PHARMALEX

Adjudicating Serious Liver Injury/Disease and Interstitial Lung Disease in Electronic Health Records or Claims Data

Arlene Tave[1], Earl Goehring, Jr.[1], Vibha Desai[2], Chuntao Wu[3], Rhonda Bohn[4], Nawar Shara[5], Sally Tamayo, CAPT, MC, USN[6], Nicholas Sicignano[7], Juhaeri Juhaeri[3], Judith K Jones[1]

[1]PharmaLex US Corp, Fairfax, VA, USA [2]HealthCore, Andover, MA, USA [3]Sanofi Pharmaceuticals, Inc., Bridgewater, NJ, USA [4]Bohn Epidemiology, Boston, MA, USA [5]Nawar Shara, Fairfax, VA, USA [6]Naval Medical Center, Portsmouth, VA, USA [7]Health ResearchTx, Trevose, PA, USA

CONFLICT OF INTEREST STATEMENT

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BACKGROUND

A retrospective cohort study in electronic health records (EHR) and claims data examined associations of dronedarone, and comparator anti-arrhythmics, with serious liver injury/disease (SLD) and interstitial lung disease (ILD). Complexity in identifying SLD and ILD was compounded by a paucity of diagnostic test results as well as presence of rule-out diagnoses in administrative records. Therefore, suspected outcomes were adjudicated in order to minimize misclassification and related bias in assessing drug - outcome associations.

OBJECTIVE

To review the methods that identified SLD and ILD events using EHR and claims data and the adjudication process.

METHODS

Data: The study used the US Department of Defense Military Health System database (DoD) with a total plan membership of 10 million patients and the HealthCore Integrated Research Database (HIRD) with a total plan membership of 45 million patients for the period from 20 July 2008 to 30 September 2014. New dronedarone users were matched by propensity score to comparators who were new users of amiodarone, sotalol and flecainide.

Outcome definitions: SLD and ILD outcomes were incident hospitalized cases. SLD was identified from inpatient ICD-9-CM diagnosis / procedure codes or CPT codes. [Table 1] ILD was identified from inpatient ICD-9-CM diagnosis codes. [Table 2]

Adjudicators: Two Independent Adjudication Panels (IAP) were convened to evaluate suspected cases of SLD and ILD on the basis of available patient diagnosis and procedure data. Each panel was comprised of three clinicians, each an established expert regarding the condition of interest. IAP members committed to abide by a committee charter, including specific procedures and rules for review and decision making. A physician member of the research team served as Chair of each IAP.

Adjudication documents: Adjudicators manually reviewed profiles consisting of up to one year of chronological patient history surrounding the suspected events in order to assess the validity of each as a true outcome event. The profiles were generated using SAS 9.2 and exported to Excel files. Color coding was used for ease of distinguishing diagnoses, procedures, prescription fills and in- versus out-patient events. [Figure 1] All records were de-identified, and panelists were blinded to patients' specific study drug exposures.

Adjudication process: Adjudicators independently reviewed each case and assigned the first inpatient occurrence of the outcome event their own determination of:

- "**Yes**"– Outcome is confirmed based on the information provided,
- "**No**"– No outcome event exists, or
- "**Indeterminate**" – More information needed to confirm / exclude the event as an outcome of interest.

Adjudicators submitted independent assessments of each case via standardized response forms, which were tallied across panel members by the research team. Unanimous independent assessments were considered final decisions. Divergent independent determinations triggered formal case review meetings, facilitated by the Chair, during which each adjudicator explained the reasoning behind their initial determination. The final decision for each suspected outcome event was based on a majority vote following the group discussions. Cases still lacking a majority opinion were assigned a final assessment of "Indeterminate."

Figure 2 depicts an ILD Patient Profile that was adjudicated as "Yes" ILD event. **Figure 3** depicts an SLD Patient Profile adjudicated as "No" SLD event.

