OBSERVATIONAL MEDICAL OUTCOMES PARTNERSHIP

An empiric exploration of analytical methods and outcome definitions for patient centered outcomes research

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INTRODUCTION

When using observational data for outcomes research, the investigator must choose a specific definition for the patient outcome based on the available data elements. The sensitivity and specificity of these definitions greatly influence the analysis. Consistency of definitions becomes particularly important when pooling or comparing results across multiple data sources. Based on the wide variation in definitions employed when studying the same, or closely related, outcomes there appears to be little consensus on best practice and the definitions used are rarely characterized in terms of validity and reliability.

While many observational data sets still consist exclusively of claims data, clinical data such as laboratory results, radiographic study report and physiologic observations are available as well, expanding the potential to create definitions that are more sensitive and specific. In fact, with sufficiently robust clinical data, outcomes definitions based on observational data can obviate the need for validation.

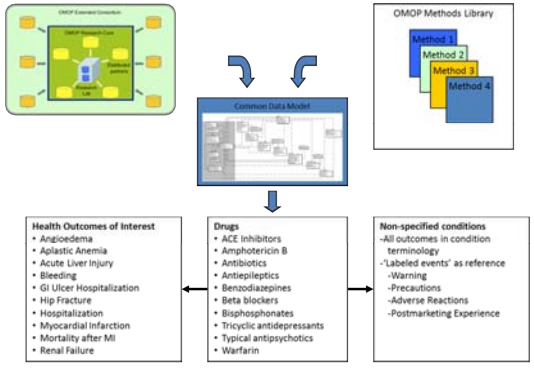
Given the variability in the extent of clinical data available in observational datasets and the potential effect on analysis results depending on the outcome's definition's sensitivity and specificity, we undertook an empirical exploration of the effect of progressively more clinically precise definitions of patient outcomes on risk estimates resulting across a range of analytical methods [1]

METHODS

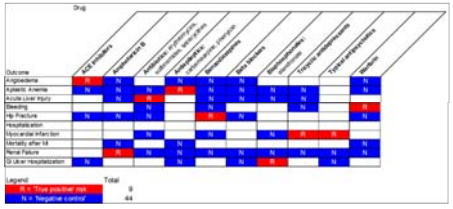
In order to carry out this analysis, we used a series of evidence based, progressively more precise definitions for each of nine patient outcomes to estimate the risk associated with specific medication exposures (9 true positive and 44 true negative associations) using eight different analytical approaches (each with multiple parameter settings representing the various combinations of method-study design decisions such as time-at-risk and specific confounding adjustment strategy). We conducted all of these analyses across 10 database ranging from pure administrative claims data to rich clinical data from electronic medical records.

We constructed outcome definitions {all materials available at http://omop.fnih.org} based on multiple independent literature reviews and expert panel synthesis followed by independent critique by experts in medical informatics, biostatistics and epidemiology. The expert panel created a framework that provided a standardized approach to constructing increasingly precise definitions. Drug-outcome pairs were based on FDA product labels, results of published observational studies and expert panel review. We used data from ten observational datasets that have been used for outcomes research which were converted to a common data model to facilitate analysis. Statistical methods commonly employed in outcomes research were implemented against this common data model and parameterized to allow us to easily examine the effect of changes in these parameters. Sensitivity, specificity, precision, and accuracy were ascertained for all methods based on statistical significance thresholds of alpha = 0.05; sensitivity analyses were performed to assess operating characteristics at alpha = 0.01, and raising the signal threshold to require the point estimate to be greater than 1.5 and 2.

Experiment Overview



Drug-Outcome Pairs Ground Truth



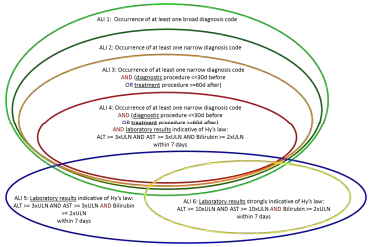
Analytical Methods

Method name	Contributor	Release date	Parameter combinations
Disproportionality analysis			
Disproportionality analysis (DP)	Columbia / Merck	15-Mar-10	112
IC Temporal Pattern Discovery (ICTPD)	Uppsala Monitoring Centre	23-May-10	84
HSIU cohort method (HSIU)	Regenstrief / Indiana University	8-Jun-10	6
Case-based methods			
Univariate self-controlled case series (USCCS)	Columbia	2-Apr-10	64
Multi-set case control estimation (MSCCE)	Columbia / GlaxoSmithKline	16-Apr-10	32
Bayesian logistic regression (BLR)	Rutgers / Columbia	21-Apr-10	24
Case-control surveillance (CCS)	Lilly	2-May-10	48
Case-crossover (CCO)	University of Utah	1-Jun-10	48
Exposure-based methods			
Observational screening (OS)	ProSanos / GlaxoSmithKline	8-Apr-10	162
High-dimensional propensity score (HDPS)	Harvard Medical School / Columbia	6-Aug-10	144
Incident user design (IUD-HOI)	University of North Carolina	26-Oct-10	160
Sequential testing methods			
Maximized Sequential Probability Ratio Test (MSPRT)	Harvard Pilgrim / Group Health	25-Jul-10	144
Conditional sequential sampling procedure (CSSP)	Harvard Pilgrim / Group Health	30-Aug-10	144

