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Original Research

Expert panel assessment of acute liver injury identification in observational data

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Abstract

Background: Observational data are useful for studying drug safety; however, to be effective, accurate outcome measurement is paramount.
Objectives: This study compared alternative outcome definitions for acute liver injury (ALI) and explored opportunities for improving ALI identification in observational data.
Methods: The Truven MarketScan® Lab Database (MSLR) was used to identify patients meeting at least 1 of 4 ALI definitions, including definitions based on diagnosis codes, laboratory measures, or combinations of diagnoses, procedures, and/or laboratory measures. Expert panelists reviewed patient data using a Web dashboard. Panelists determined whether they believed the patient had ALI and identified factors influencing their decision. Logistic regression models explored which factors were influential in case determination.
Results: Overall, only 37 of 208 reviewed patients (17.8%) were classified as cases. The diagnosis-based definition yielded no positive cases and the laboratory-based definition yielded the most positive cases (31 of 60). The most influential factors in case classification were occurrence of procedures after the index date (OR = 13.2, 95% CI = 5.3–32.9), no occurrence of drug treatments before the index date (OR = 4.6; 95% CI = 1.6–13.2), occurrence of drug treatments before the index date (OR = 0.3; 95% CI = 0.1–0.6), and no drug treatments after the index date (OR = 0.2; 95% CI = 0.0–0.5).
Conclusions: Comparing ALI definitions illustrated tradeoffs between the number of plausible cases identified and the likelihood of cases being classified as positive. Future research should refine ALI case definitions, considering the import of laboratory results, procedures, and drugs in defining a case.

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Introduction

Adverse drug events (ADEs) are both common and costly.[1–7] Approximately 3–7% of hospital admissions are due to ADEs,[1,2] with ADE-related hospitalization costing upwards of $27,000 per patient on average.[2] Because of the implications, frequency, and financial burden of ADEs, improved mechanisms for drug safety surveillance and early detection of serious adverse events is a great concern.[8] While clinical trials provide one mechanism for studying drug safety information during the early years of a product's availability, many ADEs cannot be detected in trials because of the small, narrowly defined trial populations. The Medwatch program, which collects voluntary reports from healthcare providers and consumers on serious adverse events, provides some useful information to identify drug safety concerns. However, this program and other existing post-marketing drug safety surveillance methods are subject to under-reporting, thus compromising value for identifying adverse events early in a product's lifecycle.[9,10]

Observational data sources, such as administrative claims data and electronic medical records, contain extensive patient data and are of growing interest for drug safety surveillance.[11] Observational data sources are not designed to consistently code and capture ADEs, but they provide broad capture of drugs, procedures, and diagnoses that allow for identification of statistical associations. Administrative claims data are designed for payment, while electronic medical records are designed for clinical documentation of care. Because of this, the use of these data sources presents interesting challenges when used for drug safety surveillance.

Observational studies of ADEs typically rely on diagnostic codes, procedures, laboratory values, or some combination of the 3 to define event cases. Operational definitions and performance of various outcome definitions vary widely in the literature.[12] For relatively common conditions that could be a result of an ADE, such as acute myocardial infarction, stroke, and heart failure, diagnosis code-based operational definitions have generally been accepted, and these outcome definitions are supported by validation studies that have demonstrated positive predictive values (PPV) ranging from 85% to 100%.[13] Other validation studies, however, have shown poorer performance, suggesting a PPV as low as 14% for outcomes such as heart failure.[14] The outcome measures for more rare diseases may be even more susceptible to low PPV. For example, prior studies have found a PPV of 48% for detecting viral hepatitis with diagnosis codes, and a PPV of 29% for detecting Guillain-Barre' Syndrome with diagnosis codes.[15,16] Overall, the types of codes or events included in the operational definitions of adverse events vary widely,[17] the performance of these measures is less than perfect, and improvement in methods to identify ADEs are needed if observational data sources are to be used in drug safety surveillance.

Acute liver injury (ALI) provides an interesting example of how researchers have operationalized health outcome definitions in observational data.[18–31] ALI is a potential ADE that, while relatively rare, can be particularly harmful to patients. In 2 independently conducted systematic reviews of observational studies of ALI, multiple different operational definitions were used in the published studies, and there was no apparent research consensus on the sensitivity or specificity of the definitions.[17] For instance, of the 14 studies included in the systematic review by Kachroo and colleagues,[32] 6 used only the International Classification of Diseases, 9th Revision (ICD-9) coding system to identify patients with ALI, 4 used both ICD-9 and ICD-10 codes, 1 used the Read and Oxford Medical Indexing System (OXMIS), 2 used the WHO Adverse Reaction Terminology (WHOART), and 1 did not report the coding system used. Most studies used ICD-9 code 570.x or ICD-10 code K71.1 to identify ALI, but most studies also used other diverse codes to represent hepatic symptoms or ailments and there was little consistency among these codes. In some studies, the operational definitions of ALI did not identify any specific coding. The multitude of operational definitions demonstrated here poses tremendous challenges when interpreting results of drug safety surveillance efforts.

This study aimed to understand how commonly used definitions of ALI perform, and to explore opportunities for improving ALI identification in observational data. An expert panel