan enrollment in the database (both medical and prescription coverage) for ≥6 months before study entry. The entry date was defined as the first date of a dispensing of any oral study antimicrobial—amoxicillin, amoxicillin/clavulanic acid, clarithromycin, cefuroxime, doxycycline, levofloxacin, moxifloxacin, and telithromycin—with no use of any of these drugs within the previous 6 months. Patients were excluded if they had a history of infectious hepatitis or HIV/AIDS (human immunodeficiency virus infection/acquired immunodeficiency syndrome), chronic alcoholism or alcoholic cirrhosis, or were pregnant (a temporary exclusion for 180 days before and after any claim for a pregnancy related code). Patients with hepatic, biliary, or pancreatic diseases or cancer were not excluded [13].

Case Identification

The process we used to identify potential cases of ALI involved claims screening, medical records abstraction, and validation using laboratory test data. First, we required that patients have either an ED visit or hospitalization during which one of the ICD-9-CM diagnosis or CPT procedure codes of interest was recorded (in any position in the claims records), regardless of any drug exposure. In an epidemiologic study, the focus is on detecting *any* ALI, not necessarily only *drug-induced* liver injury cases; excess risk related to exposure to any of the study drugs is then determined in the comparative (relative risk) analysis with nonuse as the reference, which accounts for ALI incidence in patients unexposed to the study drugs.

Because there is no single, well-defined ICD-9-CM code for this outcome, we explored the use of multiple codes. We distinguished between potential cases identified by several codes that we considered likely to be more specific for ALI (called "type A" codes) and those identified by codes we considered to be less specific ("type B" codes) (Table **1**). If a patient had a type A and a type B code on the event date, we classified the patient as a type A potential case. Our intention was to investigate all potential type B cases only if these codes contributed substantially to identifying cases not found using type A codes. (We did not identify any potential cases using the procedure codes for liver allotransplantation.)

Table 1. Codes Associated with Liver Injury

Code	Description
ICD-9-CM	
Study Category type A Codes	
570.xx	Acute and subacute necrosis of liver
572.2x	Hepatic coma
573.3x	Hepatitis unspecified
Study Category Type B Codes	
573.8x	Other specified disorders of liver
573.9x	Unspecified disorders of liver
782.4x	Jaundice, unspecified, not of newborn
CPT	
47135	Liver allotransplantation, orthotopic
47136	Liver allotransplantation, heterotopic

CPT = Current Procedural Terminology; ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification.

After screening potential cases *via* claims, medical records were sought for all type A and a 5% sample of type B cases. To identify a facility or facilities where records could be located, we applied an algorithm based on the liver injury date and ICD-9-CM codes of interest. For each patient, we gave higher priority to obtaining records from an inpatient facility than an ED. If a patient had information recorded for multiple inpatient facilities, higher priority was given to the facility where hospitalization included the liver injury date. After facilities were identified and charts requested, up to five attempts by telephone were made to obtain the records. Any record that could not be located after the fifth call was classified as unobtainable, as was any record that a facility indicated they could not provide.

Source record abstraction occurred between June and December 2010. Medical records were abstracted using a standardized form by a Health Insurance Portability and Accountability Act (HIPAA)–compliant third-party vendor. Abstracted information was blinded to patient and provider identities and reference to any of the study drugs. Information abstracted included discharge diagnoses and dates, medical history, clinical findings, results from diagnostic procedures (e.g., liver tests), and death during hospitalization. Copies of discharge summaries and pathology and imaging study reports were also obtained.

Prior to entry of the abstracted data, a clinical manager at the chart abstraction vendor reviewed forms for completeness and accuracy. Data entry staff created an electronic file of abstracted data, employing company procedures to minimize data entry error and enhance reproducibility. Electronic files were transferred to HealthCore, where all abstracted data were quality-control checked using HealthCore-generated SAS programs (SAS Institute, Inc., Cary, North Carolina) to find missing values,

inconsistencies between abstracted and claims data, and other identifiable errors.

