PRO-EURO DILI NETWORK

Prospective European Drug-induced Liver Injury Network

the Cost Action 17112
1st Training Course, March 14-15, 2019
Malaga, Spain

New approaches to DILI identification using electronic medical records

Ayako Suzuki, MD, PhD, MSc
Gastroenterology, Duke University
Gastroenterology, Durham VA Medical Center

Disclosure

- Partly funded by:
  - VA HSR&D
  - National Center for Toxicological Research
  - Division of Gastroenterology, Duke University
- Supported by:
  - Durham VA Medical Center
  - Durham Center of Innovation to Accelerate Discovery and Practice Transformation (ADAPT) (CIN 13-410) at the Durham VA Health Care System
- Consultancy: Pfizer

Outline

- Introduction
  - Health impact of drug-induced liver injury (DILI)
  - Knowledge gaps in DILI
  - Methodological challenges
- Advantages in big data analysis
- DILI identification using electronic medical Records (EMR)
  - Published algorithms and challenges
  - Experience using VA EMR
- Summary

Kenrokuen, Kanazawa, Japan

Introduction

Health impact of DILI

Knowledge gaps

Methodological challenges

Tiered rice fields, Yanagida, Ishikawa, Japan

DILI affects patient safety

- Incidence: 15 to 30 per 100,000 inhabitants
- Up to 16% of patients require hospitalization and develop significant comorbidities
- ~10% of patients who develop clinically significant DILI suffer acute liver failure
- Without prompt drug cessation, 11- 17% of DILI cases may progress to chronic liver disease and even cirrhosis
- *DILI negatively affects clinical outcomes and medical resources, yet we can potentially intervene*

Gastroenterology 2005;129:512; Hepatology 2002;36:451; Gastroenterology 2013;144:1419
Aliment Pharmacol Ther 2010;31:1200; Hepatology 2005;42:481-9; Hepatology 2006;44:1581;
Gastroenterology 2015;148:1340

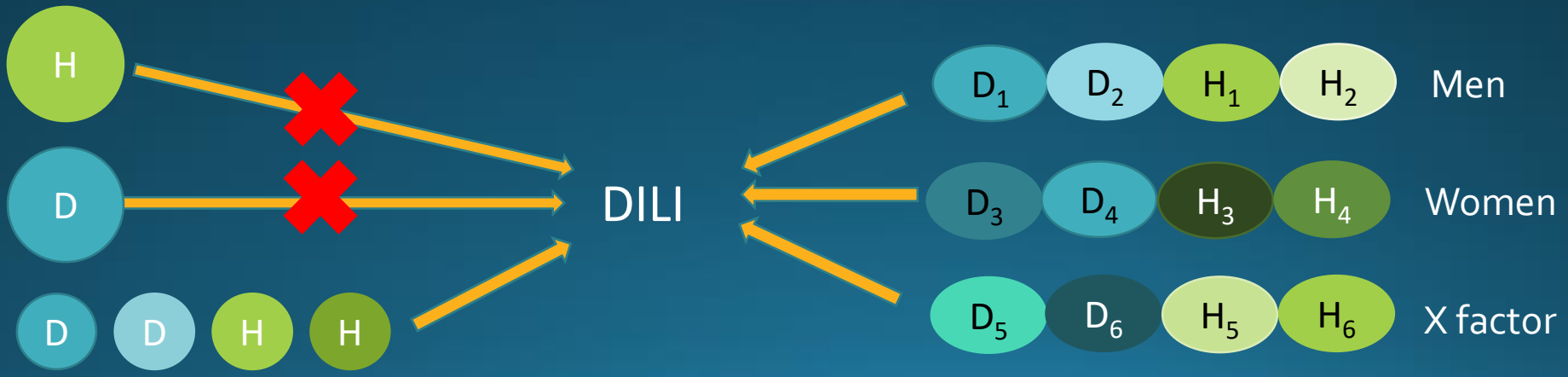
Current knowledge gaps in DILI

- DILI prediction is still challenging
- Limited contribution of individual genetic factors (i.e., HLA)
- Drug-specific DILI incidence
- Age, sex/gender, race/ethnicity – risk disparities
- Drug-host interplay in DILI risk and phenotypes
- Impact of co-medications on DILI risk
- Impact of comorbidities on DILI risk

Pharmacogenet Genomics 2012;22:784; Gastroenterology 2017;152:1078

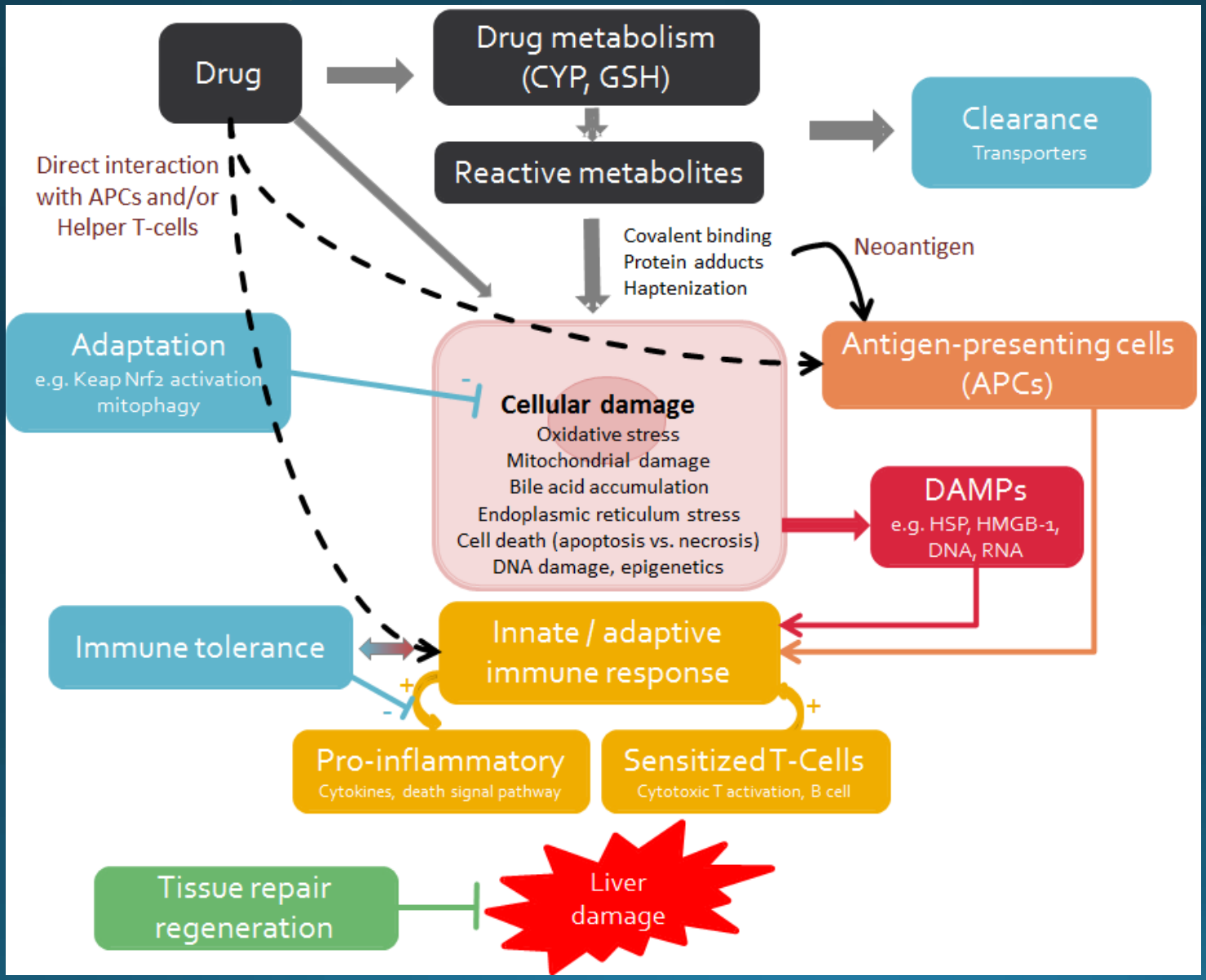
Methodological Challenges

- Well-characterized DILI cases at DILI registries
  - <2000 cases
  - no controls
- Multifactorial risks of DILI
- Multiple algorithms – explanatory/causal pluralism



D: drug factor, H: host factors

Multi-phasic DILI mechanism



J Hep 2015 63 (2): 503

Advantages in big data analysis

How should we integrate big data analysis in DILI research?

Kanazawa Castle, Kanazawa, Japan

Advantages in big data analysis

- Discover previously invisible associations and insights
- A quick tool for translating hypothesis from animals to humans and vise versa
- Time- and cost-efficient hypothesis generation
- Complements clinical DILI investigation

Influence of Medication on Injury and Repair

	Injury	Repair	
Statins	⇓	⇑	⇓ *Protective*
Adrenergic blockers	⇓	⇑	
Fibrates	⇓	-	
ACEI/AT II B	-	⇑	
Sympathetic stimulants	⇑	⇓	⇑ *Detrimental*
Anti-platelet agents	⇓	⇓	? *Effect ?*
SSRIs	⇓?	⇓?	
NSAIDs	⇓ ⇑	⇓ ⇑	

Clin Gastroenterol Hepatol 2009;7:882

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2009;7:882–888

ORIGINAL ARTICLES—LIVER, PANCREAS, AND BILIARY TRACT

Co-medications That Modulate Liver Injury and Repair Influence Clinical Outcome of Acetaminophen-Associated Liver Injury

AYAKO SUZUKI,* NANCY YUEN,‡ JOHN WALSH,§ JULIE PAPAY,‡ CHRISTINE M. HUNT,‡ and ANNA MAE DIEHL*

*Gastroenterology, Duke University, Durham, North Carolina; ‡Clinical Safety, and §Drug Metabolism and Pharmacokinetics, GlaxoSmithKline, Research Triangle Park, North Carolina

Table 4. Interaction Between Age, Gender, or Comedication and Fatal Cases of APAP-Associated Liver Injury

			P values for interaction terms	
	Adjusted OR[a]	*P* value	Age	Gender
Age	1.0 [1.0, 1.0]	.563	—	.0079
Gender	0.9 [0.8, 1.0]	.049	.0079	—
Ethanol use	2.5 [1.9, 3.4]	<.001	ns	ns
Comedication use				
Statins	0.5 [0.4, 0.7]	<.001	ns	ns
Fibrates	0.8 [0.3, 1.5]	.437	ns	.010
NSAIDs	0.7 [0.6, 0.8]	<.001	ns	.001
Adrenergic blockers				
Alpha blockers	0.9 [0.5, 1.4]	.592	ns	ns
Beta blockers	0.7 [0.6, 1.0]	.023	ns	ns
Sympathetic stimulants	1.4 [1.1, 1.8]	.003	ns	.081
ACEI/ATII blockers	0.7 [0.6, 1.0]	.026	.040	ns
SSRIs	0.9 [0.6, 1.1]	.259	ns	ns
Antiplatelet agents	0.6 [0.3, 1.0]	.032	ns	ns

ns, not significant.
[a]Adjusted for age and gender.