Table 1. SLD ICD-9-CM and CPT Codes Definition

Group A codes – Usually indicate liver injury / disease – can appear anywhere in discharge diagnoses

ICD-9-CM Diagnosis Codes
- 570 Acute and subacute necrosis of liver
- 572.2 Hepatic coma
- 572.4 Hepatorenal syndrome
- V42.7 Liver replaced by transplant

ICD-9-CM Procedures Codes
- 50.5 Liver transplant
- 50.51 Auxiliary liver transplant
- 50.59 Other transplant of liver

CPT® Procedure Codes
- 47135 Liver allotransplantation; orthotopic, partial or whole
- 47136 Liver allotransplantation; heterotopic, partial or whole

Group B codes – Highly suspicious indicators of liver injury / disease – must be primary discharge diagnosis

ICD-9-CM Diagnosis Codes
- 277.4 Disorders of bilirubin excretion
- 571.5 Cirrhosis of liver without mention of alcohol
- 572.8 Other sequelae of chronic liver disease
- 573.0 Chronic passive congestion of liver
- 573.3 Hepatitis, unspecified
- 573.8 Other specified disorders of liver
- 573.9 Unspecified disorder of liver
- 782.4 Jaundice, unspecified
- 794.8 Non-specific abnormal results of liver function test

ICD-9-CM Procedure Codes
- 50.11 Closed (percutaneous) [needle] biopsy of liver
- 50.12 Open biopsy of liver
- 50.13 Transjugular liver biopsy
- 50.14 Laparoscopic liver biopsy
- 50.91 Percutaneous aspiration of liver

CPT® Procedure Codes
- 47000 Biopsy of liver, needle; percutaneous
- 47001 Biopsy of liver, needle; done at time of other major proc
- 47100 Biopsy of liver, wedge
- 78205 Liver imaging (SPECT)
- 78206 Liver imaging (SPECT); with vascular flow

Table 2. ILD ICD-9-CM Codes Definition

515	Post-inflammatory pulmonary fibrosis
516.3	Idiopathic fibrosing alveolitis
516.30	Idiopathic interstitial pneumonia, NOS (IIP)
516.31	Idiopathic pulmonary fibrosis (IPF)
516.32	Idiopathic non-specific interstitial pneumonitis (NSIP)
516.33	Acute interstitial pneumonitis (AIP)
516.34	Respiratory bronchiolitis interstitial lung disease (RB-ILD)
516.35	Idiopathic lymphoid interstitial pneumonia (LIP)
516.36	Cryptogenic organizing pneumonia (COP)
516.37	Desquamative interstitial pneumonia (DIP)
516.8	Oth spec alveolar and parietoalveolar pneumonopathies
516.9	Unspecified alveolar and parietoalveolar pneumonopathy

Figure 1. Patient Profile Layout

Header information - this information lists the Patient ID, gender, age at index date, Index Date, and date of suspected outcome event.

Patient ID #	Age:	Gender:	Index Date:	Event Date:	Date of Death:
De-identified ID#	Patient's age as of the Index Date	Male or Female	Date of Index Study Drug	First occurrence after the index date of a suspected outcome event	Date of Death

Patient's Medical History - medical/pharmacy encounter data is laid out in chronological order by the services rendered, oldest records appearing at the beginning and recent records at the bottom.

Line #	Time from Index	Date of Service/ Admit Date	Discharge Date	Code Type	Code	POS	Provider Specialty	Seq #	Code Description	Medication Name	Days Supply	QTY	Drug Formulation	Source	Record #

Column definitions:

Line #	Sequential line number beginning with "1"
Time from Index	Displays the number of days prior to the index date (e.g., -180, 180 days prior to the index date); and the number of days after the index date (e.g., 240)
Date of Service / Admit Date	Contains the date of service for medical and pharmacy transactions. For inpatient stays, this date is the admission date.
Discharge Date	For code type=DX, PX, and CPT this date is the inpatient discharge date for inpatient stays.
Code Type	Identifies the type of service transaction: **DX** = ICD-9-CM diagnosis code; **PX** = ICD-9-CM procedure code, CPT code, or HCPCS code; **RX** = Medication
Code	Actual code value reported for that transaction. For example, ICD-9-CM diagnosis/procedure codes, CPT codes, National Drug Codes (NDC)
POS	Place of Treatment (Services): Inpt (Hospital inpatient) indicates services that were performed at an inpatient hospital setting.
Provider Specialty	See Provider Specialty Codes Tabs for definitions
Seq #	The order in which the **diagnosis codes** appear on the claim/record form. 1=Primary, 2= secondary, etc…
Code Description	Corresponding description of the code.
Medication Name	Name of the medication dispensed
Days Supply	For RX records, this value is the Days Supply.
QTY	For RX records, this value is the quantity dispensed.
Drug Formulation	For RX records, this is the drug formulation.
Source	This is the source of the transaction. **CAPER**=Direct Care-ProfessionalServices; **SIDR**=Direct Care-Inpt Records; **TEDN**=Purchased Care-Professioinal Services; **TEDI**=Purchased Care-Inpt Records; **PDTS**=Pharmacy Data Transactions
Record #	This number identifies the services/encounters associated with a transaction. There may be more than one transaction on a single day.

