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Validity of Diagnostic Codes to Identify Cases of Severe Acute Liver Injury in the U.S. Food and Drug Administration's Mini-Sentinel Distributed Database

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Abstract

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POTENTIAL CONFLICTS OF INTEREST

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Purpose—The validity of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes to identify diagnoses of severe acute liver injury (SALI) is not well known. We examined the positive predictive values (PPVs) of hospital ICD-9-CM diagnoses in identifying SALI among health plan members in the Mini-Sentinel Distributed Database (MSDD) for patients without liver/biliary disease and for those with chronic liver disease (CLD).

Methods—We selected random samples of members (149 without liver/biliary disease; 75 with CLD) with a principal hospital diagnosis suggestive of SALI (ICD-9-CM 570, 572.2, 572.4, 572.8, 573.3, 573.8, or V42.7) in the MSDD (2009–2010). Medical records were reviewed by hepatologists to confirm SALI events. PPVs of codes and code combinations for confirmed SALI were determined by CLD status.

Results—Among 105 members with available records and no liver/biliary disease, SALI was confirmed in 26 (PPV, 24.7%; 95% CI, 16.9% – 34.1%). Combined hospital diagnoses of acute hepatic necrosis (570) and liver disease sequelae (572.8) had high PPV (100%; 95% CI, 59.0% – 100%) and identified 7/26 (26.9%) events. Among 46 CLD members with available records, SALI was confirmed in 19 (PPV, 41.3%; 95% CI, 27.0% – 56.8%). Acute hepatic necrosis (570) or hepatorenal syndrome (572.4) plus any other SALI code had a PPV of 83.3% (95% CI, 51.6% – 97.9%) and identified 10/19 (52.6%) events.

Conclusions—Most individual hospital ICD-9-CM diagnoses had low PPV for confirmed SALI events. Select code combinations had high PPV but did not capture all events.

Keywords

hepatotoxicity; liver injury; validity; ICD-9 codes

INTRODUCTION

Severe acute liver injury (SALI) is defined by the presence of impaired liver synthetic function.¹ SALI due to drug-induced hepatotoxicity is the second most frequent reason (after cardiac toxicity) for withdrawal of approved drugs.^{2–5} Clinical trials are typically underpowered to detect uncommon but serious hepatic events.^{2,6} As a result, drug-induced SALI might not be identified until after a product has been approved for use and taken by large numbers of patients. To identify SALI in healthcare databases, validated definitions are needed. However, no study has developed and validated a method to identify SALI in healthcare data. The ability to identify SALI events accurately within electronic healthcare and administrative claims-based databases would greatly facilitate studies of this outcome. A valid characterization of the hepatotoxicity profile of medical products could have a major public health benefit by reducing medication-associated morbidity and enhancing medical product safety.

In 2008, the U.S. Food and Drug Administration (FDA) launched the Sentinel Initiative, a program designed to create a national electronic monitoring system for postmarketing medical product safety.^{7,8} The Mini-Sentinel pilot, a component of the Sentinel Initiative, is a collaborative effort between the FDA and more than 30 organizations.⁹ This Mini-Sentinel project sought to evaluate the ability of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes to identify SALI events within

automated healthcare data. Since the accuracy of these codes might differ by chronic liver disease (CLD) status,¹⁰ we stratified results by the presence or absence of pre-existing CLD.

METHODS

Design and data source

We conducted a cross-sectional analysis of health plan members in the Mini-Sentinel Distributed Database (MSDD) who had a principal hospital diagnosis suggestive of SALI recorded between January 1, 2009 and December 31, 2010. The MSDD is a multi-site distributed data system with a set of standardized data files common across all data partners.¹¹ It contains health plan member demographics, enrollment dates, location of encounter, outpatient and hospital-associated medical diagnoses, procedures, outpatient pharmacy dispensing, and date of death. For this analysis, we utilized administrative claims data from five Mini-Sentinel data partners, representing eight health plans (HealthCore, Inc.; HMO Research Network [HealthPartners Institute for Education and Research, Marshfield Clinic Research Foundation, Group Health Research Institute]; Humana; Kaiser Permanente Center for Effectiveness and Safety Research [Kaiser Permanente Colorado, Kaiser Permanente Northwest]; Vanderbilt University School of Medicine/TennCare Bureau). The Mini-Sentinel pilot is a public health surveillance activity and is not under the purview of Institutional Review Boards.^{12,13}

Health plan members selected for validation

Members without pre-existing liver/biliary disease—We first identified members who had: 1) a principal hospital ICD-9-CM diagnosis suggestive of SALI (Table 1) recorded between January 1, 2009 and December 31, 2010, 2) at least 12 months of continuous health plan enrollment prior to the SALI diagnosis, and 3) no inpatient or outpatient ICD-9-CM diagnosis of a liver/biliary disease (Appendix 1) within 12 months prior to the SALI diagnosis.

