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ORIGINAL ARTICLE

# Validation study in four health-care databases: upper gastrointestinal bleeding misclassification affects precision but not magnitude of drug-related upper gastrointestinal bleeding risk

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## Abstract

**Objective:** To evaluate the accuracy of disease codes and free text in identifying upper gastrointestinal bleeding (UGIB) from electronic health-care records (EHRs).

**Study Design and Setting:** We conducted a validation study in four European electronic health-care record (EHR) databases such as Integrated Primary Care Information (IPCI), Health Search/CSD Patient Database (HSD), ARS, and Aarhus, in which we identified UGIB cases using free text or disease codes: (1) International Classification of Disease (ICD)-9 (HSD, ARS); (2) ICD-10 (Aarhus); and (3) International Classification of Primary Care (ICPC) (IPCI). From each database, we randomly selected and manually reviewed 200 cases to

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calculate positive predictive values (PPVs). We employed different case definitions to assess the effect of outcome misclassification on estimation of risk of drug-related UGIB.

**Results:** PPV was 22% [95% confidence interval (CI): 16, 28] and 21% (95% CI: 16, 28) in IPCI for free text and ICPC codes, respectively. PPV was 91% (95% CI: 86, 95) for ICD-9 codes and 47% (95% CI: 35, 59) for free text in HSD. PPV for ICD-9 codes in ARS was 72% (95% CI: 65, 78) and 77% (95% CI: 69, 83) for ICD-10 codes (Aarhus). More specific definitions did not have significant impact on risk estimation of drug-related UGIB, except for wider CIs.

**Conclusions:** ICD-9-CM and ICD-10 disease codes have good PPV in identifying UGIB from EHR; less granular terminology (ICPC) may require additional strategies. Use of more specific UGIB definitions affects precision, but not magnitude, of risk estimates. 

*Keywords:* Positive predictive value; Validation study; Non-steroidal anti-inflammatory agents; Drug safety; Signal detection; Upper gastrointestinal bleeding

## 1. Introduction

Electronic health-care records (EHRs) are frequently used data sources for investigating adverse clinical outcomes that occur during the use of certain drugs [1]. The advantages of using EHR databases (containing either medical records or reimbursement claims for health-care services) arise primarily from real-world data being captured on a large scale, allowing for cost efficiency and flexibility in study design to analyze the risk of adverse events associated with a wide range of drugs. Both medical records and administrative/claims databases have been used to characterize health-care utilization patterns and to monitor patient outcomes [2,3]. The use of such databases for active drug safety surveillance is gaining worldwide interest [4−6].

One of the most important adverse events is upper gastrointestinal bleeding (UGIB), which accounts for many adverse drug reaction−related hospitalizations [7]. The accuracy of diagnosis codes for identification of UGIB has been previously assessed in several studies [8−13], but only for two disease-coding systems: International Classification of Diseases (ICD)-Ninth Revision and READ codes. To date, there are no validation studies evaluating the accuracy of International Classification of Primary Care (ICPC) and ICD-10th Revision codes for ascertainment of UGIB from EHRs. This issue is particularly important, given the increasing use of EHR databases for investigating drug safety issues post-marketing. There is currently no data from literature as to whether outcome misclassification substantially biases the risk estimation of drug-associated UGIB. The additional value of UGIB case validation for signal detection in pharmacovigilance is uncertain.

In this study, we determined the accuracy of several terminology-specific codes and unstructured clinical narratives (ie, free text) in the identification of UGIB cases from four European EHR databases. Additionally, we investigated the impact of outcome misclassification on the estimation of UGIB risk during the use of five drugs known to be associated with, and five drugs known to be not associated with UGIB [14]. This validation study was conducted within the context of the European Commission−funded exploring and understanding adverse drug reactions (EU-ADR) project by integrative mining of clinical records and biomedical knowledge (http://www.euadr-project.org), which has developed a computerized integrated system of European EHR databases geared toward the early detection of drug-safety signals [4].

## 2. Methods

### 2.1. Data sources

This validation study was conducted in four EHR databases of the EU-ADR network, which are located in three European countries: two primary care databases [Integrated Primary Care Information (IPCI), the Netherlands [15], and Health Search/CSD Patient Database (HSD), Italy [16]]; and two administrative databases (ARS-Tuscany, Italy [17] and Aarhus University Hospital Database, Denmark [18]) that collect data on hospitalization, pharmacy dispensing, and other health services. These databases employ different disease-coding systems: the Italian databases (HSD and ARS) register medical events using the ICD-Ninth Revision clinical modification (ICD-9-CM); Aarhus database uses the ICD-10th Revision; [19] and IPCI uses the ICPC [20]. All citizens in these three countries are registered with a general practitioner (GP), who acts as a gatekeeper to secondary medical care. For each individual patient, GPs from IPCI and HSD register all relevant medical information from primary and secondary care, and information on demographics, notes on symptoms and diagnoses, clinical findings, referrals, laboratory values, hospitalizations, and drug prescriptions. In these two databases, clinical notes/narratives and referral letters from specialists are available as free text.

The four databases collectively cover a population of 8 million inhabitants from 1996 to 2010 (study period). The respective Medical Ethics Committee of each database approved the study. All databases have been extensively used for epidemiological research [17,18,21]. An overview of the database characteristics is given in Appendix A at www.jclinepi.com. In general, inhabitants of all ages are included in ARS, IPCI, and Aarhus, whereas in HSD individuals get registered in the database starting the age of 15 years. The male-to-female ratio is similar in all four databases.

### 2.2. UGIB case identification

Patients with UGIB were identified through automated case retrieval using diagnosis codes (Table 1) and free text