

NEWYORK-PRESBYTERIAN/COLUMBIA UNIVERSITY MEDICAL CENTER – CLINICAL DATA WAREHOUSE DILI ALGORITHM IMPLEMENTATION **1**

Overview of implementation **1**

Baseline population **1**

Case Definition: **2**

- Acute liver injury diagnosis 2
- Administration of drugs 2
- Laboratory measurements 3
- Excluded diagnoses 3

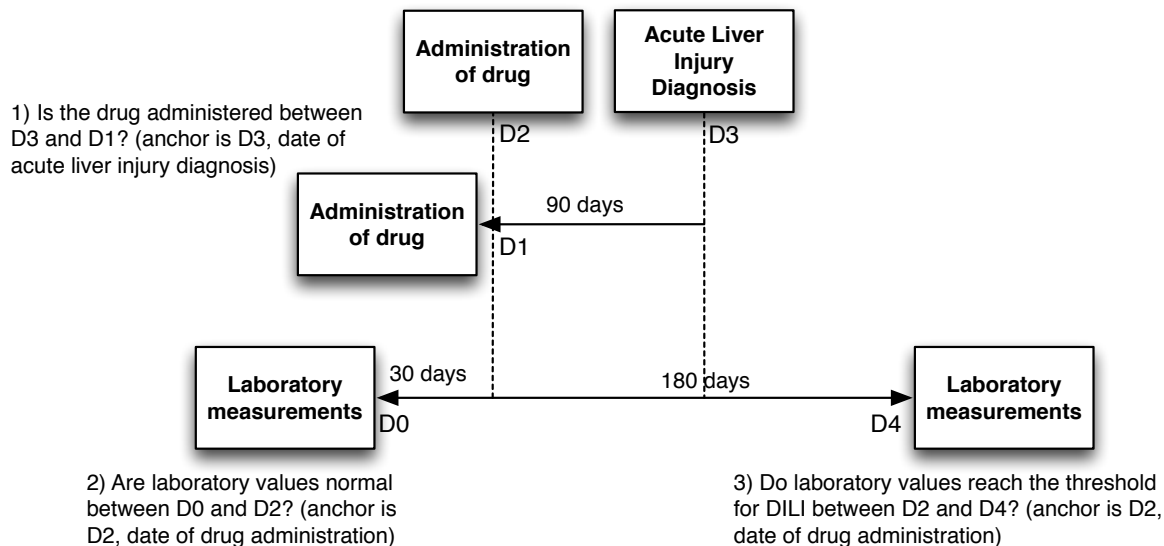
Controls Definition: **5**

Validation steps **6**

Results **6**

NewYork-Presbyterian/Columbia University Medical Center – Clinical Data Warehouse DILI algorithm Implementation

Overview of implementation



Baseline population

- Clinical data warehouse (CDW) population 2004-2010 (N=1,045,125)
- Other limits: Inpatients, > 1 years old

Case Definition:

Acute liver injury diagnosis

- Structured data (ICD-9 codes) and NLP (discharge summary notes only)
- Date of first instance of acute liver injury code, becomes D3.

Acute liver injury related diagnoses and procedures	ICD-9 codes
Disorders of bilirubin excretion	277.4
Acute and subacute necrosis of the liver	570*
Hepatic coma (hepatorenal syndrome)	572.2
Hepatorenal syndrome	572.4*
Other disorders of the liver, including chemical or drug induced	573*
Other specified disorders of biliary tract	576.8
Jaundice, unspecified, not of newborn	782.4
Hepatomegaly	789.1*
Nonspecific elevation of transaminase or lactic dehydrogenase levels	790.4*
Abnormal liver function test results	794.8*

Administration of drugs

- Structured data (ICD-9 codes) and NLP (discharge summary notes only)
 - For structured data, date of administration is estimated by date of a new medication order.
 - For NLP, date of administration is estimated by date mentioned in the discharge summary note.
- Date of drug administration within 90 days prior to D3, becomes D2.
- Limited to Drug Induced Liver Injury (DILIN) study protocol medication preparations: ciprofloxacin, clinafloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin, sparfloxacin, trovafloxacin, isoniazid, phenytoin, amoxicillin, valproic acid, nitrofurantoin, trimethoprim, minocycline.

Preparations	UMLS CUIs
Ciprofloxacin Preparations	C0282104
Clinafloxacin Preparations	C0070191
Levofloxacin Preparations	C0282386
Minocycline	C0026187
Moxifloxacin Preparations	C0536495
Norfloxacin Preparations	C0699473
Ofloxacin Preparations	C0699173
Sparfloxacin	C0052585
Trovafloxacin Preparations	C0379881
Isoniazid Preparations	C0022209
Phenytoin Preparations	C0305916
Amoxicillin Preparations	C0041058
Valproic Acid Preparations	C0304356
Nitrofurantoin Preparations	C0700187
Trimethoprim Preparations	C0041041