The ICD-9-CM codes selected (Table 1) focused on diagnoses suggestive of toxic hepatitis and acute liver failure (ALF). Selection of these codes was based on discussions with hepatologists in the workgroup and results of prior observational studies that suggested that these codes were frequently recorded among SALI cases.^{14,15} The rationale for excluding members with pre-existing liver/biliary disease was to reduce identification of SALI events due to these conditions and increase the likelihood that SALI cases would be medical product-related.

To ensure sufficient sample sizes to evaluate the validity of inpatient toxic hepatitis and ALF ICD-9-CM diagnoses for medical record-confirmed SALI and to enable a separate determination of the accuracy of the ALF ICD-9-CM codes for confirmed ALF, we randomly sampled 75 members who had a principal hospital diagnosis of toxic hepatitis and 74 with a principal inpatient diagnosis of ALF. The number of members selected was divided among the data partners. For data partners with multiple health plans, we divided the number of members selected within their network based on membership size. Further, within each health plan, we selected an equal number of members with an inpatient

diagnosis of toxic hepatitis and ALF for medical record review. Thus, we sampled 149 members with a principal hospital diagnosis suggestive of SALI with no indication of pre-existing liver/biliary disease.

Members with CLD—To evaluate the validity of SALI diagnoses in individuals with CLD, we identified members who had: 1) a principal hospital SALI ICD-9-CM diagnosis (Table 1) between January 1, 2009 and December 31, 2010, 2) at least 12 months of continuous enrollment prior to SALI diagnosis, and 3) at least two outpatient CLD ICD-9-CM diagnoses (Appendix 2) on two separate dates within 12 months prior to the SALI diagnosis. We excluded members with a diagnosis of biliary tract obstruction or cancer in the liver, biliary tree, or pancreas (since our focus was on CLD) or with a diagnosis suggestive of hepatic decompensation (indicating chronic liver failure) within 12 months prior to the SALI diagnosis (Appendix 3). We randomly sampled 75 CLD members with a principal hospital SALI diagnosis. The number of members selected was divided among the data partners using the same method as described above.

Main outcomes

The primary outcome was confirmed SALI, which was determined based on abnormalities of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and/or international normalized ratio (INR). SALI was confirmed if, at any time during a hospitalization, a member had: 1) ALT or AST >3 times upper limit of normal (ULN) + total bilirubin >2 times ULN (definition 1), or 2) total bilirubin >2 times ULN + INR 1.5, off anticoagulation therapy (definition 2). The ULNs for ALT, AST, and total bilirubin were determined by the assay from which each result was measured. The combination of results for each definition did not need to occur on the same day.

The rationale for definition 1 was that hepatocellular injury great enough to interfere with bilirubin excretion in a SALI case caused by drug-induced hepatotoxicity, which represents Hy's Law,^{16–18} involves a large fraction of the liver cell mass, indicates liver synthetic dysfunction, and predisposes a patient to a high risk of mortality.^{19,20} The rationale for definition 2 was that some cases with SALI might present in an advanced stage of ALF, such that serum liver aminotransferases might not be as high as levels that meet definition 1.

Elevations in alkaline phosphatase alone, without increases in ALT, AST, or total bilirubin, as specified above, were not used to classify SALI events because this finding may indicate cholestasis in the absence of SALI. Further, we did not perform a causality assessment for each SALI event. However, among cases that were confirmed to not have SALI, we determined the potential etiology for the hospitalization.

Among members without liver/biliary disease, we also determined ALF, which represents the most serious clinical outcome of SALI.^{21,22} A diagnosis of ALF was confirmed if, at any time during the hospitalization, a member had: 1) coagulopathy (INR 1.5 off anticoagulation therapy), and either 2a) hepatic encephalopathy (altered mentation due to liver dysfunction), or 2b) orthotopic liver transplant due to ALF. This definition was based on those developed by the U.S. Acute Liver Failure Study Group and American Association for the Study of Liver Diseases.^{21,23,24}

Confirmation of outcomes

Medical records were requested and redacted of data elements that directly identified individuals except for dates of service, which were not redacted. Two trained abstractors reviewed the redacted records of potential cases and abstracted data onto structured forms (Appendix 4) in a Research Electronic Data Capture (REDCap) database.²⁵ The form captured information from laboratory results, admission history and physical examinations, physician progress notes, hospital discharge summaries, brain imaging reports, and liver biopsy reports (Table 2).

Data forms were independently reviewed by two hepatologists (K.A.F and D.G.), who served as endpoints adjudicators. They classified each SALI case as: 1) definite, 2) no event, or 3) unable to determine (for members with a missing ALT, AST, or total bilirubin result). Among members with a hospital ICD-9-CM diagnosis suggestive of ALF, each ALF case was classified as: 1) definite, 2) no event, or 3) unable to determine (for members with insufficient records). Disagreement on any classification resulted in review by a third adjudicator (K.R.R. or V.L.R.) to arbitrate the event.