Table 5. Multiple Logistic Regression Models in Males and Females

	Females		Males	
	Adjusted OR	*P* value	Adjusted OR	*P* value
Age, for a 10-year interval	—	—	1.1 [1.0, 1.1]	.032
Ethanol use	2.6 [1.7, 3.8]	<.001	2.2 [1.4, 3.3]	.0002
Co-medication use				
Statins	0.5 [0.4, 0.8]	.003	0.6 [0.4, 0.9]	.023
Fibrates	0.3 [0.1, 0.9]	.024	—	—
NSAIDs	0.6 [0.5, 0.7]	<.001	—	—
Sympathetic stimulants	—	—	1.8 [1.3, 2.6]	.0007

Regulatory Toxicology and Pharmacology 72 (2015) 481–490

Contents lists available at ScienceDirect

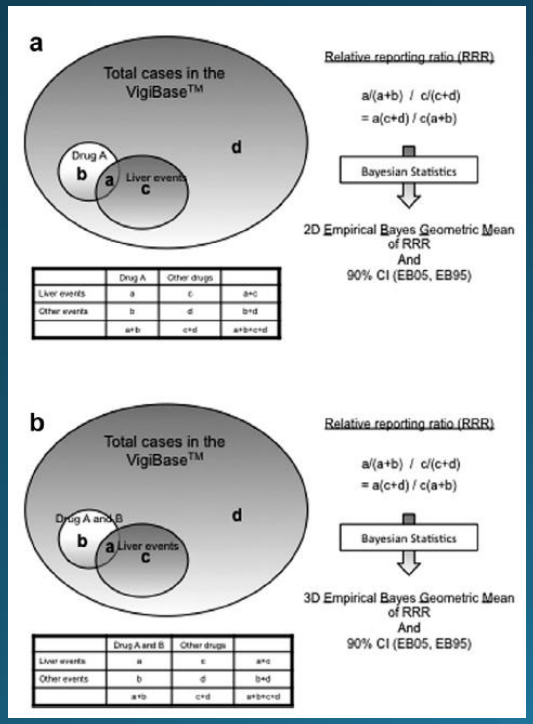
Regulatory Toxicology and Pharmacology

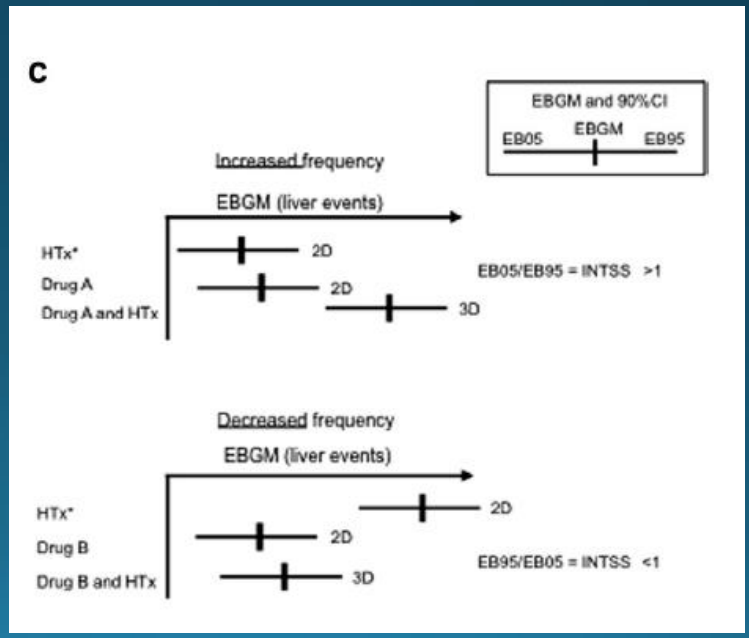
journal homepage: www.elsevier.com/locate/yrtph

Comedications alter drug-induced liver injury reporting frequency: Data mining in the WHO VigiBase™

Ayako Suzuki [a], Nancy A. Yuen [b], Katarina Ilic [c], Richard T. Miller [d], Melinda J. Reese [e], H. Roger Brown [d], Jeffrey I. Ambroso [d], J. Gregory Falls [d], Christine M. Hunt [f,*]

[a] Gastroenterology, Central Arkansas Veterans Healthcare System and Gastroenterology and Hepatology, Univ. of Arkansas for Med. Sciences, Little Rock, AR, United States
[b] Clinical Safety, GlaxoSmithKline, Research Triangle Park, NC, United States
[c] Pharmacovigilance and Risk Management, Raptor Pharmaceuticals, CA, United States
[d] Safety Assessment, GlaxoSmithKline, Research Triangle Park, NC, United States
[e] Drug Metabolism and Pharmacokinetics, GlaxoSmithKline, Research Triangle Park, NC, United States
[f] Gastroenterology, Duke University Medical Center and Durham Veterans Administration Medical Center, Durham, NC, United States





Drug classes that significantly influence DILI reporting frequency

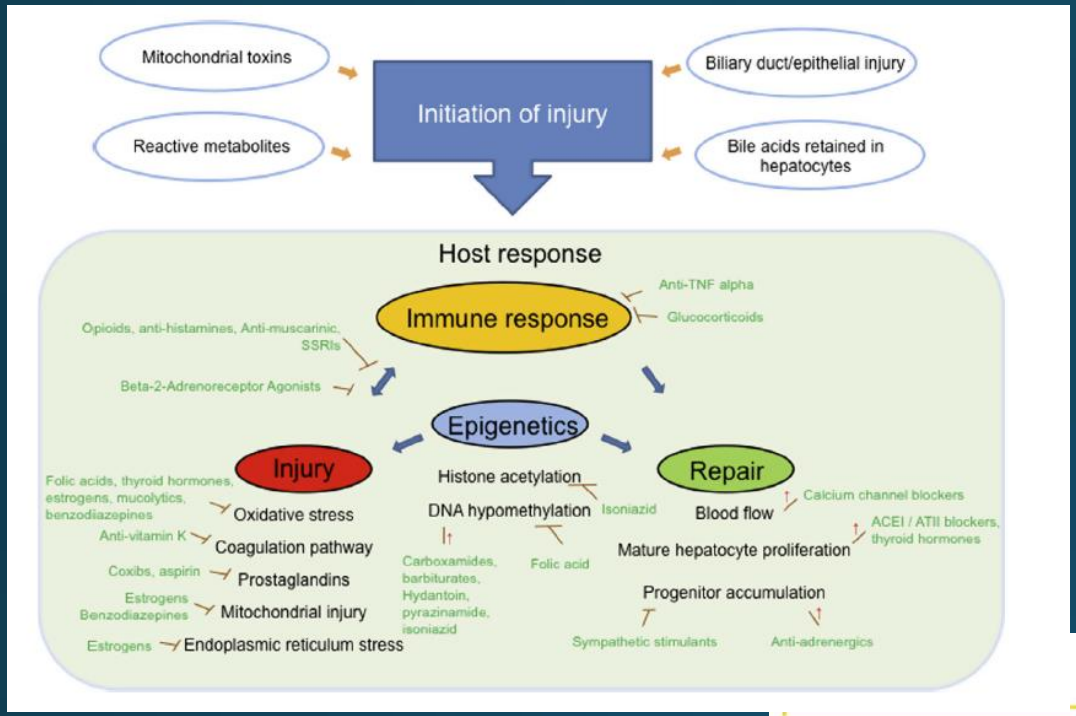
Table 3
Impact of 48 drug classes (ATC4) on liver events co-reported with acetaminophen, isoniazid, valproic acid, and amoxicillin/clavulanic acid in unadjusted and adjusted analyses.

