Comparing the impact of alternative phenotype definitions: insights from developing cohorts for COVID-19 adverse events of special interest

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Background

COVID-19 vaccines being authorized for emergency use have prompted researchers and regulators to prepare safety surveillance approaches that involve the use of real-world data to study adverse events of the vaccines. The Adverse Events of Special Interest (AESI) represent a collection of phenotypes that can be applied in observational data to study adverse event background rates. Developing accurate phenotypes is critical in obtaining reliable and reproducible background rates. Observational data can vary by geographic region and data composition, which can impact phenotype development. Since any given outcome may be represented by multiple alternative phenotype algorithms, we sought to characterize the differences between definitions and assess diagnostic accuracy (sensitivity and specificity errors) and potential index date misclassification errors for a cohort that represents a given phenotype.

Methods

A set of 15 phenotypes were assessed (Table 1). Cohort definitions were developed in ATLAS. The differences between the cohorts largely can be categorized into 4 major differences, differences by place of service, differences by concept set expression and place of service, concept set expression, and index date shift (Table 1). Evaluation was done using a process to compare characteristics and attributes from CohortDiagnostics in a set of cohorts for a given phenotype. The background rates were calculated using a time-at-risk as a 365-day period following the index date. People contributed time-at-risk from 1 January to 31 December for each qualifying year in 2017 to 2019. We compared the overall incidence rate by database for the cohort pairs in the phenotype. The databases used in this study included Optum© De-Identified Clinformatics® Data Mart Database – Date of Death-(DOD) (Optum DOD) dataset, IBM MarketScan® Databases [Commercial Claims (CCAE), Medicaid (MDCD) and Medicare (MDCR)] and Optum® de-identified Electronic Health Record Dataset (Panther), Columbia University Irving Medical Center (CUMC), Japan Medical Data Center (JMDC), IQVIA Australia Electronic Medical Records (IQVIA Australia), IQVIA Disease Analyzer Germany (IQVIA Germany), Clinical Practice Research Datalink (CPRD).

Category	Phenotype	Cohort definition #1	Cohort definition #2
Place of service variant	Acute myocardial infarction	Inpatient only	All settings
	Anaphylaxis	Inpatient only	All settings
	Appendicitis	Inpatient only	All settings
	Pulmonary embolism	Inpatient only	All settings
	Guillain Barre syndrome	Inpatient only	All settings
	Disseminated intravascular coagulation	Inpatient only	All settings
	Encephalomyelitis	Inpatient only	All settings
Place of service variant and code set variant	Hemorrhagic stroke	Inpatient only; and variation of codes	All settings
	Non-hemorrhagic stroke	Inpatient only; and varation of codes	All settings
Code set variant	Bell's palsy	Includes codes for unspecified and other disorders of facial nerve	Bell's palsy codes only
	Deep vein thrombosis	Broad code set	Narrow code set
	Immune thrombocytopenia (ITP)	Broad code set	Narrow code set
	Myocarditis/Pericarditis	Broad code set	Narrow code set
Index date shift variant	Transverse myelitis	Transverse myelitis indexed on condition	Transverse myelitis indexed on condition OR symptoms and subsequent TM code
	Narcolepsy	Narcolepsy concept set	Narcolepsy excluding prior hypersomnia in the 365 days prior

Table 1. Phenotypes evaluated and short description for each cohort variant. Each variant is organized by type of change into 4 categories.