Electronic data from members selected for medical record review

For members selected for chart review, age at SALI date and sex were collected from the MSDD. Liver biopsy ICD-9-CM and Current Procedural Terminology codes (Appendix 5) recorded 182 days before or after the principal hospital SALI diagnosis were determined. External-Cause-of-Injury codes (E-codes) associated with SALI diagnoses were also collected.²⁶

Electronic data from members with SALI diagnoses in the MSDD

Across the five data partners, we identified all members with at least 12 months of continuous membership who had a hospital SALI ICD-9-CM diagnosis in any position between 2009 and 2010. For these members, we collected: 1) position of the SALI diagnosis codes, 2) presence of any E-codes, and 3) presence of liver biopsy codes recorded 182 days before or after the hospital SALI diagnosis.

Statistical analyses

We determined the positive predictive values (PPVs) with 95% confidence intervals (CIs) of each ICD-9-CM code and common code combinations for confirmed SALI separately among members without liver/biliary disease and with CLD. We examined if the addition of a liver biopsy or E-code increased PPVs. Further, among members without liver/biliary disease who had a diagnosis suggestive of ALF, we determined the PPVs of these codes for adjudicator-confirmed ALF. We sought to identify codes and code-based algorithms with a PPV exceeding 80%. Our focus was on PPV because a sufficiently high PPV provides confidence that identified outcomes are true events.

Among all members of the five data partners with a hospital SALI diagnosis in any position between 2009 and 2010, we determined the frequency of each SALI code and common code combinations. We then assessed the frequency with which these codes were accompanied by liver biopsy or E-codes. Finally, we determined the proportion that had a hospital SALI

diagnosis in a principal (compared to non-principal) position. Results were stratified by CLD status.

We estimated that a random sample of 100 members without pre-existing liver/biliary disease (50 with a toxic hepatitis diagnosis; 50 with an ALF diagnosis) would allow determination of the PPV for confirmed SALI with a maximum 95% CI of ± 0.10 , assuming a PPV of 80%. Because of the possibility that some medical records might not be retrieved, we increased our sample size by 50%, targeting 150 total members. We then targeted 50 members with CLD who had either a toxic hepatitis or ALF diagnosis and again inflated our sample size by 50% to account for non-retrievable records, selecting 75 members. Data were analyzed using Stata 12.0 (Stata Corp, College Station, TX).

RESULTS

Analyses of SALI diagnoses in the MSDD

Among 55,334,046 members enrolled between 2009 and 2010 across the five data partners in the MSDD, 28,321 (0.05%) had a hospital SALI ICD-9-CM diagnosis recorded in any position. The frequencies of each diagnosis code and common code combinations are presented in Appendices 6 and 7. The most frequently recorded code was other specified liver disorder (573.8; 55.2%) for members without liver/biliary disease and hepatic coma (572.2; 28.2%) for those with CLD.

Among members with a hospital SALI ICD-9-CM diagnosis, 8,324 (29.4%) had a liver biopsy code. Members with CLD were more likely to have had a liver biopsy code than those without liver/biliary disease (506/1,020 [49.6%] versus 7,818/27,301 [28.6%]; $p < 0.001$). Further, 363 (1.3%) had an E-code recorded with the SALI diagnosis. The most commonly recorded E-code was E935 (analgesics, antipyretics, anti-rheumatics; 0.18%). No difference was observed in the prevalence of an E-code between members without liver/biliary disease and those with CLD (352 [1.3%] versus 11 [1.1%]; $p = 0.67$). Finally, among the 28,321 members with a hospital SALI diagnosis code, 2,249 (7.9%) had the code recorded in a principal position. Those with CLD were more likely to have the code in a principal position than those without liver/biliary disease (113/1,020 [11.1%] versus 2,136/27,301 [7.8%], $p < 0.001$).

Validity of SALI diagnoses in members without liver/biliary disease

Among the 149 members with a principal inpatient SALI diagnosis and no pre-existing liver/biliary disease, charts could not be obtained for 27 (18.1%; Figure 1). Medical records of 122 (81.9%) members were therefore available for abstraction.

The median age of the 122 members was 68 years (interquartile range [IQR], 50–80), and 78 (63.9%) were female. Nineteen (15.6%) had a liver biopsy within 182 days of the SALI diagnosis, and 6 (4.9%) had an E-code accompanying the SALI diagnosis.

Among the 122 members with available chart components, the adjudicators determined that 17 (13.9%) did not have sufficient laboratory records to permit SALI confirmation (Figure 1). After adjudication, 26/105 (24.8%; 95% CI, 16.9%–34.1%) were confirmed to have

SALI. The overall percent agreement in events between the two adjudicators was 83.6% (102/122; 95% CI, 75.8%-89.7%), and the kappa was 0.69. ICD-9-CM code 570 (hepatic necrosis) accounted for the largest number of disagreements (9/20 [45%]).