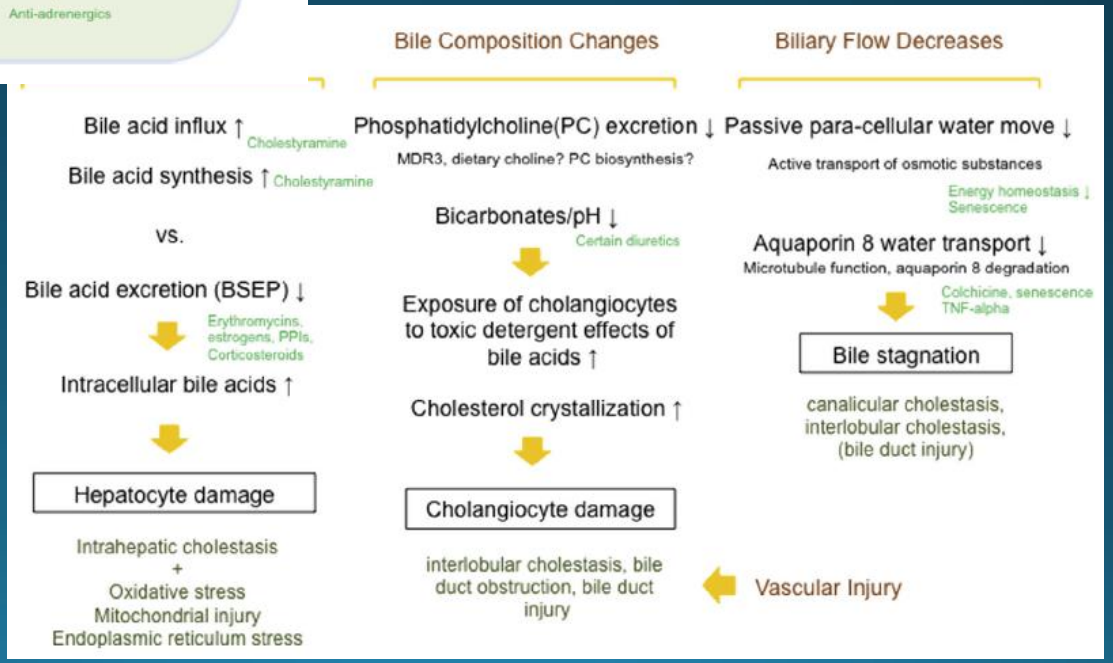
Drug classes (ATC4)	Non-systemic use	Unadjusted impact on 4 DILI				Adjusted impact on 4 DILI			
		APAP	INH	VA	AMX	APAP	INH	VA	AMX
Tumor Necrosis Factor Alpha (Tnf-) Inhibitors		dec	dec			dec	dec	dec	dec
Other Opioids		dec		dec	dec	dec	dec	dec	dec
Folic Acid And Derivatives		dec	dec	dec		dec	dec	dec	dec
Natural Opium Alkaloids			dec	dec	dec	dec	dec	dec	dec
Selective Beta-2-Adrenoreceptor Agonists		dec		dec		dec	dec	dec	
Other Antihistamines For Systemic Use		dec	dec	dec		dec	dec	dec	
Glucocorticoids		dec	dec			dec	dec	dec	
Salicylic Acid And Derivatives		dec	dec	dec		dec	dec	dec	
Sulfonamides, Plain		dec	dec	dec	dec	dec	dec	dec	
Beta Blocking Agents, Selective		dec	dec	dec		dec	dec	dec	
Thyroid Hormones		dec	dec	dec		dec	dec	dec	
Adrenergics And Oth.Drugs For Obstruct.Airway Dis.	*	dec		dec	inc	dec	dec	dec	
Mucolytics		dec			dec	dec	dec		dec
Comb.Sulfonamides & Trimethoprim Incl. Derivatives		dec	dec		dec	dec	dec		
Dihydropyridine Derivatives		dec	dec			dec	dec		
Coxibs		dec		dec	dec	dec		dec	dec
Vitamin K Antagonists		dec		dec	dec	dec		dec	dec
Alpha-Adrenoreceptor Antagonists		dec		dec		dec		dec	
ACE Inhibitors, Plain		dec		dec		dec		dec	
Natural And Semisynthetic Estrogens, Plain		dec		dec	inc	dec		dec	
Urinary Antispasmodics		dec		dec		dec		dec	
Softeners, Emollients		dec		dec		dec		dec	
Penicillins With Extended Spectrum		dec			dec	dec			dec
Benzodiazepine Derivatives			dec	dec	dec		dec	dec	dec
Proton Pump Inhibitors			dec	dec	inc		dec	dec	inc
Nucleosides And Nucleotides Excl Rev.Transcr.Inhibitor			dec		dec		dec		dec
Third-Generation Cephalosporins			dec		dec		dec		dec
Selective Serotonin Reuptake Inhibitors			dec	dec	dec			dec	dec
H2-Receptor Antagonists		dec		dec				dec	
Phenothiazines With Piperazine Structure		dec		dec				dec	
Non-Selective Monoamine Reuptake Inhibitors				dec	dec			dec	
Carboxamide Derivatives		inc	inc	inc		inc	inc	inc	
Halogenated Hydrocarbons		inc			inc	inc	inc		inc
Other Drugs For Treatment Of Tuberculosis		inc	inc			inc	inc		
Bile Acid Sequestrants					inc	inc		inc	inc
Hydantoin Derivatives		inc		inc		inc		inc	
Barbiturates, Plain		inc	inc	inc		inc		inc	
Macrolides		inc			inc	inc			inc
Bile Acid Preparations		inc			inc	inc			inc
Barbiturates And Derivatives		inc		inc				inc	
High-Ceiling Diuretics And Potassium-Sparing Agent					inc				inc
Beta-Lactamase Resistant Penicillins					inc				inc
Thiazides, Plain					inc				inc
Corticosteroids	*				inc				inc
Second-Generation Cephalosporins					inc				
Expectorants					inc				
Other General Anesthetics		inc		inc					

APAP, acetaminophen; INH, isoniazid; VA, valproic acid; AMX, amoxicillin/clavulanic acid. The results from unadjusted (3D EBGM analysis) and adjusted analysis (logistic regression models including age, gender, 47 drug classes, and the 4 key drugs) are summarized. 'dec' and green indicate negative interaction (i.e., decreased reporting frequency in combination with a drug class) while 'inc' and red indicate positive interaction (i.e., increased reporting frequency in combination with a drug class). 'Blank' and beige indicate no significant interaction.

Regul Toxicol Pharmacol 2015 72(3): 481

Theoretical framework of DILI mechanism





Regul Toxicol Pharmacol 2015 72(3): 481

Regulatory Toxicology and Pharmacology 70 (2014) 519–526

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Age-related differences in reporting of drug-associated liver injury: Data-mining of WHO Safety Report Database

Christine M. Hunt [a,b,*], Nancy A. Yuen [c], Heide A. Stirnadel-Farrant [d], Ayako Suzuki [e,f]

[a] Division of Gastroenterology, Duke University Medical Center, Durham, NC, United States
[b] Durham Veterans Administration Medical Center, Durham, NC, United States
[c] Global Clinical Safety and Pharmacovigilance, GlaxoSmithKline, Research Triangle Park, NC, United States
[d] Worldwide Epidemiology, GlaxoSmithKline, Stockley Park, UK
[e] Division of Gastroenterology, University of Arkansas for Medical Sciences, Little Rock, AR, United States
[f] Division of Gastroenterology, Central Arkansas Veterans Healthcare System, Little Rock, AR, United States

Regulatory Toxicology and Pharmacology 94 (2018) 101–107

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Interplay of gender, age and drug properties on reporting frequency of drug-induced liver injury

Nayana George[a], Minjun Chen[b], Nancy Yuen[c], Christine M. Hunt[d,e], Ayako Suzuki[d,e,*]

[a] Department of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, USA
[b] Division of Bioinformatics and Biostatistics, The FDA's National Center for Toxicological Research, Jefferson, AR, USA
[c] Global Patient Safety, UCB BioSciences Inc., Raleigh, NC, USA
[d] Department of Medicine, Duke University, Durham, NC, USA
[e] Department of Medicine, Durham VA Medical Center, Durham, NC, USA

Why EMR data?

- Provides controls and cases
  - Risk factor analysis
  - Age, sex/gender, racial differences in drug-specific DILI
- Non-genetic risk factors
  - Drug exposure (duration, dose)
  - Co-medications
  - Comorbidities
- Limitations in existing data source (i.e., AERS)
- Pharmacovigilance without counting on voluntary reporting
- Automated EMR alerting system

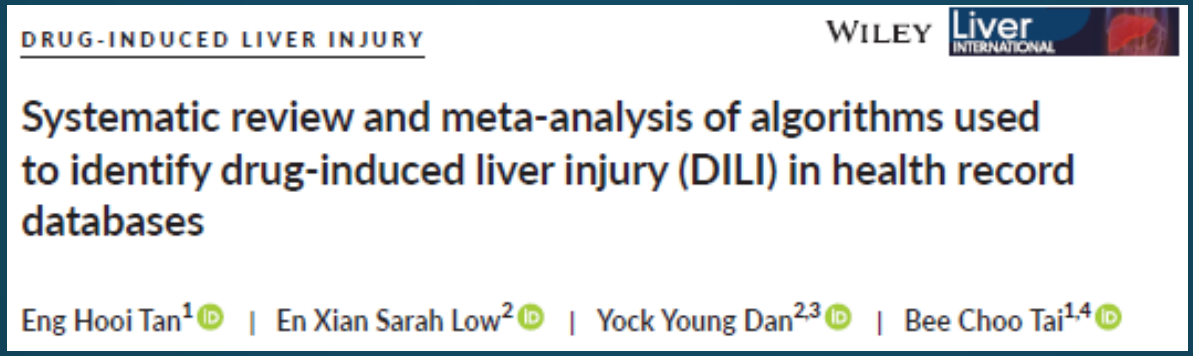
DILI identification using electronic medical Records (EMR)

Published algorithms and challenges

Asanogawa, Kanazawa, Japan

Strategies for developing DILI phenotype algorithm

- ICD-9/ICD-10 codes
- Laboratory data
- ICD-9/ICD-10 codes and Laboratory data
- With/without exclusion of alternative causes
- Text mining for DILI diagnosis



- Out of 420 citations (1993-2016), 84 articles were reviewed for eligibility, 29 were selected for detailed review, and 25 studies met the study criteria
- Most of the studies from the US or Europe
- 62% adult population only
- 55% targeted specific study drugs
- 86% used medical record review for confirmation
- 55% relied on expert opinion
- 34% used standardized causality assessment tools (e.g., RUCAM)
- 48% used laboratory data only (CIOMS was used in 48%)
- ICD-9/10 alone or with lab data: 3-15 ICD-9 codes or 19-25 Oxford Medical Information System (OXMIS)

Low performance of published DILI phenotype algorithms

Pooled PPV =14.6% 95% CI [10.7-18.9]

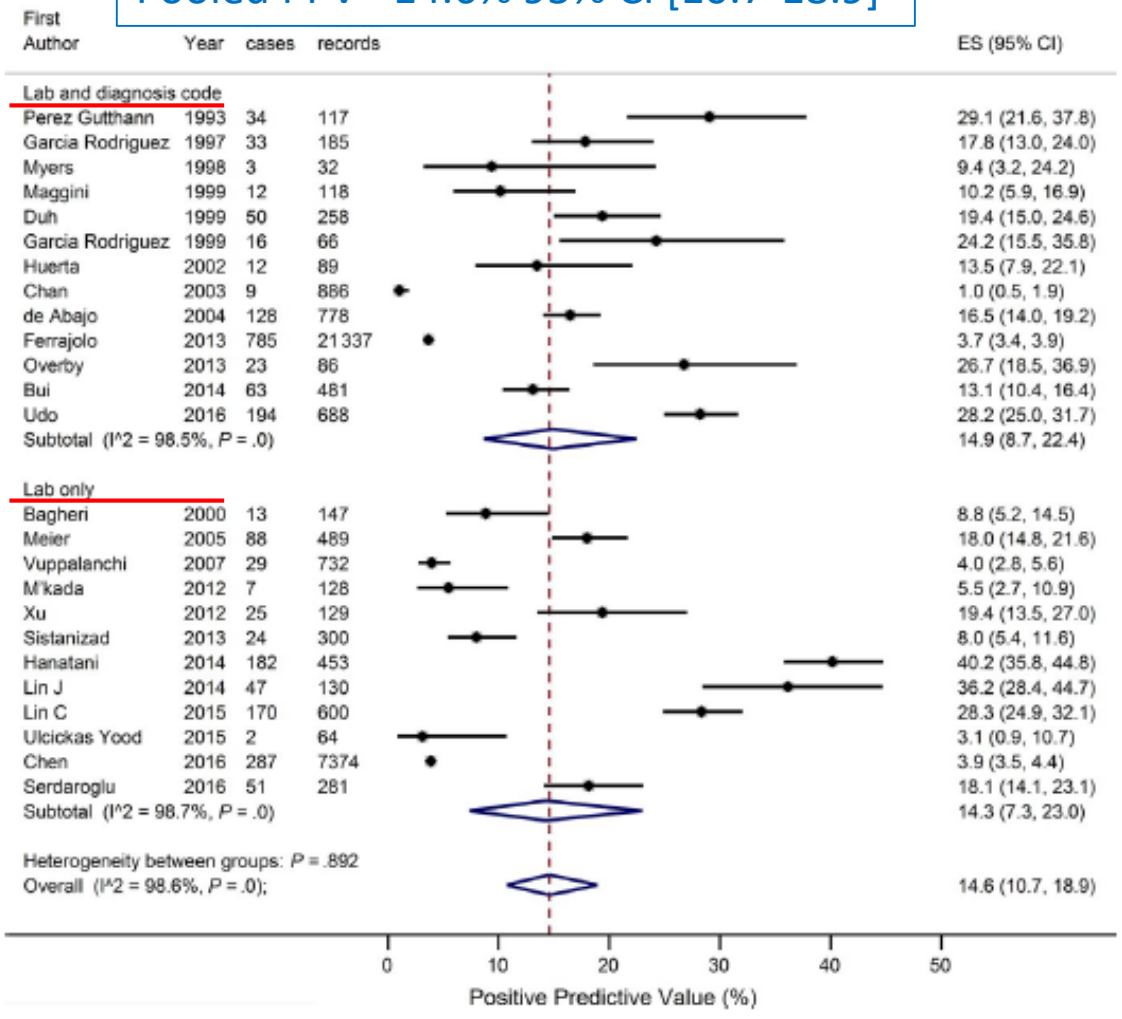


FIGURE 3 Forest plot of positive predictive values of detection algorithms by laboratory and/or diagnosis code criteria (n = 25)*. *Study by Udo et al had various algorithms ranging from 22% to 48%. However, data for unique number of patients per algorithm is unavailable, hence the overall number of DILI cases over the number of unique medical records reviewed was reported