After the electronic files created from medical record abstraction were finalized, we applied laboratory test criteria based on those for drug-induced liver disorders established by participants in a 1990 International Consensus Meeting [11] (Table **2**). We chose the highest liver test values recorded during a hospitalization or ED episode of ALI to categorize the severity of injury. Although updated liver test criteria can be found in the literature [14], our study was initiated before those definitions were published.

Table 2. Definition of Acute Liver Injury (Primary Endpoint)

Primary Endpoint	Definition
Liver injury	ALT > 2 × ULN or TB > 2 × ULN or Any increase of AST, ALP, and TB, with one of them > 2 × ULN

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TB = total bilirubin; ULN = upper limit of normal range.
Source: International Consensus Meeting [11].

To confirm case status, we reviewed the abstracted medical records and blinded copies of discharge summaries, pathology reports, and results of radiologic examinations, whenever available. A computer-based algorithm was used initially to classify potential cases on the basis of liver test results obtained from the medical record (Table **2**). Potential cases with insufficiently elevated liver test results to meet the study-defined criteria of liver injury were classified as noncases. Potential cases found on review of hospital or ED records to have an exclusion diagnosis not recorded in their claims were also classified as noncases. Those with sufficiently abnormal liver test results and no exclusions were considered valid cases. Potential cases with missing information for liver test results (and no excluded diagnosis) were retained as possible ("uncertain") cases for sensitivity analysis. If the upper limit of normal value for liver test results was missing, we imputed this value as the median of upper limit of normal values for potential cases with known values. Two medical doctors (JK and JC), blinded to study drug exposure, reviewed all abstractions and other blinded records, as noted above, to confirm event status and classify event type.

Analysis

To assess the coding algorithm used, the results of case screening and validation were used to calculate PPVs with corresponding 95% confidence intervals (CIs) for the type A screening diagnostic codes (570.xx "acute and subacute necrosis of liver," 572.2x "hepatic coma," and 573.3x "hepatitis unspecified") collectively and individually.

Ethics Approval

The RTI International institutional review board reviewed the study protocol and documentation and judged the study to be exempt from informed consent requirements and from full review. HealthCore submitted the study protocol to the Quorum Review Institutional Review Board, an ethics review board established in accordance with 21CFR56.107 (Code of Federal Regulations, Title 21, Section 56.107) that serves as HealthCore's national institutional review board provider, and a waiver of HIPAA authorization was granted to HealthCore pursuant to 45CFR164.512(i)(1)(i)(A). The study was registered at ClinicalTrials.gov (Identifier: NCT01434173).

RESULTS

After applying inclusion and exclusion criteria and sampling strategies for the most commonly used study antimicrobials, the cohort from which potential cases were identified contained 1,299,056 patients. Using claims codes, 2,907 potential cases of ALI were identified, 715 by type A codes and 2,192 by type B codes (see Table **3**). A total of 827 potential cases were designated for chart abstraction: all type A (n = 715) and, for exploratory purposes, a random 5% sample of type B (n = 112).

For each of the 827 patients identified for chart abstraction, we applied the algorithm for identifying the appropriate medical facility(ies) housing the medical record(s) of interest. At least one facility was identified for 89.7% (742 of 827) of the patients; a targeted manual review of the claims history identified a facility for 18 of the

Table 3. Summary of Potential Liver Injury Cases by Qualifying ICD-9-CM Codes (in Any Position)

ICD-9-CM Code	Description, N (%)*	Liver Injury Class	
		A (n = 715)	B (n = 2,192)
570.xx	Acute and subacute necrosis of liver	214 (29.9)	0 (0)
572.2x	Hepatic coma	99 (13.8)	0 (0)
573.3x	Hepatitis unspecified	435 (60.8)	0 (0)
573.8x	Other specified disorders of liver	23 (3.2)	1,351 (61.6)
573.9x	Unspecified disorders of liver	12 (1.7)	399 (18.2)
782.4x	Jaundice, unspecified, not of newborn	31 (4.3)	496 (22.6)

ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification.
*Patients who had more than one diagnosis code on the same date appear in multiple rows.

remaining 85 patients. No facility was identified for the remaining 67 patients (57 type A cases and 10 type B cases). For 35 of these patients (52%), the claim of interest was from a non-WellPoint (out of network) provider, and it was not possible to obtain any identifying information. For the other 32 patients (48%), the claim of interest was from an individual physician with no inpatient or ED facility identifiable on or near the event date.