Table 3 reports the PPVs of individual ICD-9-CM codes and code combinations for confirmed SALI. The PPVs of individual codes for SALI were generally low, ranging from 6.5%-54.3%. In contrast, a hospital diagnosis of acute hepatic necrosis (570) plus liver disease sequelae (572.8) (i.e., either one principal and one secondary or two secondary diagnoses) had high PPV (100%; 95% CI, 59.0% – 100%) and captured the highest proportion of events (7/26 [26.9%]) among the coding algorithms evaluated (Table 3). In addition to the prior coding algorithm, a hospital diagnosis of toxic hepatitis (573.3) plus either hepatic coma (572.2) or liver disease sequelae (572.8), as well as a hospital diagnosis of acute hepatic necrosis (570) plus other specified liver disorders (573.8) had PPVs of 100% (Table 3), but these algorithms identified few SALI cases.

Table 4 provides a list of the diseases observed among the 79 members who were adjudicated as not having had SALI, by diagnosis code. The majority of these members had a liver cyst (20.3%), normal liver-related laboratory tests with no documented hepatic abnormality (18.9%), or alcoholic liver disease (10.1%).

Validity of ALF diagnoses in members without liver/biliary disease

Among 57 members with a principal hospital diagnosis suggestive of ALF and available records (Figure 1), one (1.8%; 95% CI, 0.04% – 9.4%) had adjudicator-confirmed ALF. Both hepatologists agreed that this case was an ALF event. Table 5 reports the PPVs of the codes and combinations for confirmed ALF. The PPVs for individual ICD-9-CM codes for confirmed ALF were all very low (range, 1.8% – 9.1%).

Validity of SALI diagnoses in members with CLD

Among the 75 CLD members with a principal hospital SALI diagnosis, charts could not be obtained for 25 (33.3%; Figure 2). Medical records from 50 (66.7%) members were therefore available for abstraction.

The median age of these 50 members was 56 years (IQR, 46–64), and 20 (40.0%) were female. Four (8.0%) members had a liver biopsy code, and one (2.0%) had an E-code recorded with a SALI diagnosis.

Among the 50 members with available chart components, the adjudicators determined that 4 did not have sufficient laboratory records to permit SALI confirmation (Figure 2). After adjudication, 19/46 (38.0%; 95% CI, 27.0% – 56.8%) were confirmed to have SALI. The overall percent agreement in SALI events between the two adjudicators was 94.0% (47/50; 95% CI, 83.5%-98.7%), and the kappa was 0.38. ICD-9-CM codes 570 (hepatic necrosis), 572.2 (hepatic coma), and 573.8 (other specified liver disorders) accounted for the disagreements.

The PPVs of the codes and combinations for confirmed SALI for these members are reported in Table 6. The PPVs of the individual codes for confirmed SALI among CLD

members were higher in magnitude than for those without liver/biliary disease, but only the diagnosis code for hepatorenal syndrome (572.4), accompanying 4/19 cases that were adjudicated as SALI, had a high PPV (4/4; 100%; 95% CI, 39.8% – 100%).

A hospital diagnosis of either acute hepatic necrosis (570) or hepatorenal syndrome (572.4) plus any other SALI code had a PPV of 83.3% (95% CI, 51.6% – 97.9%) and identified the highest proportion of cases (10/19 [52.6%]). Several other algorithms had PPVs exceeding 80% (Table 6), but these identified fewer SALI cases.

Table 7 provides a list of the diseases observed among the 27 CLD members who were adjudicated as not having had SALI. The majority had hepatic encephalopathy with abnormal liver-related laboratory tests that did not meet SALI criteria (16/27; 59.3%).

DISCUSSION

These analyses determined that the individual ICD-9-CM codes for identifying hospitalized SALI and ALF generally yielded low PPVs. For members without liver/biliary disease, a hospital diagnosis of acute hepatic necrosis (570) and liver disease sequelae (572.8) had high PPV (100%; 95% CI, 59.0% – 100%) and captured the highest proportion of events (26.9%) among the algorithms evaluated. For members with CLD, a hospital diagnosis of either acute hepatic necrosis (570) or hepatorenal syndrome (572.4) plus any other SALI code had a high PPV of 83.3% (95% CI, 51.6% – 97.9%) and identified the highest proportion of events (52.6%).

The PPVs of the individual SALI ICD-9-CM codes selected were low both for members without pre-existing liver/biliary disease and for those with CLD. Further, PPVs for the ALF ICD-9-CM codes were very low. This was likely due to the lack of specificity of the diagnostic codes and the overall low prevalence of ICD-9-CM diagnoses for both toxic hepatitis and ALF. The 95% CIs around these PPV estimates were wide because of the relatively small sample sizes of members with each code and with confirmed SALI.

Due to the observed low PPVs of the individual ICD-9-CM SALI codes, we examined coding algorithms that required the presence of combinations of hospital SALI codes. For members without pre-existing liver/biliary disease and with CLD, we identified coding algorithms that had PPVs exceeding 80%, though at the cost of missing confirmed cases identified by other codes. We believe that these algorithms require further validation because: 1) the PPVs were not determined using random samples of members with these specific combinations of codes, and 2) sample sizes of the subjects identified by these algorithms were small and insufficient to adequately determine their validity. If their validity is confirmed, future use of these coding algorithms will depend upon the specific research question. If the objective is to identify as many cases as possible (i.e., a sensitive diagnostic test), it may be advisable to utilize all of the SALI codes evaluated in these analyses to broadly screen cohorts of interest and then confirm these events using medical record review. Alternatively, if the aim is to reduce false positive events (i.e., a specific diagnostic test), the coding algorithms developed could be used without the need to confirm events via medical records, but this would be at the cost of missed events.