Liver Int 2018;38:742

Pre-specified study drugs improved the performance

PPV =17.7% vs. 11.6% (p=0.053)

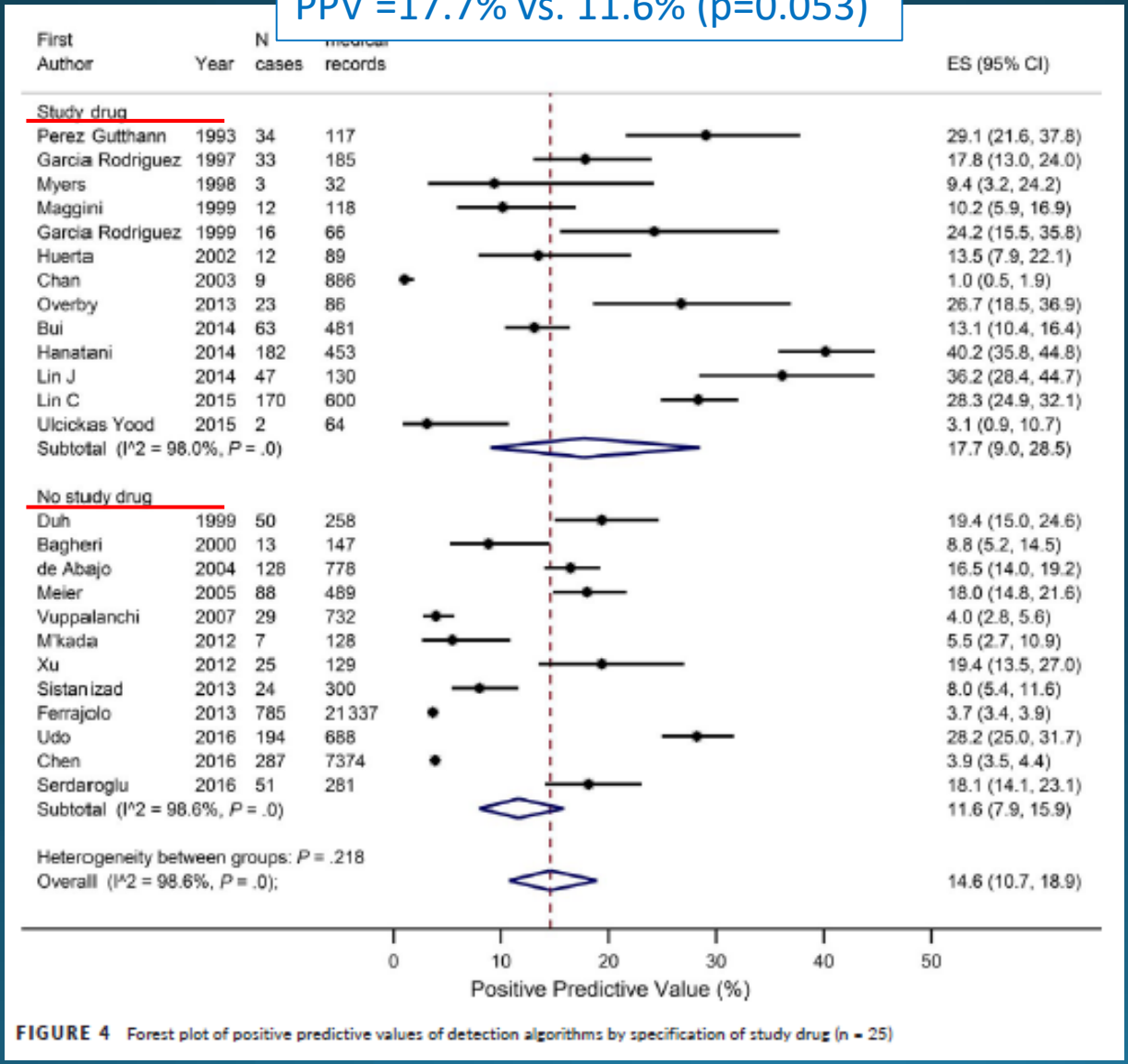


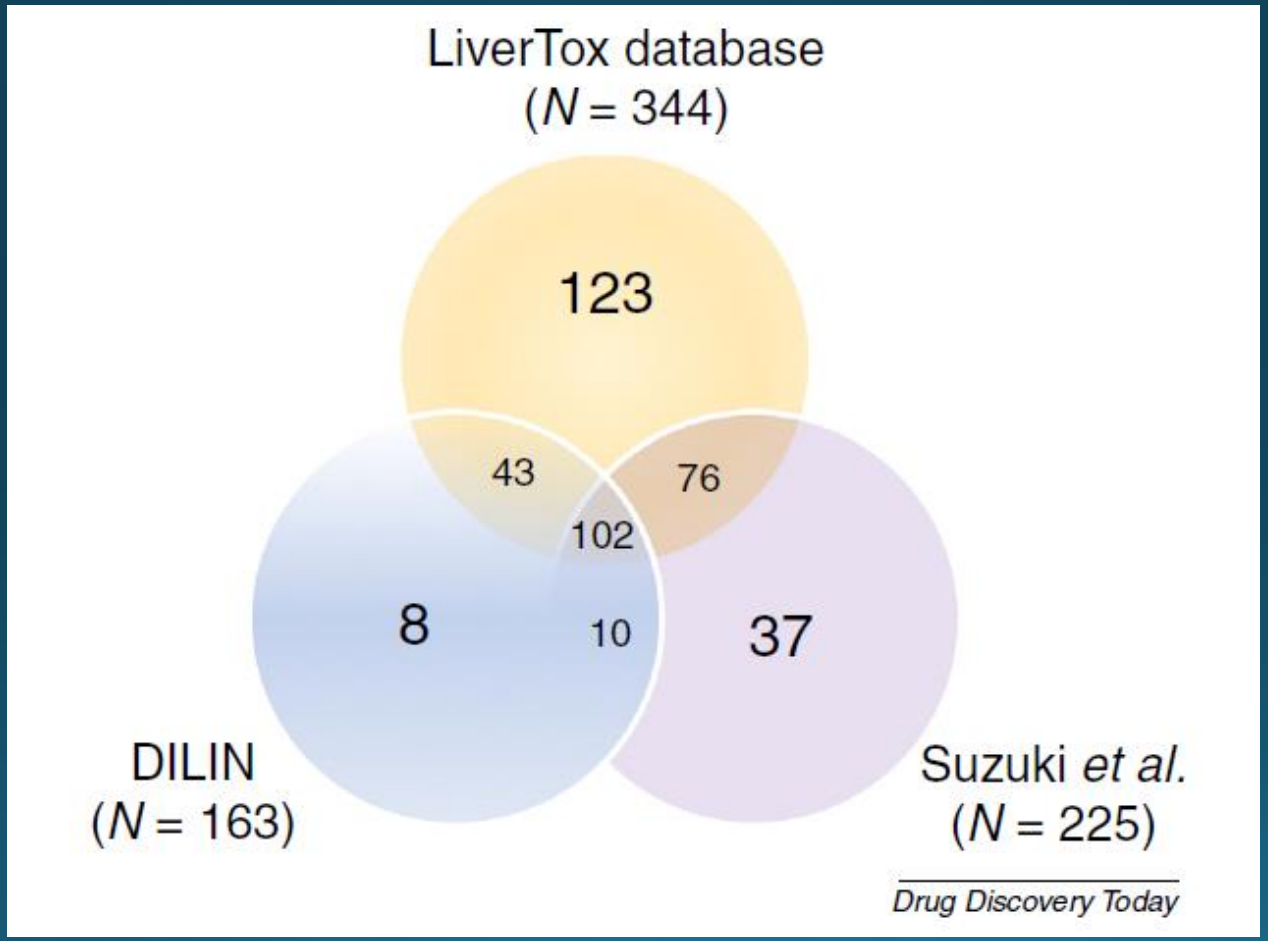
FIGURE 4 Forest plot of positive predictive values of detection algorithms by specification of study drug (n = 25)

Liver Int 2018;38:742

Available drug references

- Suzuki A, Andrade RJ, Bjornsson E, Lucena MI, Lee WM, Yuen NA, Hunt CM, Freston JW. Drug Saf. 2010; 33(6):503
  - Positive drugs (N=385) with degree of hepatotoxic drugs
  - Adjudicated/well-vetted DILI cases
  - Publications, regulatory actions due to hepatotoxicity, DILI/ALF registries, WHO VigiBase™
  - International data
- Chen M, Vijay V, Shi Q, Liu Z, Fang H, Tong W Drug Discov Today. 2011;16(15-16):697
  - Positive drugs (N=287) based on labeling and regulatory actions due to hepatotoxicity
  - US-marketed drugs only
- Ryan PB, Schuemie MJ, Welebob E, Duke J, Valentine S, Hartzema AG. Drug Saf. 2013;36 Suppl 1:S33
  - Positive/negative drugs based on publications and labeling
  - Observational Medical Outcomes Partnership (OMOP): US databases (claims data, EMR)
- Björnsson ES, Hoofnagle JH. Hepatology. 2016;63(2):590
  - Positive/negative drugs (N=671) ranked based on numbers of published case reports
  - US-marketed drug only
- Chen M, Suzuki A, Thakkar S, Yu K, Hu C, Tong W. Drug Discov Today. 2016;21(4):648
  - Positive/negative drugs with ranks based on DILI registries, publications, labeling, and regulatory actions taken due to hepatotoxicity
  - US-marketed drugs only