We received medical records for 85 of the 112 type B cases; by liver test results, 24 (28%) met criteria for cases, 2 (2%) were excluded by diagnosis, 38 (45%) were not cases, and the remaining 21 (25%) were uncertain because of missing laboratory data. Thus, 24 of 64 (38%) with adequate medical records met the case criteria for liver injury. Because all of these cases had other diagnoses that were likely causes of abnormal liver tests, and because resources were constrained and relative risk estimates based on cases identified using only type A codes should be unbiased, we pursued only the type A cases for complete validation. We project that this decision resulted in underestimation of the number of cases of liver injury by 888 cases and, a corresponding underestimation of incidence rates.

Of 715 type A potential cases, records were obtained for 481 (67%) (Fig. **1**), and 420 of those had adequate information on liver test results. Of the 420 cases with adequate information, 312 met all study criteria and were considered to be valid cases (PPV, 74%; 95% CI, 70%-78%); 82 of these cases had severe hepatocellular injury and 11 had liver failure. PPVs and 95% CIs for the individual diagnostic codes and for each observed combination of the three diagnostic codes are shown in Table **4**. Case status remained uncertain for 295 of the 715 potential cases (41%).

Table 4. Positive Predictive Values for Study Category Type A Diagnostic Codes, Singly and in Combination

ICD-9-CM Code(s)	Positive Predictive Value [95% CI]
570.xx	84% (108 of 128) [77%-90%]
573.3x	76% (201 of 265) [70%-81%]
572.2x	48% (26 of 54) [35%-61%]
570.xx and 573.3x only	88% (15 of 17) [66%-98%]
570.xx and 572.2x only	67% (4 of 6) [26%-94%]
570.xx, 572.2x, and 573.3x	100% (2 of 2) [16%-100%]

CI = confidence interval; ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification.

Of the 312 valid cases that had a claim meeting the screening criteria and liver test results that were abnormal by case criteria, 14 (4.5%) had no diagnoses at all listed in the chart and another 14 (4.5%) had no diagnosis relevant to liver test abnormalities. For 221 of the valid cases (70.8%), the medical chart listed nonstudy diagnoses (e.g., cholecystitis, metastatic cancer, congestive heart failure, sepsis) that are known potential causes of liver test abnormalities. The remaining 63 patients (20.2%) had "hepatitis" (or "drug-induced hepatitis") listed in their charts and did not have other diagnoses listed that are known potential causes of liver test abnormalities. One analysis of the main study results was restricted to these 63 cases [13].

DISCUSSION

Large insurance claims databases containing administrative data and adjudicated medical and prescription