Few previous studies have been performed to evaluate the accuracy of diagnosis codes for liver injury within administrative data. Myers and colleagues⁷ evaluated the validity of ICD-9-CM and ICD-10 codes for ALF, defined by chart-confirmed encephalopathy and an INR ≥ 1.5 , in the setting of acetaminophen overdose within the Calgary Health Region in Canada. Among 36 members with a diagnosis code of interest, 20 (PPV, 56%; 95% CI, 38% – 72%) had confirmed ALF. Jinjuvadia and colleagues⁶ examined the ability of ICD-9-CM codes to identify patients with drug-induced liver injury (defined by a total bilirubin ≥ 2.5 mg/dL and/or evidence of liver synthetic dysfunction) due to amoxicillin/clavulanic acid, phenytoin, valproic acid, and isoniazid within the University of Michigan Health System. Among 7,395 patients who were prescribed these medications and who had a suggestive ICD-9-CM code, 119 (1.6%) were confirmed to have drug-induced liver injury. The PPVs of individual ICD-9-CM codes ranged from 0.4% – 3.0%. Coding algorithms were not developed in either study.

This project has several potential limitations. First, it is possible that SALI events could have been misclassified during adjudication, particularly given the lower than expected kappa statistics and percent agreement in SALI events between the two adjudicators. However, we minimized this likelihood by: 1) using standardized definitions for SALI, 2) classifying events using a standard definition, and 3) employing two endpoints adjudicators to confirm events, with a third to adjudicate cases in instances of disagreement. Second, each code-based algorithm missed some SALI events. Since the most severe strata of SALI, such as ALF, are especially rare, missing even a few of these events may be particularly problematic for future analyses evaluating such outcomes. Surveillance activities seeking to identify all possible SALI events should utilize the ICD-9-CM codes employed in these analyses to screen for potential events and then confirm endpoints by medical record review. Third, we did not determine the negative predictive value of the SALI codes, since we did not evaluate SALI among a sample of MSDD members without the SALI codes of interest. Fourth, the small number of confirmed SALI cases limited the precision of our PPV estimates. Fifth, cases in these analyses were drawn from databases of mostly commercially-insured persons, potentially limiting the generalizability of our results to other populations. However, one of the selected data partners (Vanderbilt University School of Medicine/ TennCare Bureau) includes members from the Tennessee Medicaid program. Finally, these analyses focused on the validity of ICD-9-CM codes, since these are currently utilized by the data partners in the MSDD. Because ICD-9-CM codes do not always correspond directly to ICD-10 codes, future studies evaluating the validity of ICD-10 codes should be conducted within data sources that use these diagnostic codes.

This study had a number of strengths. We evaluated several ICD-9-CM codes suggestive of SALI and ALF. We classified both SALI and ALF events using standardized definitions and required two adjudicators to confirm outcomes, with a third arbitrating cases in instances of disagreement. Further, among members without SALI, we determined the etiology of their hospitalization to better understand which conditions the ICD-9-CM codes of interest were actually identifying. Finally, our use of the MSDD permitted our evaluation of the validity of the ICD-9-CM codes across a variety of administrative and claims-based data sources.

In conclusion, the individual pre-specified ICD-9-CM codes for identifying hospitalized SALI yielded low PPVs for members without liver/biliary disease and with CLD. However, select combinations of SALI ICD-9-CM codes had high PPV for confirmed outcomes in both groups, but these algorithms missed some events. These algorithms could potentially be used within claims-based and electronic health record databases in future projects, after further validation, to examine the comparative risk of SALI associated with medical products of interest.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of abbreviations

ALF	acute liver failure
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CI	confidence interval
CLD	chronic liver disease
E-code	External-Cause-of-Injury code
FDA	U.S. Food and Drug Administration
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
INR	international normalized ratio
IQR	interquartile range

MSDD	Mini-Sentinel Distributed Database
PPV	positive predictive value
REDCap	Research Electronic Data Capture
SALI	severe acute liver injury
ULN	upper limit of normal

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KEY POINTS

- The validity of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes to identify hospital diagnoses of severe acute liver injury (SALI) is not well known.
- ICD-9-CM codes for hospitalized SALI generally yielded low positive predictive values (PPVs) for health plan members in the Mini-Sentinel Distributed Database (MSDD) without pre-existing liver/biliary disease and for those with CLD. The PPVs for ICD-9-CM codes suggestive of acute liver failure were also low.
- Select combinations of ICD-9-CM codes indicative of SALI had high PPV for confirmed outcomes in members without pre-existing liver/biliary disease and with CLD, though these algorithms did miss some SALI events. These algorithms could be used in future surveillance activities to examine the comparative risk of SALI associated with medical products of interest. Surveillance activities seeking to identify all possible SALI events should utilize the ICD-9-CM codes employed in these analyses to screen for potential events and then confirm endpoints by medical record review.