US-marketed drugs (N=399) identified three different studies



Drug Discov Today. 2016 Apr;21(4):648

ORIGINAL ARTICLE

A Text Searching Tool to Identify Patients with Idiosyncratic Drug-Induced Liver Injury

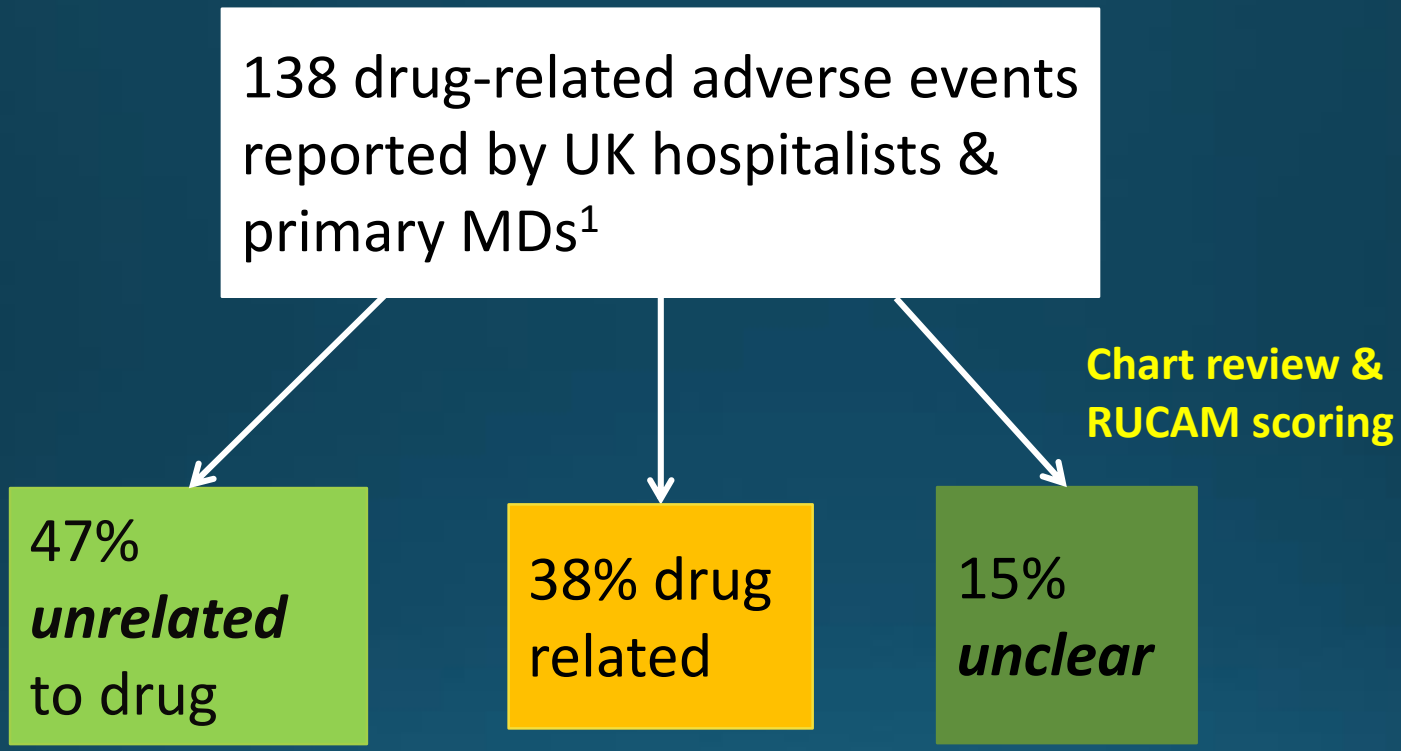
Lauren Heidemann[1] · James Law[2] · Robert J. Fontana[1]

Dig Dis Sci 2017 62: 615-625

- 527,000 outpatient/ER encounters were searched for 200 characters of test around 14 liver injury terms
- Identified DILI cases were reviewed by physician investigators
- 101 (62 probably, 25 possible) DILI cases out of 2564 cases
- PPV of 4%
- PPV 19% by removing “liver disease,” increasing false negative

Drug-induced liver toxicity
Drug-Induced liver injury
DILI
Drug-induced hepatitis
Liver injury
Drug-induced liver disease
Hepatotoxicity
Liver damage
Liver toxicity
Liver disease
Drug-induced hepatotoxicity
Drug-induced liver damage
Drug hepatotoxicity
Adverse liver reaction

Drug-induced liver injury misdiagnosed



- A minority of these hepatic adverse events were drug-related
- correct diagnosis was delayed an average of ≥3mos

Aithal et al. Br Med J 1999: 319:1541

A novel algorithm for detection of adverse drug reaction signals using a hospital electronic medical record database

Man Young Park[1†], Dukyong Yoon[1†], KiYoung Lee[1], Seok Yun Kang[2], Inwhee Park[3], Suk-Hyang Lee[4], Woojae Kim[1], Hye Jin Kam[1], Young-Ho Lee[5], Ju Han Kim[6] and Rae Woong Park[1*]

[1]*Department of Biomedical Informatics, Ajou University School of Medicine, Suwon, Korea*
[2]*Department of Hematology-Oncology, Ajou University School of Medicine, Suwon, Korea*
[3]*Department of Nephrology, Ajou University School of Medicine, Suwon, Korea*
[4]*College of Pharmacy, Ajou University, Suwon, Korea*
[5]*Department of Information Technology, Gachon University of Medicine and Science, Incheon, Korea*
[6]*Seoul National University Biomedical Informatics (SNUBI), Seoul National University College of Medicine, Seoul, Korea*

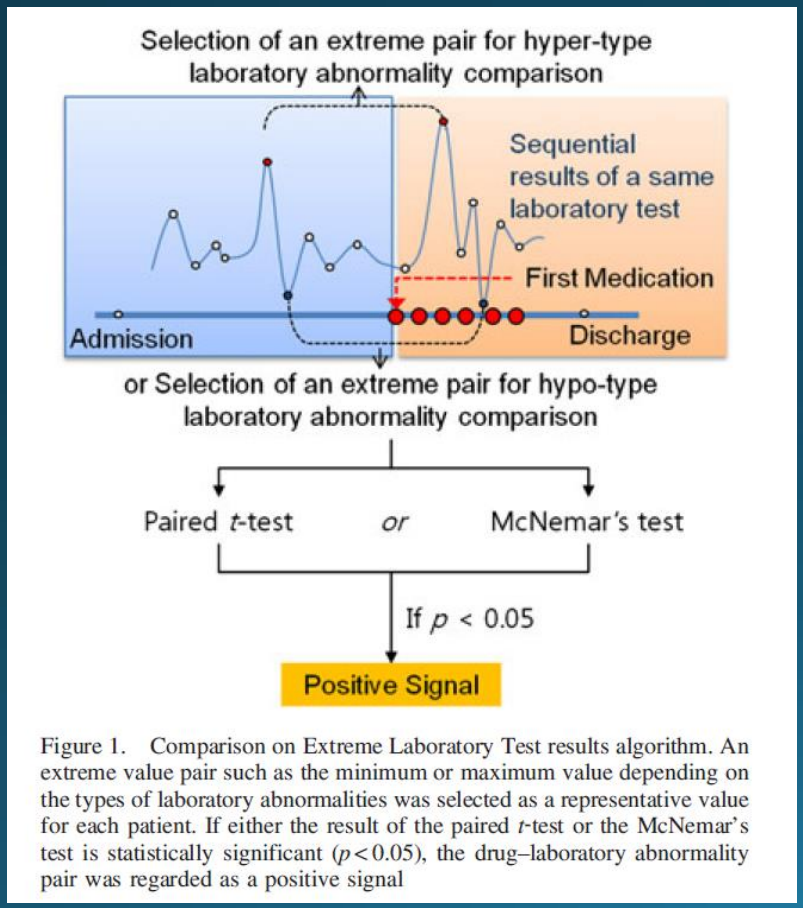


Figure 1. Comparison on Extreme Laboratory Test results algorithm. An extreme value pair such as the minimum or maximum value depending on the types of laboratory abnormalities was selected as a representative value for each patient. If either the result of the paired *t*-test or the McNemar's test is statistically significant ($p<0.05$), the drug–laboratory abnormality pair was regarded as a positive signal

- Extreme values (maximum or minimum) before and after drug exposure
- A minimum of two cases to run statistical analysis
- Paired t-test or McNemar's
- A significant pair is considered a positive signal