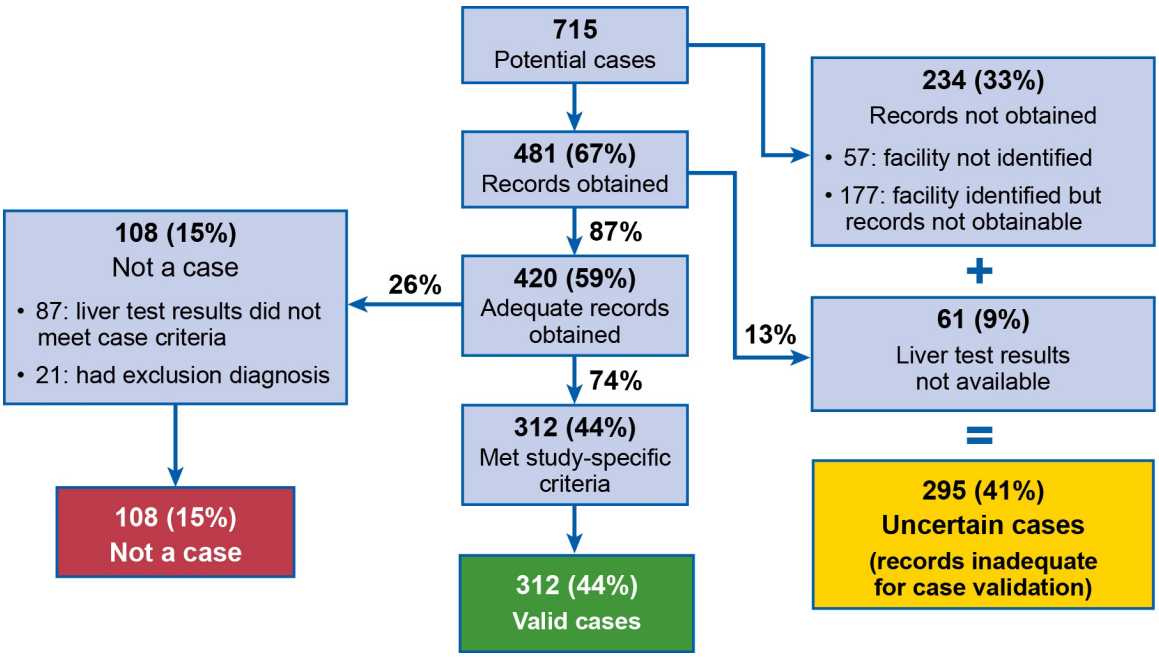

Fig. (1). Diagram of the case validation process. "Potential cases" met the claims diagnosis screening criteria. Percentages in the boxes refer to percentage of the total 715 potential cases, whereas percentages outside of boxes refer to percentage of the patients in the preceding box of the flow diagram. Exclusion diagnoses for the 21 potential cases determined not to be valid cases were identified during review of hospital and emergency records. (Patients who had exclusion diagnoses in their claims data were not considered to be potential cases.) "Valid" cases were those confirmed to meet all case definition criteria by review of hospital or emergency department records.

dispensing information provide researchers with a valuable resource for examining outpatient drug use and its link to rare outcome events. Evaluating the validity of the information is critical for the quality of the study. However, source record validation of study endpoints requires resources and extends the study timeline. Use of a validated algorithm for certain diseases may help minimize some of the time and expense associated with source record validation, but such an algorithm is not always available to researchers owing to the limited specificity of existing diagnostic codes.

This is one of the largest source validation studies on acute liver injury; 481 of 715 records (67%) were abstracted. The overall PPV was 74%, and the code with the highest PPV (84%) was 570.xx (acute and subacute necrosis of liver). Although case validation was limited by the number of medical records that could be obtained and that contained adequate liver test results, the codes we used performed well collectively and individually. In our study population, which did not exclude patients with known potential causes of liver injury such as cancer and other hepatic, biliary, or pancreatic diseases, PPV was high for the broad case definition of ALI (74% for cases with inpatient or ED diagnoses 570.xx, 572.2x, or 573.3x and adequate medical records) and for the individual diagnostic codes of 570.xx (84%) and 573.3x (76%). Inclusion of the type B codes would have identified a substantial number of additional valid ALI cases; therefore, we underestimated the true incidence rates of liver injury in the population, but the estimated relative risks should be valid [13].

We reported elsewhere that the relative risk of liver injury for nearly all antimicrobials studied was higher when the analysis was restricted to valid cases than when cases of uncertain validity were also included in the analysis [13]. This difference is presumably related to misclassification of case status for some of the uncertain cases. The possibility of such an effect on study results should be considered when investigators ponder whether to undertake case validation in studies of outcomes that are not reliably determined by claims coding.