Figure 1.

Flow chart of case retrieval results for health plan members without liver/biliary disease. All percentages are based on the number of records requested.

SALI=severe acute liver injury; ALF=acute liver failure

Figure 2.

Flow chart of case retrieval results for health plan members with chronic liver disease. All percentages are based on the number of records requested.

Table 1

List of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes evaluated for their ability to identify potential cases of severe acute liver injury.

Toxic Hepatitis	
CODE	DESCRIPTION
573.3	Toxic (non-infectious) hepatitis
573.8	Other specified disorder of the liver
Acute Liver Failure	
CODE	DESCRIPTION
570	Acute and subacute necrosis of the liver
572.2	Hepatic coma
572.4	Hepatorenal syndrome
572.8	Sequelae of liver disease
V42.7	Liver replaced by transplant

Table 2

Data collected from hospital medical records to permit determination of severe acute liver injury and acute liver failure.

Laboratory Results	Physician Progress Notes	Brain Imaging Reports ⁺
Alanine aminotransferase [*]	Diagnoses of:	Diagnoses of:
Alkaline phosphatase [*]	1. Acute (or fulminant) hepatitis (or liver injury)	1. Acute cerebral ischemia
Alpha-fetoprotein		2. Acute stroke
Ammonia [*]	2. Asterixis [‡]	3. Cerebral edema
Anti-kidney liver microsomal type 1 Ab	3. Acute (or fulminant) liver failure	4. Intracranial/cerebral bleed
Anti-mitochondrial Ab		5. Intracranial/cerebral mass
Anti-nuclear Ab	4. Hepatic encephalopathy [‡]	6. Uncal herniation
Anti-smooth muscle Ab	5. Jaundice	
Aspartate aminotransferase [*]	Drugs to treat encephalopathy ^ψ	
Ceruloplasmin	Liver transplantation	
Cytomegalovirus IgG Ab	Pre-existing liver disease	
Ethanol	Suspected SALI etiology	
Gamma-glutamyl transpeptidase [*]	Use of argatroban, warfarin	
Hepatitis A IgM, IgG Ab	Use of mechanical ventilation	
Hepatitis B core IgM Ab		
Hepatitis B surface antigen	Admission History/Exam and Hospital Discharge Summaries	
Hepatitis C Ab	Diagnoses of:	
Hepatitis C RNA	1. Acute (or fulminant) hepatitis (or liver injury)	
Hepatitis D Ab	2. Asterixis [‡]	
Hepatitis E Ab	3. Acute (or fulminant) liver failure	
International normalized ratio [*]	4. Hepatic encephalopathy [‡]	
Total bilirubin [*]	5. Jaundice	
	Pre-existing liver disease	
	Suspected SALI etiology	

Ab=antibody; SALI=severe acute liver injury

^{*} Admission and peak results

[‡] Hepatic encephalopathy was recorded if there was a report of altered mentation and a diagnosis was recorded in a physician's note.

[‡] Asterixis was recorded if documented in a physician's physical examination.

^ψ Drugs to treat hepatic encephalopathy included: lactulose, flumazenil, intravenous mannitol, methylprednisolone, pentobarbital, rifaximin, and thiopental.

⁺ Reports from computed tomography and magnetic resonance imaging studies of the brain.

Table 3

Positive predictive values (with 95% confidence intervals) of hospital International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes and combinations for adjudicated cases of severe acute liver injury among 105 health plan members without pre-existing liver/biliary disease.