Pharmacoepidemiology and Drug Safety, 2011

High PPV to detect drugs with hepatotoxicity

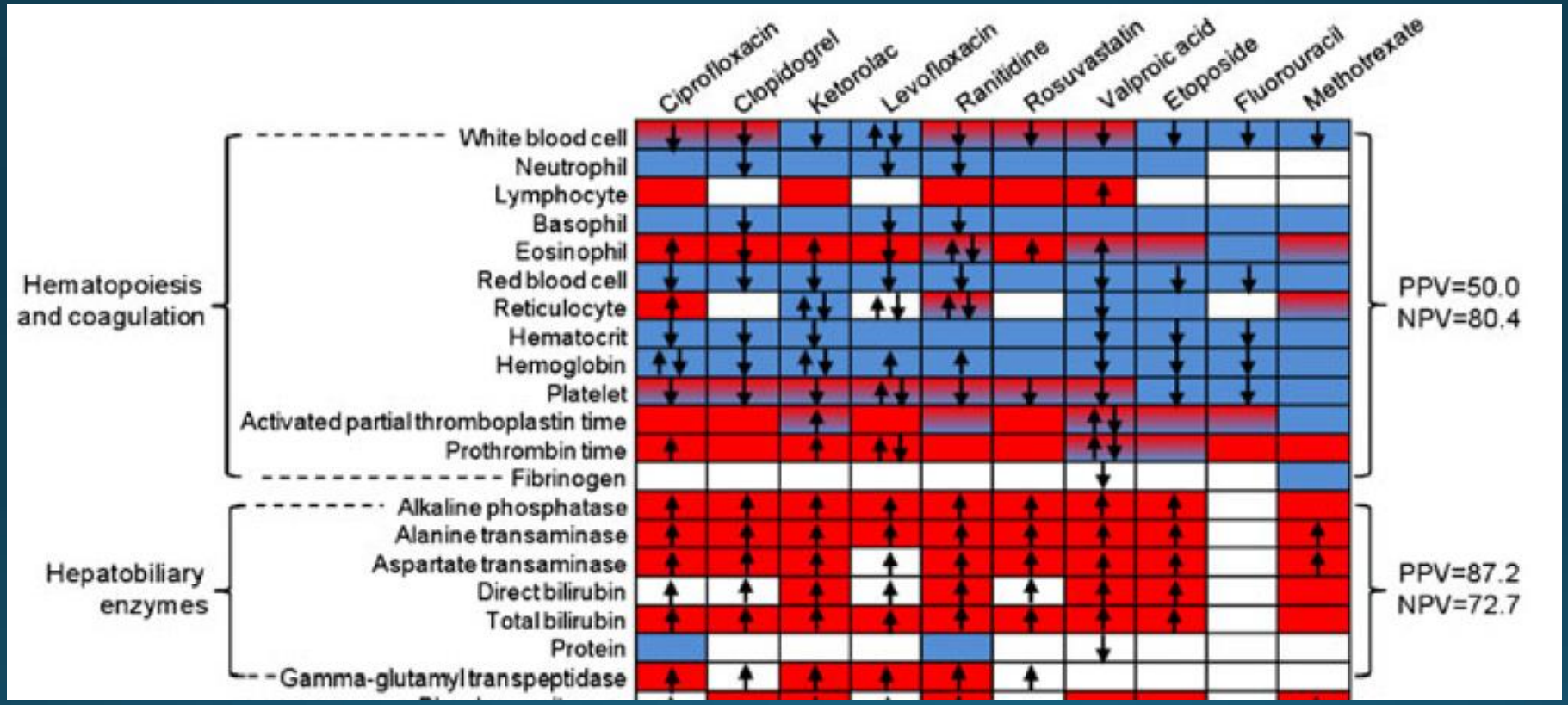


Figure 4. Previously reported laboratory abnormalities and detected laboratory abnormalities by Comparison on Extreme Laboratory Test results (CERT) algorithm. Rows represent laboratory abnormalities, and columns represent drugs. The arrows indicate laboratory abnormalities transformed from previously reported adverse drug reactions using the mapping table for each drug: "↑" and "↓" designate elevation and reduction, respectively. The colors in the cells mean signals detected by CERT. The red, blue, and red-to-blue gradient cells indicate "increase," "decrease," and "both increase and decrease" on laboratory tests after medication, respectively. PPV, positive predictive value; NPV, negative predictive value; LDL, low-density lipoprotein

ORIGINAL REPORT

Application and optimisation of the Comparison on Extreme Laboratory Tests (CERT) algorithm for detection of adverse drug reactions: Transferability across national boundaries

Mun Yee Tham[1] | Qing Ye[1,2] | Pei San Ang[1] | Liza Y. Fan[1,2] | Dukyong Yoon[3,4] | Rae Woong Park[3,4] | Zheng Jye Ling[5] | James W. Yip[5] | Bee Choo Tai[6,9] | Stephen JW Evans[7] | Cynthia Sung[1,8]

Abstract

Purpose: The Singapore regulatory agency for health products (Health Sciences Authority), in performing active surveillance of medicines and their potential harms, is open to new methods to achieve this goal. Laboratory tests are a potential source of data for this purpose. We have examined the performance of the Comparison on Extreme Laboratory Tests (CERT) algorithm, developed by Ajou University, Korea, as a potential tool for adverse drug reaction detection based on the electronic medical records of the Singapore health care system.

Methods: We implemented the original CERT algorithm, comparing extreme laboratory results pre- and post-drug exposure, and 5 variations thereof using 4.5 years of National University Hospital (NUH) electronic medical record data (31 869 588 laboratory tests, 6 699 591 drug dispensings from 272 328 hospitalizations). We investigated 6 drugs from the original CERT paper and an additional 47 drugs. We benchmarked results against a reference standard that we created from UpToDate 2015.

Results: The original CERT algorithm applied to all 53 drugs and 44 laboratory abnormalities yielded a positive predictive value (PPV) and sensitivity of 50.3% and 54.1%, respectively. By raising the minimum number of cases for each drug-laboratory abnormality pair from 2 to 400, the PPV and sensitivity increased to 53.9% and 67.2%, respectively. This post hoc variation, named CERT400, performed particularly well for drug-induced hepatic and renal toxicities.

Discussion: We have demonstrated that the CERT algorithm can be applied across national boundaries. One modification (CERT400) was able to identify adverse drug reaction signals from laboratory data with reasonable PPV and sensitivity, which indicates potential utility as a supplementary pharmacovigilance tool.

DILI identification using electronic medical Records (EMR)

Experience using VA EMR

Kenrokuen, Kanazawa, Japan

VHA DILI database project (PPO 15-155)

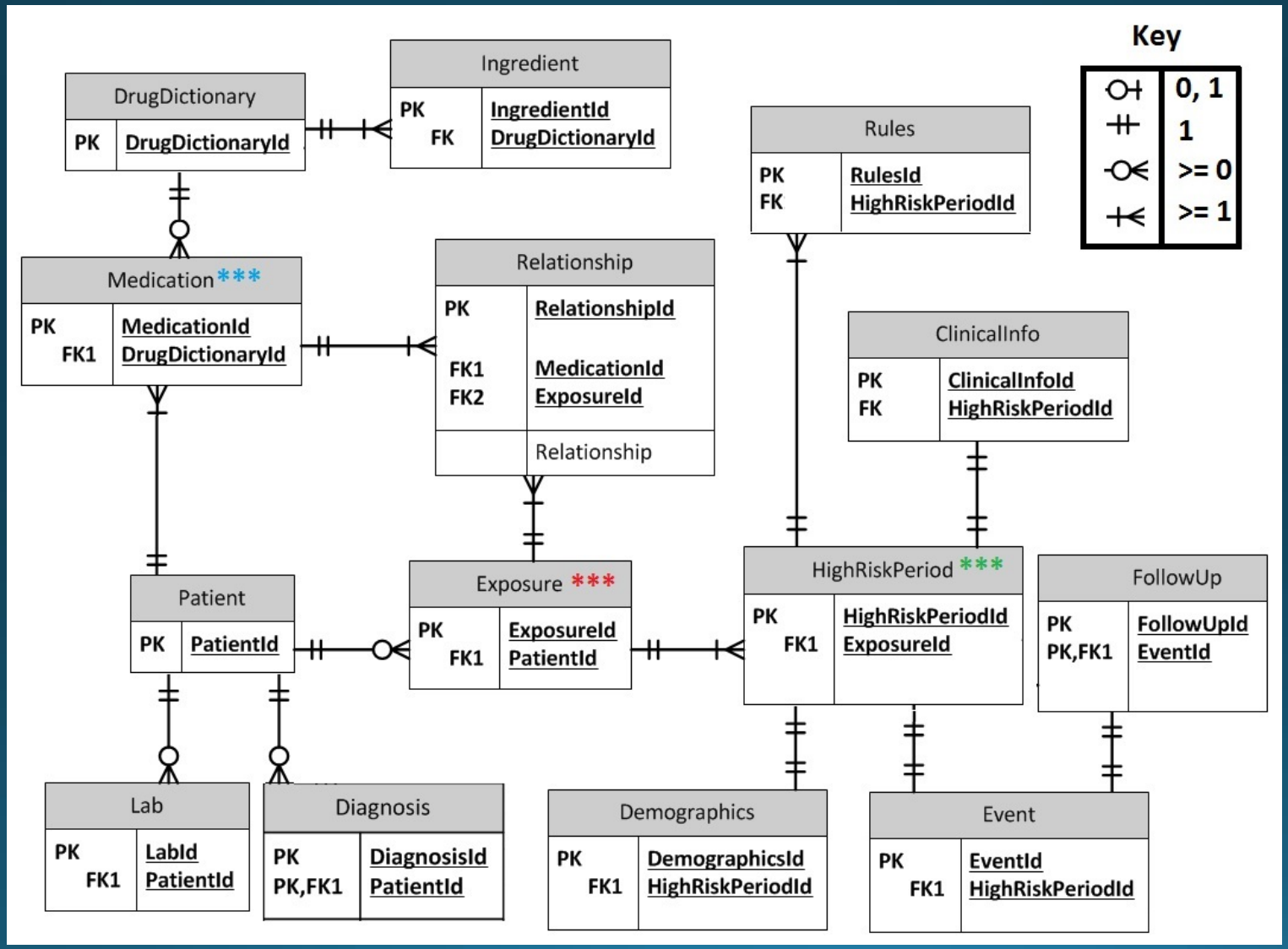
- ***Multidisciplinary research team***: hepatologists, pharmacist, biomedical informaticians, and mathematical scientists

- ***~8.7 million veterans who received any of 124 study drugs exhibiting hepatotoxicity*** included in clinical & administrative dataset (1999-2015)

- Will ***explore risk factors and disparities in risks and phenotypes*** **for drug-specific DILI**

- Topic modeling ***discovers "unrealized" combinations of DILI risk factors*** (i.e., multifactorial risks)

Database Design



Methods – pilot study population

- Identify exposures to amoxicillin/clavulanate using 2860 unique drug IDs
- Drug exposure:
  - **Single prescription**: drug dispensing or shipping date, *whichever was later*, plus number of dispensed days
  - **Recurring prescriptions**: concatenated into a single drug exposure, assuming 'continuous exposure' when an interval between the original prescription and the next refill was less than a half of dispensed days in the original prescription or 30 days, *whichever was smaller**