Other researchers have conducted validation studies of liver injury using claims databases in North America, but these have concentrated mainly on different classes of drugs, and few details of claims-screening algorithms and their performance are published. For example, Enger and colleagues [15] conducted a study of the occurrence of hospitalizations for several outcomes, including hepatic injury, among new statin users in the Normative Health Informatics database, employing ICD-9-CM codes for hepatic injury similar to those used in our study. Although medical records were used to confirm outcomes, the study did not provide sufficient information on PPVs to determine the performance of the diagnostic criteria either collectively or for individual codes. In a similar study of hospitalizations for ALI and several other outcomes among statin users in the Saskatchewan Health Databases, results were not comparable to those of our study, as no specific ICD-9-CM or ICD-10 (International Statistical Classification of Diseases and Related Health Problems, 10th Revision) codes were reported and no cases of ALI occurred among patients taking the study drug [16]. Another Saskatchewan Health Databases study evaluating the association between nonsteroidal antiinflammatory drug use and serious ALI, which excluded patients with prior risk factors for liver injury, did not provide sufficient information to estimate performance of the screening criteria; data specific enough to compare with our study results were not reported [1,17].

Other investigations have focused on populations too limited to allow for a meaningful direct comparison with our study results. For example, Myers and colleagues [18] used an algorithm for hepatotoxicity, but focused on diagnostic criteria and accuracy of administrative data in a group of patients hospitalized for acetaminophen overdose. Also, the alanine aminotransferase (ALT) criterion used for identification of acetaminophen-related hepatotoxicity (ALT > 1,000 U/L) was more stringent than that used in our study for hospitalization with noninfectious acute liver injury (ALT > 2 × upper limit of normal range). Other validation studies [19-21], while offering insight into the sensitivity and specificity of different algorithms, focused on non–liver disease outcomes and offer little insight into the nuances of our ALI research. However, in comparing the precision of our algorithm with the algorithms in their research, we see that our overall PPV of 74.3% is quite high and in the range of estimates for studies that validate other clinical endpoints.

The Observational Medical Outcomes Partnership (OMOP) has outlined operational definitions of 10 health outcomes of interest and has evaluated seven algorithms for acute liver injury [22]. OMOP's examination of algorithms used in database studies found that broader diagnostic criteria yield more potential cases than narrower criteria. To our knowledge, validation of these algorithms against source records has not yet been conducted by or for OMOP. The challenge in developing coding algorithms for conditions such as liver injury, as noted by OMOP, is in "boosting specificity, as sensitivity is largely controlled by how well clinicians use the appropriate code to identify potential cases" [23]. We would add that pharmacoepidemiology researchers are also dependent on the inherent specificity of available diagnostic codes in relation to the disease(s) of interest.

Our study has several important limitations. In identifying cases for inclusion, we used two different groups of diagnostic codes for liver injury and then restricted our analysis to those cases with only the more specific codes. By eliminating less specific codes, we probably failed to identify some cases that were truly eligible (false negatives). We looked at diagnosis codes in any position, not just the primary diagnosis, which was probably more sensitive than if only the primary diagnosis had been used. We also looked only at ALI outcomes associated with inpatient stays or ED visits. Although less severe or critical cases may have been missed, such cases are less likely to be clinically significant than those resulting in hospitalization or an ED visit. In addition, although we required a hospitalization or ED visit to identify potential cases of ALI, our methods did not exclude the possibility that patients may have had previously elevated liver test levels. Also, because a substantial portion of potential cases were uncertain (i.e., liver test results were not available), we have not presented details of our case validation by subgroups of liver injury pattern (hepatocellular versus cholestatic). Finally, our study population was different from

those of other liver injury studies in allowing other comorbid conditions.

In summary, claims databases such as the HIRD[SM] provide a valuable resource for studies of outpatient drug exposure and clinical outcomes that require validation using medical records. By definition, source record validation is limited by the proportion of medical records that can be obtained and that contain adequate information on the clinical outcome of interest. Although the results obtained in one database may not be directly applicable to other databases, we found high PPVs for both our broad case definition of ALI and individual diagnostic codes. Source record validation of potential cases identified through diagnostic code–based algorithms is always preferred in these endpoints using database studies; however, in studies where validation is not possible for logistical, time, or resource constraints, researchers may prefer to focus on outcomes with proven high PPVs, for example, diagnostic code 570.xx (PPV=84% in this study), although with the understanding that this approach is likely to be less sensitive.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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PATIENT CONSENT

The study was found to be exempt from informed consent requirements by the RTI International institutional review board.

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