ICD-9-CM Code or Combination		No with Code(s)*	No with SALI	Positive Predictive Value (95% Confidence Interval)
Any SALI code		105	26	24.8% (16.9% – 34.1%)
573.3	Toxic hepatitis	26	11	42.3% (23.4% – 63.1%)
573.8	Other liver disorder	31	2	6.5% (0.8% – 21.4%)
570	Acute/subacute hepatic necrosis	35	19	54.3% (36.7% – 71.2%)
572.2	Hepatic coma	23	3	13.0% (2.8% – 33.6%)
572.4	Hepatorenal syndrome	0	0	-
572.8	Liver disease sequelae	13	7	53.8% (25.1% – 80.8%)
V42.7	Liver transplant	0	0	-
573.3 + 570	Toxic hepatitis + hepatic necrosis	10	6	60.0% (26.2% – 87.8%)
573.3 or 570 [†]	Toxic hepatitis or hepatic necrosis	51	24	47.1% (32.9% – 61.5%)
573.3 + 572.2	Toxic hepatitis + hepatic coma	1	1	100% (2.5% – 100%)
573.3 + 572.8	Toxic hepatitis + liver disease sequelae	2	2	100% (15.8% – 100%)
573.8 + 570	Other liver disorder + hepatic necrosis	1	1	100% (2.5% – 100%)
573.8 + 572.2	Other liver disorder + hepatic coma	0	0	-
573.8 + 572.8	Other liver disorder + liver disease sequelae	0	0	-
570 + 572.2	Hepatic necrosis + hepatic coma	3	2	66.6% (9.4% – 99.2%)
570 + 572.8	Hepatic necrosis + liver disease sequelae	7	7	100% (59.0% – 100%)
573.3 + liver biopsy code	Toxic hepatitis + liver biopsy	4	3	75.0% (19.4% – 99.4%)
573.8 + liver biopsy code	Other liver disorder + liver biopsy	6	1	16.7% (0.4% – 64.1%)
570 + liver biopsy code	Hepatic necrosis + liver biopsy	4	3	75.0% (19.4% – 99.4%)
572.8 + liver biopsy code	Liver disease sequelae + liver biopsy	1	1	100% (2.5% – 100%)
Any SALI code + liver biopsy		14	6	42.9% (17.7% – 71.1%)
Any SALI code + any E-code		6	2	33.3% (4.33% – 77.72%)
Any Two SALI codes		19	12	63.2% (38.4% – 83.7%)
570 + any other SALI code		17	12	70.6% (44.0% – 89.7%)
573.3 + any other SALI code		10	6	60.0% (26.2% – 87.8%)
572.8 + any other SALI code		9	7	77.8% (40.0% – 97.2%)

* This table includes codes from any position; therefore, more than one code may have been applied to a single member.

[†] Refers to members who had either ICD-9-CM code 573.3 or 570 recorded.

Table 4

Conditions observed among 79 health plan members without pre-existing liver/biliary disease who were adjudicated as not having had severe acute liver injury, by primary International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) code.

ICD-9-CM Code	Code Description	No. with Primary Code	Condition
570	Acute and subacute necrosis of liver	15	n=5, Drug-induced liver injury, not meeting severe acute liver injury criteria n=3, Abnormal liver-related laboratory tests of unclear etiology, not meeting severe acute liver injury criteria n=2, Alcoholic liver disease n=2, Cancer in the liver n=1, Ischemic hepatopathy n=1, Normal liver-related laboratory tests with no reported hepatic abnormality n=1, Systemic infection with abnormal liver-related laboratory tests
572.2	Hepatic coma	19*	n=6, Alcoholic liver disease with altered mental status n=5, Chronic liver disease-induced cirrhosis, with hepatic encephalopathy n=4, Toxic/metabolic encephalopathy n=2, Normal liver-related laboratory tests with altered mental status and no reported hepatic abnormality n=1, Normal liver-related laboratory tests and no reported altered mental status or hepatic abnormality n=1, Systemic infection with altered mental status and abnormal liver-related laboratory tests
572.4	Hepatorenal syndrome	0	
572.8	Sequelae of liver disease	5*	n=2, Normal liver-related laboratory tests with no reported hepatic abnormality n=1, Alcoholic liver disease n=1, Hepatic cyst n=1, Systemic infection with abnormal liver-related laboratory tests
573.3	Toxic (non-infectious) hepatitis	12	n=3, Cholelithiasis n=3, Systemic infection with abnormal liver-related laboratory tests not meeting severe acute liver injury criteria n=2, Abnormal liver-related laboratory test of unclear etiology, not meeting severe acute liver injury criteria n=2, Drug-induced liver injury, not meeting severe acute liver injury criteria n=1, Normal liver-related laboratory tests with no reported hepatic abnormality n=1, Ischemic hepatopathy
573.8	Other specified liver disorder	29	n=15, Hepatic cyst n=5, Hemangioma n=4, Normal liver-related laboratory tests with no reported hepatic

ICD-9-CM Code	Code Description	No. with Primary Code	Condition
			abnormality n=2, Cancer in the liver n=2, Ischemic hepatopathy n=1, Hepatic fluid collection
V42.7	Liver transplant	0	

* One member had both a primary ICD-9-CM 572.2 and 572.8.

Table 5

Positive predictive values (with 95% confidence intervals) of hospital International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes and combinations for adjudicated cases of acute liver failure among 57 health plan members without pre-existing liver/biliary disease.

ICD-9-CM Code or Combination		No with Code(s)	No with ALF	Positive Predictive Value (95% Confidence Interval)
570	Acute/subacute hepatic necrosis	33	1	3.0% (0.08% – 15.8%)
572.2	Hepatic coma	22	1	4.6% (0.12% – 22.8%)
572.4	Hepatorenal syndrome	0	0	0%
572.8	Sequelae of liver disease; hepatic failure	11	1	9.1% (0.2% – 41.3%)
V42.7	Liver transplant	0	0	0%
Any ALF code		57	1	1.8% (0.04% – 9.4%)
Any ALF code + biopsy		5	1	20.0% (0.5% – 71.6%)
Any ALF code + E-code		3	0	0%

ALF=acute liver failure

Table 6

Positive predictive values (with 95% confidence intervals) of hospital International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes and combinations for adjudicated cases of severe acute liver injury among 46 health plan members with chronic liver disease.