Color Coding

Yellow highlight	Index study drugs will be highlighted in yellow.	Hospitalizations will be highlighted in gray.
Orange highlight	Non-index study drugs will be highlighted in orange.	Hospitalized events will be in bold red text & highlighted in gray.
Olive highlight	Skilled nursing facility stays will be highlighted in olive green.	Non-hospitalized outcome events will be in red text.

Figure 2. ILD Patient Profile

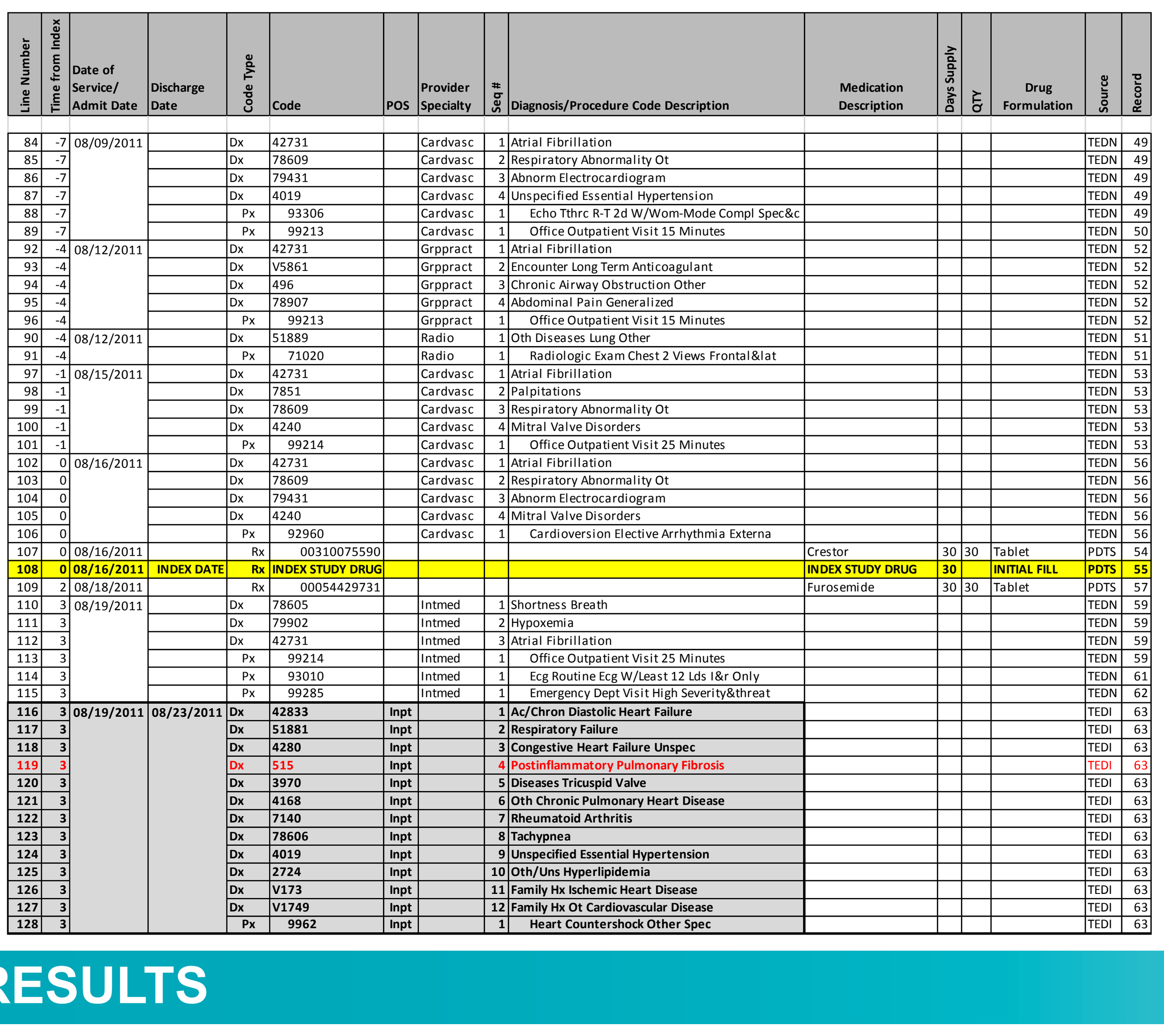
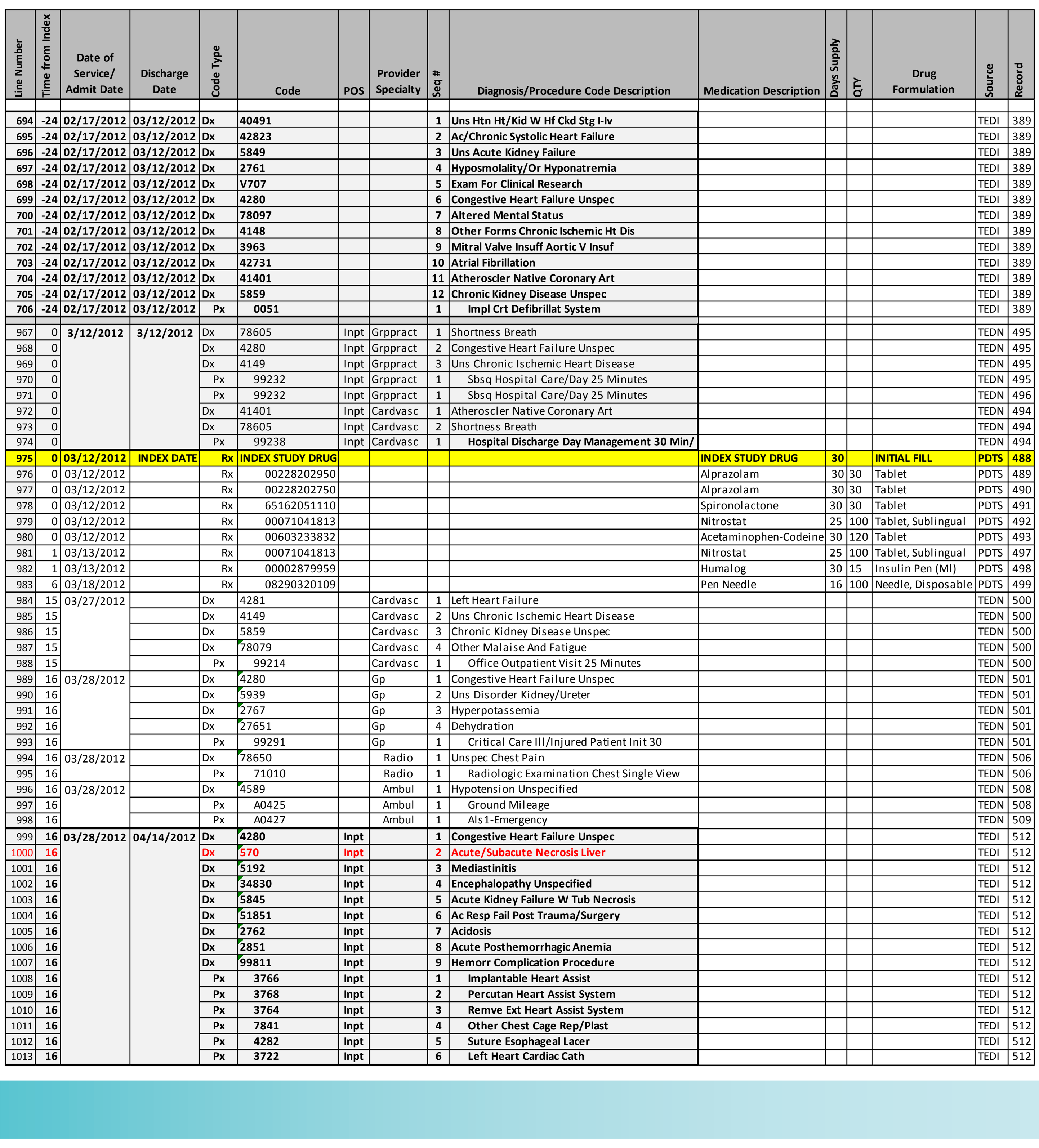