Laboratory measurements

- Upper limit of normal (ULN) is International Serious Adverse Events (iSAEC) study protocol specified.
 - ALP (Alkaline Phosphatase) ULN: 120 U/L (international units/liter)
 - ALT (Alanine Aminotransferase) ULN: 45 U/L (international units/liter)
 - Bilirubin (Indirect or Unconjugated) ULN: 40 umol/L (2.34 mg/dL)
- Threshold laboratory values for DILI
 - ALP $\geq 2x$ ULN
 - ALT $\geq 5x$ ULN
 - ALT $\geq 3x$ ULN AND Bilirubin $\geq 2x$ ULN
- All laboratory values should be below thresholds for DILI (normal) between D0 and D1.
- Date peak laboratory values between D2 and D4 reach threshold for DILI, becomes D5 (not shown)

Excluded diagnoses

- Structured data (ICD-9 codes) and NLP (discharge summary notes only)
 - Chronic liver disease; organ transplantation or liver operation; viral hepatitis; alcohol abuse/liver damage/toxic effects; overdose; sclerosing cholangitis; death.

Chronic liver disease diagnosis description	ICD-9 code
Alcoholic fatty liver	571.0
Alcoholic cirrhosis of liver	571.2
Alcoholic liver damage	571.3
Chronic hepatitis	571.40
Chronic persistent hepatitis	571.41
Other chronic hepatitis	571.49
Cirrhosis of liver without mention of alcohol	571.5
Biliary cirrhosis	571.6
Other chronic nonalcoholic liver disease	571.8
Autoimmune hepatitis	571.42
Unspecified Chronic Liver Disease without Mention of Alcohol	571.9

Organ transplantation and liver therapeutic operation descriptions	ICD-9 codes
Compl kidney transplant	996.81
Compl liver transplant	996.82
Compl heart transplant	996.83
Compl lung transplant	996.84
Complications of bone marrow transplant	996.85
Compl pancreas transplnt	996.86
Complications of other transplanted organ	996.89
Complication of intestine transplantation	996.87
Complications of transplanted organ	996.88
Complications of transplanted organ	996.80
Kidney replaced by transplant	V42.0
Heart replaced by transplant	V42.1
Heart valve replaced by transplant	V42.2
Skin replaced by transplant	V42.3
Bone replaced by transplant	V42.4
Cornea replaced by transplant	V42.5
Lung replaced by transplant	V42.6
Liver replaced by transplant	V42.7
Other specified organ or tissue replaced by transplant	V42.89
Bone marrow replaced by transplant	V42.81
Peripheral stem cells replaced by transplant	V42.82
Pancreas replaced by transplant	V42.83
Intestines replaced by transplantation	V42.84

Organ transplantation and liver therapeutic operation descriptions	ICD-9 codes
Unspecified organ or tissue replaced by transplant	V42.9
Allogeneic bone marrow transplant with purging	41.02
Allogeneic bone marrow transplant without purging	41.03
Cord blood stem cell transplant	41.06
Autologous hematopoietic stem cell transplant with purging	41.07
Allogeneic hematopoietic stem cell transplant	41.08
Autologous bone marrow transplant with purging	41.09
Autologous bone marrow transplant without purging	41.01
Autologous hematopoietic stem cell transplant without purging	41.04
Allogeneic hematopoietic stem cell transplant without purging	41.05
Bone marrow transplant	41.00
Unilat lung transplant	33.51
Bilateral lung transplantation	33.52
Lung transplantation	33.50
Reimplantation of pancreatic tissue	52.81
Homotransplant of pancreas	52.82
Heterotransplant of pancreas	52.83
Autotransplantation of cells of islets of langerhans	52.84
Allotransplantation of cells of islets of langerhans	52.85
Transplantation of cells of islets of langerhans	52.86
Operations on pancreas: pancreatic transplant	52.80
Hepatotomy	50.0
Marsupialization of lesion of liver	50.21
Partial hepatectomy	50.22
Lobectomy of liver	50.3
Total hepatectomy	50.4
Auxiliary liver transplant	50.51
Other transplant of liver	50.59
Closure of laceration of liver	50.61
Other repair of liver	50.69
Percutaneous aspiration of liver	50.91
Extracorporeal hepatic assistance	50.92
Localized perfusion of liver	50.93
Other injection of therapeutic substance into liver	50.94
Unlisted proc	50.99
Open ablation of liver lesion or tissue	50.23
Percutaneous ablation of liver lesion or tissue	50.24
Laparoscopic ablation of liver lesion or tissue	50.25
Other and unspecified ablation of liver lesion or tissue	50.26
Other destruction of lesion of liver	50.29