ICD-9-CM Code or Combination		No with Code(s) *	No with SALI	Positive Predictive Value (95% Confidence Interval)
Any SALI code		46	19	41.3% (27.0% – 56.8%)
573.3	Toxic hepatitis	6	4	66.7% (22.3% – 95.7%)
573.8	Other liver disorder	6	2	33.3% (4.3% – 77.7%)
570	Acute/subacute hepatic necrosis	9	7	77.8% (40.0% – 97.2%)
572.2	Hepatic coma	33	14	42.4% (25.5% – 60.8%)
572.4	Hepatorenal syndrome	4	4	100% (39.8% – 100%)
572.8	Liver disease sequelae	15	9	60.0% (32.3% – 83.7%)
V42.7	Liver transplant	3	1	33.3% (0.8% – 90.6%)
573.3 + 570	Toxic hepatitis + hepatic necrosis	0	0	-
573.3 + 572.2	Toxic hepatitis + hepatic coma	4	3	75.0% (19.4% – 99.4%)
573.3 + 572.4	Toxic hepatitis + hepatorenal syndrome	0	0	-
573.3 + 572.8	Toxic hepatitis + liver disease sequelae	2	1	50.0% (1.3% – 98.7%)
573.3 + V42.7	Toxic hepatitis + liver transplant	0	0	-
573.8 + 570	Other liver disorder + hepatic necrosis	1	1	100% (2.5% – 100%)
573.8 + 572.2	Other liver disorder + hepatic coma	2	2	100% (15.8% – 100%)
573.8 + 572.4	Other liver disorder + hepatorenal syndrome	1	1	100% (2.5% – 100%)
573.8 + 572.8	Other liver disorder + liver disease sequelae	2	2	100% (15.8% – 100%)
573.8 + V42.7	Other liver disorder + liver transplant	2	1	50.0% (1.3% – 98.7%)
570 + 572.2	Hepatic necrosis + hepatic coma	5	4	80.0% (28.4% – 99.5%)
570 + 572.4	Hepatic necrosis + hepatorenal syndrome	1	1	100% (2.5% – 100%)
570 + 572.8	Hepatic necrosis + liver disease sequelae	5	5	100% (47.8% – 100%)
570 + V42.7	Hepatic necrosis + liver transplant	1	1	100% (2.5% – 100%)
573.3 + liver biopsy code	Toxic hepatitis + liver biopsy	0	0	-
573.8 + liver biopsy code	Other liver disorder + liver biopsy	1	0	0% (0.0% – 97.5%)
570 + liver biopsy code	Hepatic necrosis + liver biopsy	1	1	100% (2.5% – 100%)
572.8 + liver biopsy code	Liver disease sequelae + liver biopsy	1	0	0% (0.0% – 97.5%)
Any SALI code + liver biopsy		3	1	33.3% (0.8% – 90.6%)
Any SALI code + any E-code		1	0	0% (0.0% – 97.5%)
Any Two SALI codes		18	12	66.7% (41.0% – 86.7%)
570 + any other SALI code		6	5	83.3% (35.9% – 99.6%)
572.8 + any other SALI code		13	9	69.2% (38.6% – 90.9%)
573.3 + any other SALI code		4	3	75.0% (19.4% – 99.4%)
573.8 + any other SALI code		3	2	66.7% (9.4% – 100.0%)
(570 or 573.3) + any other SALI code		10	8	80.0% (44.4% – 97.5%)
(570 or 572.4) + any other SALI code		12	10	83.3% (51.6% – 97.9%)

SALI=severe acute liver injury

* This table includes codes from any position; therefore, more than one code may have been applied to a single member.

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Table 7

Conditions observed among 27 chronic liver disease health plan members who were adjudicated as not having had severe acute liver injury, by primary International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) code.

ICD-9-CM Code	Description Code	No. With Primary Code	Condition
570	Acute and subacute necrosis of liver	1	n=1, Hepatic encephalopathy with abnormal liver-related laboratory tests, not meeting severe acute liver injury criteria
572.2	Hepatic coma	19	n=15, Hepatic encephalopathy with abnormal liver-related laboratory tests, not meeting severe acute liver injury criteria n=3, Abnormal liver-related laboratory test of unclear etiology, not meeting severe acute liver injury criteria n=1, Alcoholic liver disease
572.4	Hepatorenal syndrome	0	
572.8	Sequelae of liver disease	2	n=1, Systemic infection with abnormal liver-related laboratory tests, not meeting severe acute liver injury criteria n=1, Drug hypersensitivity reaction, normal liver-related laboratory tests
573.3	Toxic (non-infectious) hepatitis	1	n=1, Abnormal liver-related laboratory test of unclear etiology, not meeting severe acute liver injury criteria
573.8	Other specified liver disorder	4	n=2, Abnormal liver-related laboratory test of unclear etiology, not meeting severe acute liver injury criteria n=2, Cancer in the liver
V42.7	Liver transplant	0	