Figure 3. SLD Patient Profile



RESULTS

SLD: A total 48 suspected cases of SLD (32 DoD and 16 HIRD) were identified. Unanimous independent assessments confirmed 10 cases as "No" SLD events. Of the 38 cases submitted for group discussion, 34 were confirmed as "No" SLD events and four deemed "Indeterminate." None were confirmed as "Yes" SLD events. [Table 3]

Table 3. Suspected and Confirmed Cases of Serious Liver Injury/Disease Events: 20 July 2009 to 30 September 2014

SLD Adjudicated Cases	DoD		HIRD	
	N	%	N	%
Suspected SLD Outcomes	**32**	***100%***	**16**	***100%***
Cases with unanimous initial decisions	**9**	***28.1***	**1**	***6.25***
Yes (case confirmed)	0	*0.0*	0	*0.0*
No (not a case)	9	*28.1*	1	*6.25*
Cases requiring discussion	**23**	***71.9***	**15**	***93.8***
Results after discussion				
Yes (case confirmed)	0	*0.0*	0	*0.0*
No (not a case)	22	*95.6*	12	*80.0*
Indeterminate	1	*4.3*	3	*20.0*
Total Yes (case confirmed)	**0**	***0.0***	**0**	***0.0***

ILD: A total of 146 suspected cases of ILD (113 DoD and 33 HIRD) were identified. Independent assessments were unanimous for 53 cases (46 "Yes", 7 "No"). Of the 93 cases submitted for group review, 26 were confirmed as "Yes" ILD events, 50 were confirmed as "No" ILD events, and 17 "Indeterminate." The final total was 72 confirmed "Yes" ILD events. [Table 4]

Table 4. Suspected and Confirmed Cases of Interstitial Lung Disease Events: 20 July 2009 to 30 September 2014

ILD Adjudicated Cases	DoD		HIRD	
	N	%	N	%
Suspected ILD Outcomes	**113**	***100%***	**33**	***100%***
Cases with unanimous initial decisions	**31**	***27.4***	**22**	***66.7***
Yes (case confirmed)	27	*23.9*	19	*57.6*
No (not a case)	4	*3.5*	3	*9.1*
Cases requiring discussion	**82**	***72.6***	**11**	***33.3***
Results after discussion				
Yes (case confirmed)	25	*22.1*	1	*3.0*
No (not a case)	45	*39.8*	5	*15.2*
Indeterminate	12	*10.6*	5	*15.2*
Total Yes (case confirmed)	**52**	***46.0***	**20**	***60.6***

CONCLUSIONS

We identified suspected outcome cases from the EHR and claims databases using algorithms based on diagnoses, procedures and pharmaceutical dispensing records. Chronological listings from the digital patient records provided adjudicators with contextual longitudinal profiles of all features of suspect cases so the clinical experts could assess patient conditions.

SLD adjudicators confirmed zero SLD events. Their consensus was that liver function test results would have simplified their decision making. The ILD adjudicators confirmed 72 ILD events. Their consensus was that pulmonary function tests and pulmonary imaging results would have simplified their decision making. The SLD panel's decisions differed more than that of the ILD group despite established standards for assessment of serious liver injury / disease. Overall, while definitive adjudication of most cases was accomplished using only EHR and claims records, access to diagnostic test results might have simplified reconciliation of cases with divergent opinions.