Results

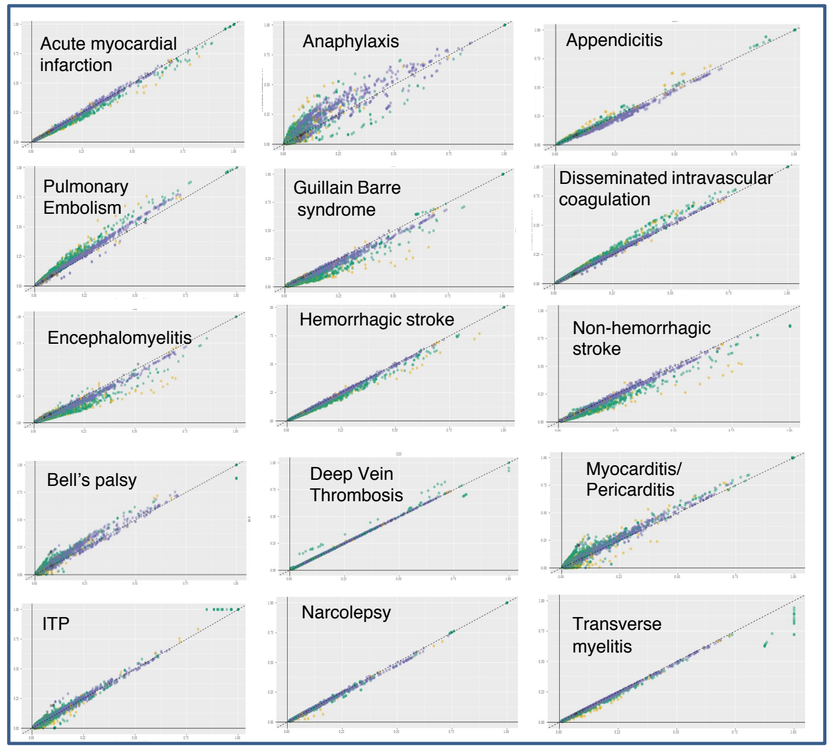

Figure 1. Standardized difference plots from Optum© De-Identified Clinformatics® Data Mart Database – Date of Death-(DOD)for all cohort covariates in various time bins prior to index date by data domain.

Standardized difference plots show variation across cohorts and phenotypes. Large variation was observed for the anaphylaxis phenotype, Bell's palsy, encephalomyelitis phenotypes (Figure 1). Background rates by cohort show a downward trend as cohorts become restricted by place of service and highly varied by database (Figure 2). MDCR shows the largest change by database and on higher overall incidence rates. For definitions that utilize inpatient setting, the IQVIA datasets, CPRD and JMDC cannot be evaluated. Code set variation cohorts also see a downward trend for alternative cohorts. Index date shift cohorts for Narcolepsy shows a very similar cohort characteristics between the two cohorts but has a downward trend on the background rates.

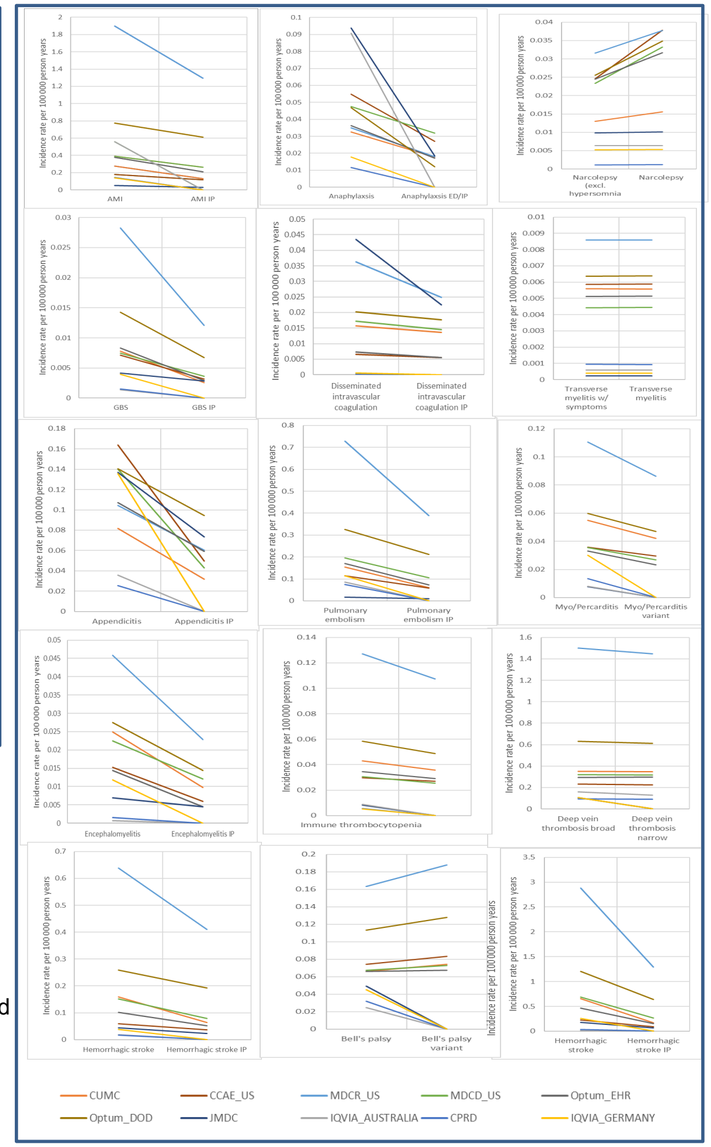

Figure 2. Standardized difference plots from Optum DOD for all cohort covariates in various time bins prior to index date by data domain.

Conclusions

Empirical assessment of phenotypes yields insights of trade-offs in sensitivity, specificity and misclassification of index events for a given phenotype. The composition of baseline patient characteristics can vary greatly by cohort within a phenotype. Background incidence rates have substantial variation by cohort for a phenotype.

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