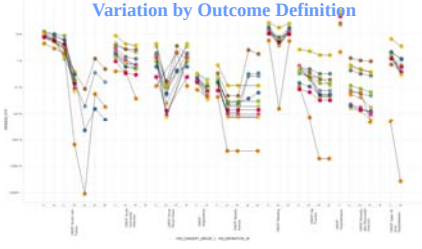
Acute Liver Injury Definition Examples

Definition 1 - Broad:
277.4 "Disorders of bilirubin excretion"
570* "Acute and subacute necrosis of the liver"
572.2 "Hepatic coma (hepatorenal syndrome)"
572.4* "Hepatorenal syndrome"
573* "Other disorders of the liver, including chemical or drug induced"
576.8 "Other specified disorders of biliary tract"
782.4 "Jaundice, unspecified, not of newborn"
789.1* "Hepatomegaly"
790.4* "Nonspecific elevation of transaminase or lactic dehydrogenase levels"
794.8* "Abnormal liver function test results"

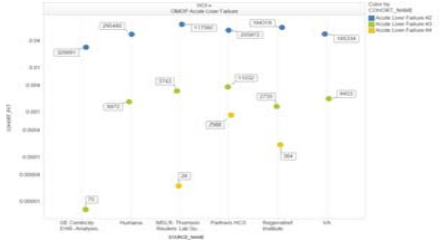
Definition 2 - Narrow:
570* "Acute and subacute necrosis of the liver"
572.2 "Hepatic coma (hepatorenal syndrome)"
572.4* "Hepatorenal syndrome"
573* "Other disorders of the liver, including chemical or drug induced"



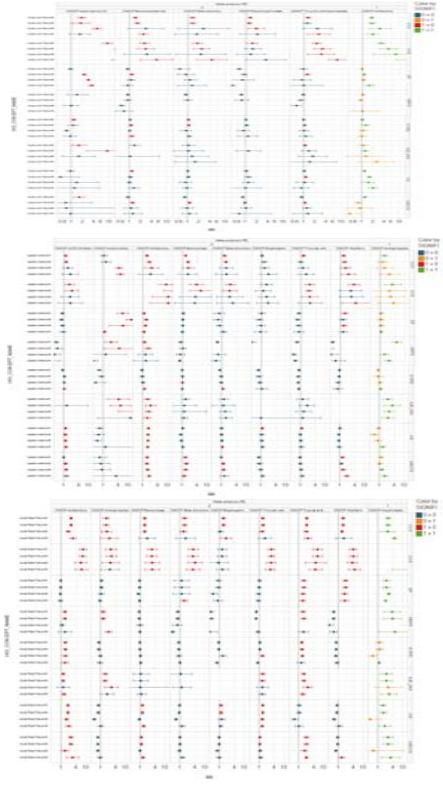
Variation by Outcome Definition



Variation by Outcome Definition



Variation Across Drug-Outcome, Methods and Databases



RESULTS

Applying increasingly precise outcome definitions generally resulted in progressively smaller numbers of patients being identified. Definitions that required relevant diagnostic or therapeutic procedures generally results in a marked decrease in the number of patients identified. Applying definitions that required diagnostic test data in databases that lacked these values, resulted in no patients being identified.

The effect of the clinical precision of the outcome definition on risk estimates varied by analytical method but this pattern was minimally affected by variations in parameter changes within the methods. While risk estimates were relatively stable across outcome definitions for a given analytical method for some outcomes such as acute renal failure, the estimates varied by method. In general, more specific outcome definitions result in fewer cases with that outcome which increases variability in the estimates as illustrated by acute liver failure. For some outcomes, aplastic anemia for example, despite the smaller number of cases the more precise outcome definition resulted in more consistent identification of true positives (eg. Resulting from anti-epileptics) and fewer false positives than less specific definitions such as those based on broad sets of diagnosis codes alone.

CONCLUSIONS

Our results provide empiric evidence to help guide the choice of optimal analytic approach and degree of specificity of the definition used for the clinical outcome of interest. The large (logarithmic) effect of increasingly precise outcomes definitions on the numbers of patients is a particularly informative finding. As illustrated by the aplastic anemia example, this reduction in the number of patients can be offset by the greater specificity. More precise definitions provide a complementary perspective to broader diagnostic code based definitions with comparable or better predictive values but performance varies by method.

Our findings suggest several useful directions for further exploration including examining the role of severity of the outcome and how to optimize the tradeoffs between sensitivity and specificity of definitions.

REFERENCES

[1] Ryan PB, Welebob E, Hartzema AG, Stang PE, Overhage JM. Surveying US observational data sources and characteristics for drug safety needs. Pharm Med. 2010; 24 (4): 231-238.