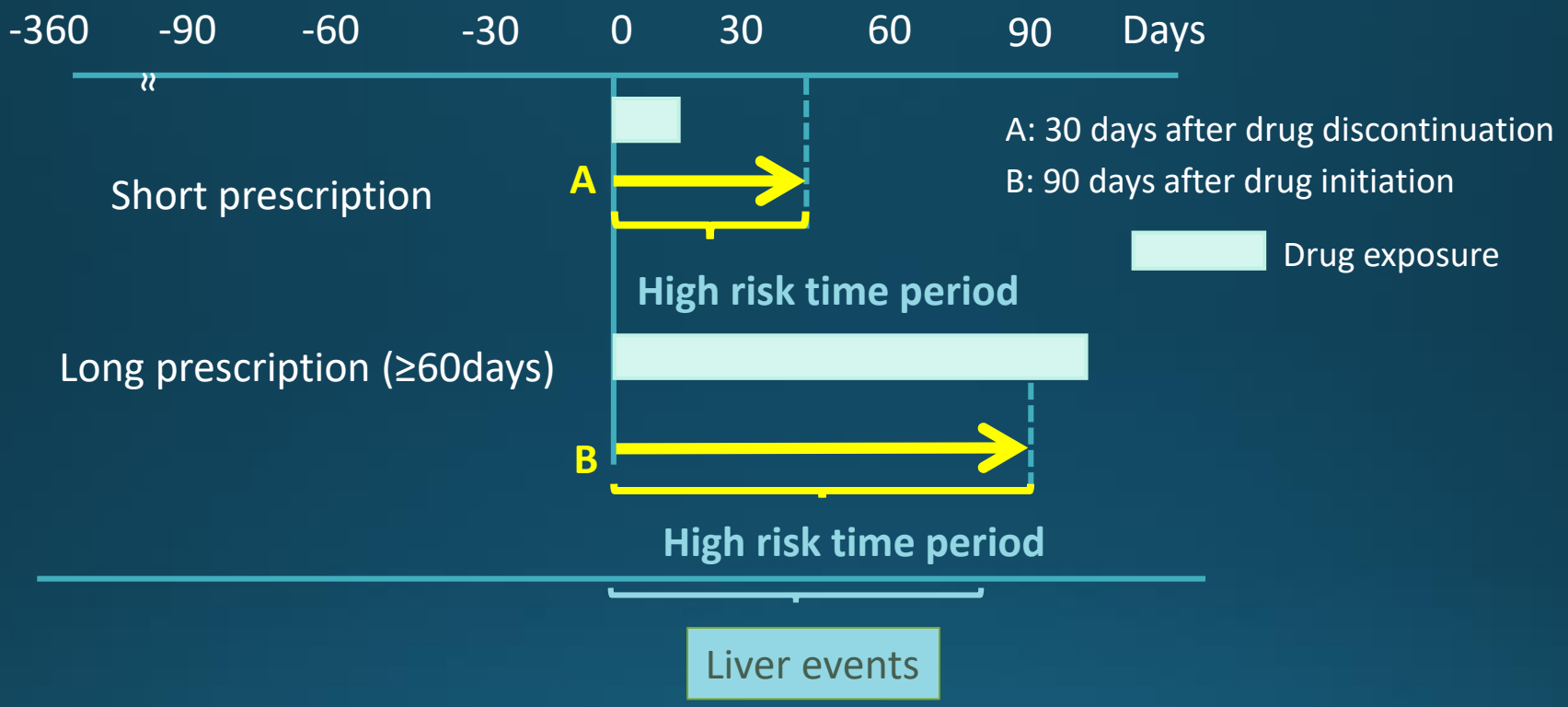
Pharmacoepidemiol Drug Saf 2013;22:190

DILI case identification

- High-risk DILI period:
  - first 90 days after drug initiation or
  - within 30 days following drug discontinuation
- Liver events: acute liver injury in high-risk periods of:
  - ALT ≥ 5xULN or ALP ≥ 2xULN if pre-exposure liver chemistry data were completely normal
  - ALT ≥ 5x or ALP ≥ 2x median pre-exposure values (BLM)
- Non-DILI liver events excluded by ICD-9 codes or relevant labs

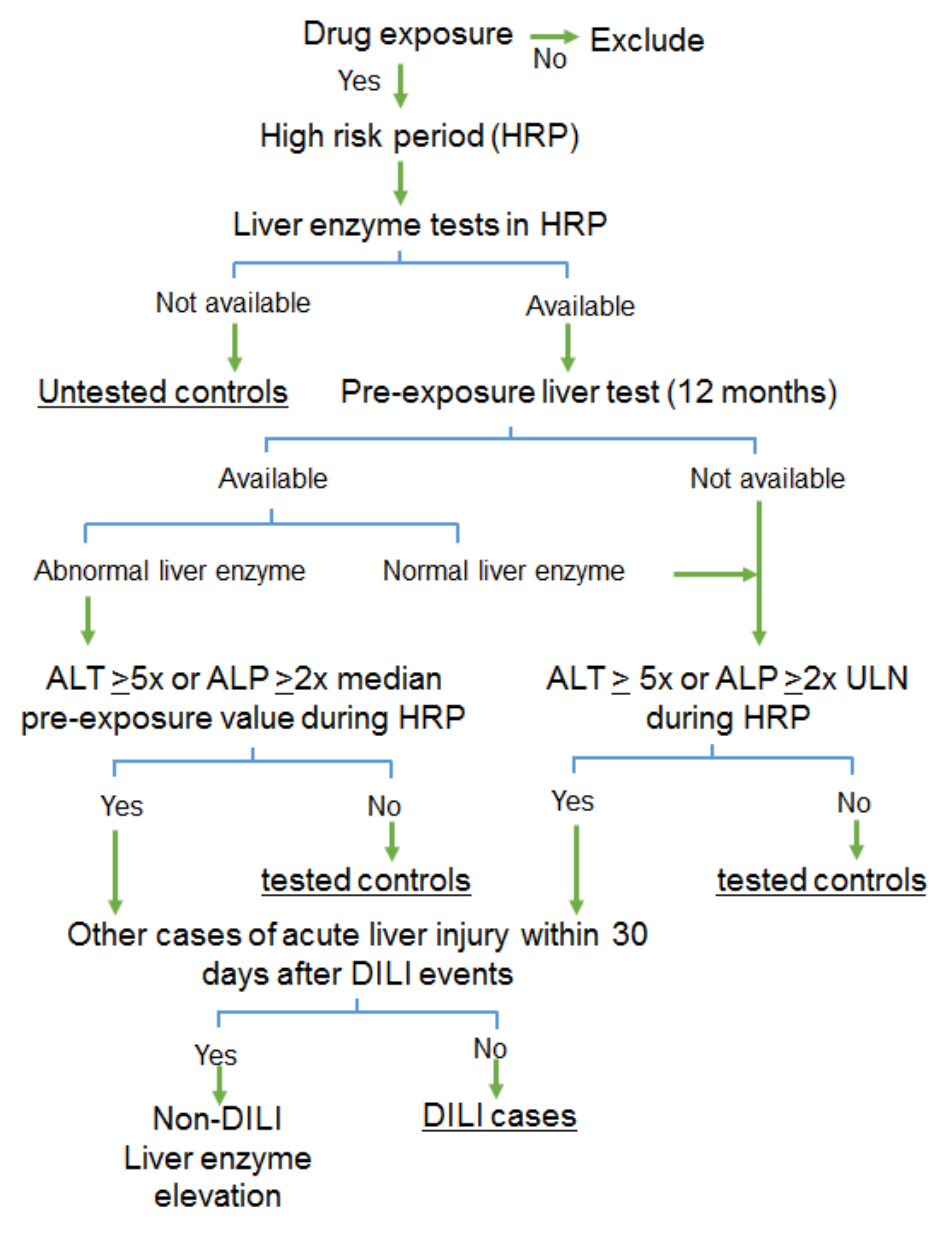
Pharmacoepidemiol Drug Saf 2013;22:190-8

Exposure definition and case identification

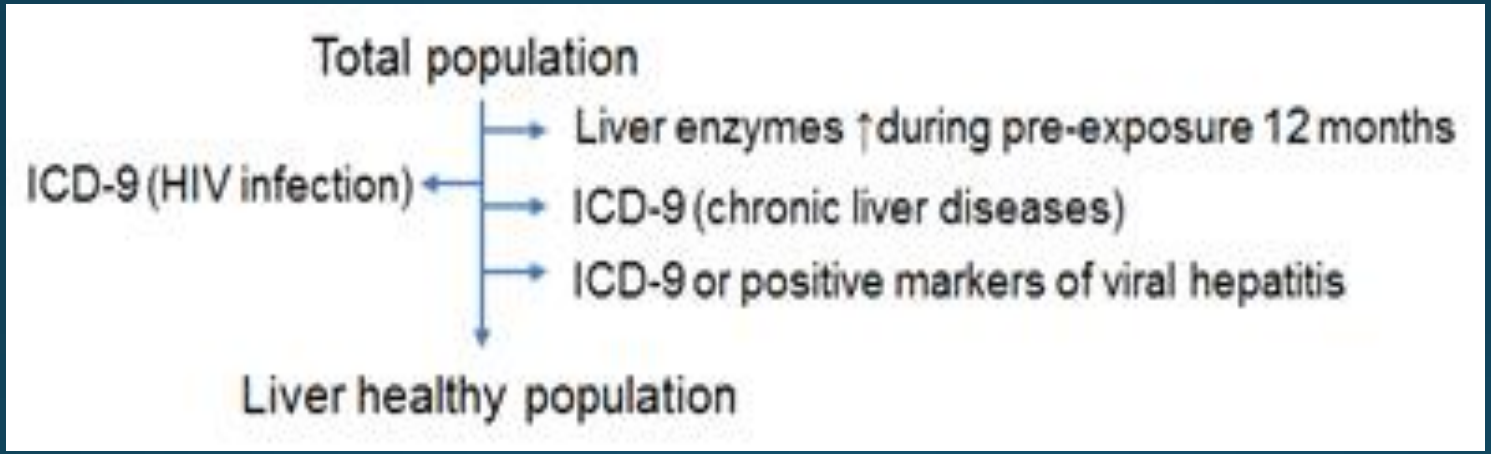


1) ALT>5 ULN/BLM or ALP>2 ULN/BLM
2) High risk period
3) Excluding other causes of acute liver injury within 30 days after liver events

DILI phenotype algorithm using AMX/CA pilot cohort



Study sub-populations



ICD-9 codes exclude other acute liver injury

- ICD-9 codes (N=230) to exclude cases with non-DILI liver injury within 30 days after the DILI event date:
  - Acute biliary events (e.g., acute cholecystitis, and acute biliary obstruction/infection)
  - Acute hepatitis (e.g., viral, ischemic, autoimmune)
  - Acute heart failure
  - Congestive heart failure/heart failure
  - Alcoholic hepatitis
  - Systemic inflammatory condition/sepsis

Pharmacoepidemiol Drug Saf 2013;22:190-8

Study demographics

	Summary statistics
Total exposures	1,843,650
Total patients	1,096,231
Age, years	59 ± 15
Gender	
Men	999223 (91%)
Women	97008 (8.8%)
Race/ethnicity	
White	697465 (63.6%)
Black	190989 (17.4%)
Hispanic	56287 (5.1%)
others	151490 (13.8%)

84% and 33% had liver chemistries during pre- and post-exposure periods, respectively

	Pre-exposure period		
High-risk period	Available	Not available	Sum
Available	308281 28%	56620	364901 33%
Not available	610328	121002	731330
SUM	918609 84%	177622	1096231

731330 'controls' had no liver chemistries in high risk period
- implies **'clinically significant' DILI is absent**
- resulting in potential underestimation of DILI incidence