Viral Hepatitis Descriptions	ICD-9 codes
Unspecified Viral Hepatitis Without Mention Of Hepatic Coma	070.9
Unspecified Viral Hepatitis With Hepatic Coma	070.6
Other Specified Viral Hepatitis With Hepatic Coma	070.49
Other Specified Viral Hepatitis Without Mention Of Hepatic Coma	070.59
Viral Hepatitis A Without Mention Of Hepatic Coma	070.1
Viral Hepatitis A With Hepatic Coma	070.0
Viral Hepatitis B Without Mention Of Hepatic Coma, Acute Or Unspecified	070.30
Viral Hepatitis B With Hepatic Coma, Acute Or Unspecified	070.20
Viral Hepatitis B With Hepatic Coma, Acute Or Unspecified, With Hepatitis Delta	070.21
Viral Hepatitis B, Acute Or Unspecified, With Hepatitis Delta	070.31
Acute Hepatitis C With Hepatic Coma	070.41
Hepatitis Delta Without Mention Of Active Hepatitis B Disease With Hepatic Coma	070.42
Hepatitis E With Hepatic Coma	070.43
Unspecified Viral Hepatitis C Without Hepatic Coma	070.70
Hepatitis In Viral Diseases Classified Elsewhere	573.1
Carrier Or Suspected Carrier Of Viral Hepatitis	V02.60

Viral Hepatitis Descriptions	ICD-9 codes
Need For Prophylactic Vaccination And Inoculation Against Viral Hepatitis	V05.3
Chronic Viral Hepatitis B Without Mention Of Hepatic Coma Or Hepatitis Delta	070.32
Viral Hepatitis B With Hepatic Coma, Chronic, Without Mention Of Hepatitis Delta	070.22
Viral Hepatitis B With Hepatic Coma, Chronic, With Hepatitis Delta	070.23
Viral Hepatitis B Without Mention Of Hepatic Coma, Chronic, With Hepatitis Delta	070.33
Other Icd9 Viral Hepatitis Carrier	V02.69
Unspecified Viral Hepatitis C With Hepatic Coma	070.71

Alcohol Abuse, Liver Damage, and Toxic Effects Descriptions	ICD-9 codes
Alcohol Abuse, Unspecified Drinking Behavior	305.00
Alcohol Abuse, Continuous Drinking Behavior	305.01
Alcohol Abuse, Episodic Drinking Behavior	305.02
Alcohol Abuse, In Remission	305.03
Alcoholic fatty liver	571.0
Acute alcoholic hepatitis	571.1
Alcohol cirrhosis liver	571.2
Alcohol liver damage	571.3
Toxic effect of ethyl alcohol	980.0
Toxic effect of methyl alcohol	980.1
Toxic effect of isopropyl alcohol	980.2
Toxic effect fusel oil	980.3
Toxic effect of other specified alcohols	980.8
Toxic effect of unspecified alcohol	980.9

Overdose diagnosis descriptions	ICD-9 codes
Suicide and self-inflicted poisoning by solid and liquid substances	E950.9
Suicide/self-inflicted poisoning by analgesics, antipyretics, and antirheumatics	E950.0
Suicide and self-inflicted poisoning by barbiturates	E950.1
Suicide and self-inflicted poisoning by other sedatives and hypnotics	E950.2
Suicide/self-inflicted poisoning by tranquilizers and other psychotropic agents	E950.3
Suicide/self-inflicted poisoning by other drugs and medicinal substances	E950.4
Suicide and self-inflicted poisoning by unspecified drug or medicinal substance	E950.5
Suicide/self-inflicted poisoning by agricultural/horticultural chemical	E950.6
Suicide and self-inflicted poisoning by corrosive and caustic substances	E950.7
Suicide and self-inflicted poisoning by arsenic and its compounds	E950.8
Suicide and self-inflicted injury by other specified means	E958.8
Late eff of self-injury	E959.
Suicide and self-inflicted injury by unspecified means	E958.9

Sclerosing cholangitis description	ICD-9 code
Cholangitis	576.1

Death diagnosis descriptions	ICD-9 codes
Instantaneous death	798.1
Death occurring in less than 24 hours from onset of symptoms	798.2
Unattended death	798.9

Controls Definition:

- No acute liver injury codes
- EVER taken ANY medication
- No exclusion codes (10 excluded diagnoses: cancer, gallbladder disease, pancreatic disease, heart failure, alcohol abuse, HIV infection, rheumatoid arthritis, sarcoidosis, systemic lupus, viral hepatitis)

Validation steps

- Cases
 - (a) First-pass visualization of temporal data to assign preliminary status (TP, FP or unknown); (b) Manual chart review to confirm suspected TPs and assign TP/FP for unknown status from previous step.
 - 4 reviewers (2 clinical and 2 non-clinical reviewers)
 - Consensus, determination by 5th clinical reviewer for questionable results
- Controls
 - Classify as TP if manual review of liver enzymes show no instances crossing thresholds for DILI. Classify as TP, if cross the thresholds for DILI but no mention of DILI-related terms in clinical notes.
 - 1 non-clinical reviewer
 - Consensus, determination by 2nd clinical reviewer for questionable results

Results

- Cases:
 - 37 algorithm-selected DILI cases
 - 12 out of 37 are true positives
 - 25 out of 37 are false positives
- Controls:
 - 50 controls randomly selected from a pool of 279851 patients satisfying our controls definition
 - 50 out of 50 are true controls
 - No false negative and no false positive controls