DILI frequency increased with age, male gender, Hispanic/unknown races

	Unadjusted	Adjusted	Lab test availability, %	
	Odds [95%CI]	Odds [95%CI]	Pre-exposure	HRP
Age group				
18-25	0.60 (0.39 - 0.93)	0.65 (0.42 - 1.01)	46.3	20.45
26-35	0.35 (0.25 - 0.49)	0.38 (0.27 - 0.54)	54.3	21.54
36-45	0.41 (0.31 - 0.54)	0.44 (0.33 - 0.59)	64.2	25.54
46-55	0.54 (0.44 - 0.66)	0.57 (0.46 - 0.70)	73.3	29.68
56-65	0.79 (0.67 - 0.93)	0.81 (0.69 - 0.96)	84.3	32.97
66-75	0.90 (0.75 - 1.08)	0.91 (0.76 - 1.09)	88.1	33.32
76 and older	-	-	86.8	32.97
Gender				
Women	0.44 (0.34 - 0.58)	0.58 (0.43 - 0.77)	70.03	23.93
Men	-	-	79.31	31.37
Race/Ethnicity				
AI/AN	1.41 (0.70 - 2.82)	1.55 (0.77 - 3.11)	77.71	31.24
Asian	1.00 (0.45 - 2.23)	1.14 (0.51 - 2.56)	68.88	29.59
Black	0.95 (0.78 - 1.12)	1.11 (0.93 - 1.31)	73.97	29.86
NH/PI	1.30 (0.65 - 2.60)	1.47 (0.73 - 2.95)	73.81	28.66
White Hispanic	1.32 (1.03 - 1.69)	1.36 (1.06 - 1.75)	78.51	29.67
White Non-Hispanic	-	-	81.25	31.59
Unknown	1.24 (1.05 - 1.47)	1.30 (1.10 - 1.53)	70.14	27.2

Computed using ‘Healthy’ Population

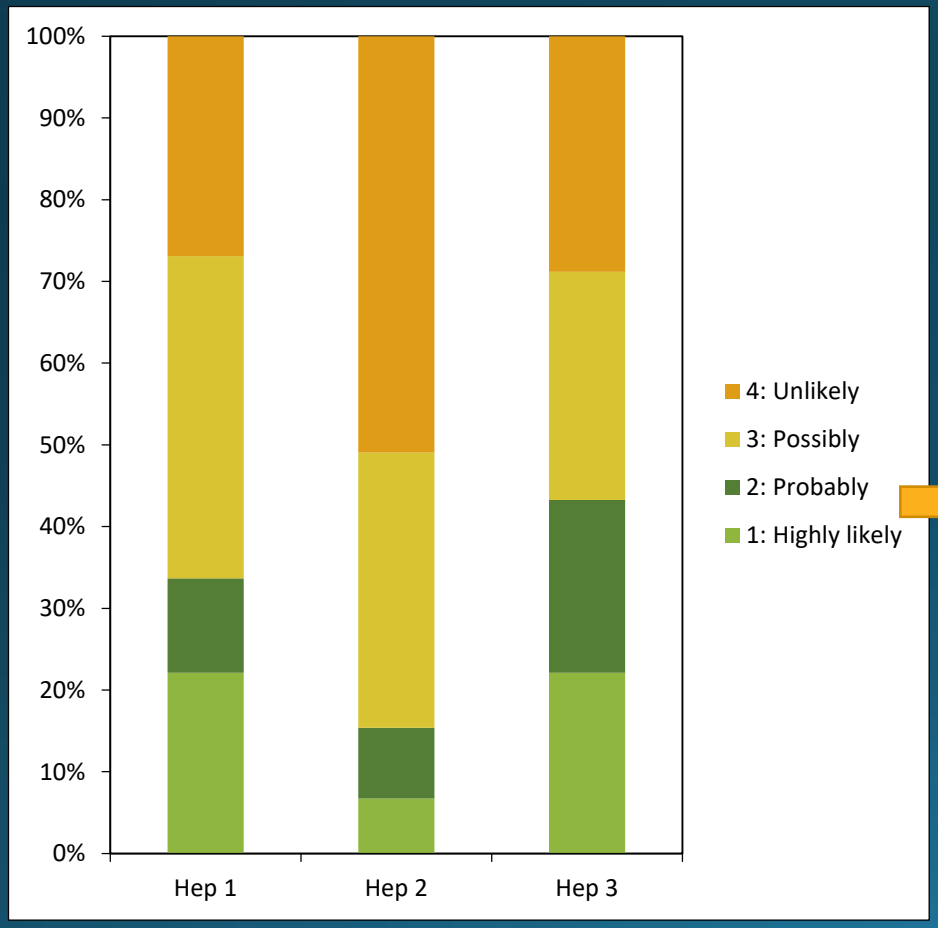
Validation analyses of DILI phenotype algorithm

- Systemic review in comparison with DILI phenotypes at DILI registries
- Structured data review (i.e., drug exposure, laboratory data, ICD-9 codes) by three hepatologists (18% randomly selected cases)

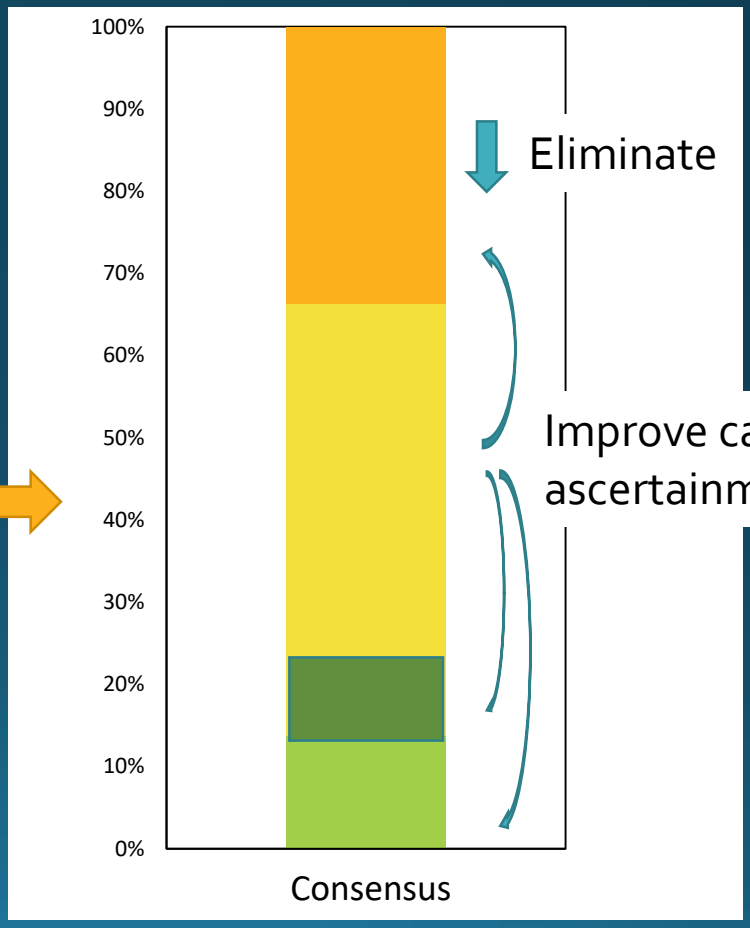
Categories	Criteria	DILI
Highly likely	Favorable for DILI diagnosis	yes
Probably	Favorable for DILI diagnosis but some uncertainty	yes
Possibly	No sufficient supporting evidence or evidence against DILI diagnosis	Yes/No
Unlikely	Strong evidence against DILI diagnosis	No

Review results

Highly likely vs. unlikely in 10%



PPV=66%, possible=42%



	Problems	Solutions
Events	Chronic elevation detected as event	Lab pattern recognition for peak and resolution
	No follow-up (one point lab)	Exclude from analysis
	Co-medications	Prescription records (flag other drugs causing DILI)
	Other medication use around event	Prescription records or progress notes (flag drugs causing DILI)
Exclusion	Time window	Change from 30 days to -30 days to +60 days
	High AST>ALT in hepatocellular injury	
	Muscle injury	ICD-9 codes of muscle injury & high AST/ALT
	Acute myocardial infarction	ICD-9 codes, CK-MB↑, or troponin↑
	Congestive heart failure*	ICD-9 codes, radiology reports/progress notes (e.g., pulmonary congestion, cardiomegaly, SOB), ICD-9, or delta BNP, progress notes (e.g., increased BNP)
	Right heart failure*	ICD-9 codes, radiology reports/progress notes (e.g., right-sided heart failure, pulmonary hypertension), delta BNP
	Ischemic heart disease	Chest pain (ICD-9) plus (CK-MB↑ or troponin↑)
	Isolated ALP elevation	
	Bone disorder	ICD-9 codes & isolated ALP elevation (lab pattern recognition)
	Acute or chronic pancreatitis	ICD-9 codes & AMYLASE↑ or radiology reports (e.g., pancreatic atrophy, pancreatic duct dilatation)
	Abdominal pain around event	Radiology reports and progress notes (e.g., biliary obstruction, RUQ pain, epigastric pain, colicky, postprandial abdominal pain)
	Insufficient etiological information	
	No ICD-9 around the time of event	Progress notes to search for alternative causes (e.g., viral hepatitis, alcoholic liver disease, heart failure), lab data (viral markers)
Sub-classification	Pre-existing cirrhosis**	Expand timeframe for detecting pre-existing condition (including 3 months after event) Progress notes around events for cirrhosis
	Alcohol misuse	Progress notes around events for excess alcohol use (e.g., ongoing alcohol abuse, excess alcohol), Alcohol Use Disorders Identification Test (AUDIT)≥5
	No baseline lab within 12 months	Include Day 1 exposure as baseline Include 3 years before exposure

*: combinatory: exclude if two of the criteria met.

**: cirrhotic patients may manifest DILI differently – evaluate separately

Challenges in DILI identification using EMR data from multiple sources

- Differences in practice (coding, documentation, insurance..)
- Differences in use of EMR
- Differences in EMR configuration
- Differences in EMR customization
- Differences in data location/storage
- Differences in field names/definitions
- Difference in schematic structure, coding, and vocabulary
- Transformations within intermediary repositories
- Translations of data in-flight (health information exchange)
- Use of non-standard encoding
- Data disassociated with corresponding information (drug-indication)

Summary

- EMR big data can complement clinical investigation of DILI
  - Incidence
  - Drug-specific incidence, disparities (age, sex/gender, race/ethnicity)
  - Non-genetic risk factors
  - Multifactorial risks
  - Multiple algorithms
- EMR provides opportunities for pharmacovigilance without counting on voluntary reporting
- Challenges
  - Development/validation of accurate DILI phenotype algorithm
  - Data irregularity
  - Potential bias
  - Multiple data sources - stay close to the data source

Acknowledgements

- **Durham VAMC**
  - Christine M. Hunt
  - Hans Tillmann (Greenville VA)
  - Dawn Provenzale
  - Beth Hauser
  - Avisheck Nagi
  - Marsha Turner
- **CAVHS**
  - Teresa Hudson
  - James Williams
  - Kate Dishongh
- **Duke Center for Health Informatics**
  - William Hammond
  - Vivian West
- **Mathematical Science, University of Memphis**
  - Dale Bowman
  - E. Olusegun George
- **Biomedical informatics, UAMS**
  - Fred Prior
  - Mathias Brochhausen
  - Jonathan Bona
- **Bioinformatics and Biostatistics, National Center for Toxicological Research**
  - Weida Tong
  - Wen Zou
  - Minjun Chen

Partnership: Spanish DILI Registry, OMOP/VINCI

Thank you for your attention