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Validation of Novel Identification Algorithms for Nonfatal Myocardial Infarction Using Uniform Objective Criteria and Pooled Clinical Trial Data

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BACKGROUND & OBJECTIVE

- Acute myocardial infarction (MI) is a leading global cause of morbidity and mortality and a key outcome used for assessing pharmaceutical safety and efficacy in therapeutic areas including diabetes and metabolic syndrome[1,2]
- Real-world data (RWD) MI identification algorithms have primarily utilized ICD-9/10 diagnosis codes recorded in the inpatient setting to identify MI events, which are vulnerable to misclassification and coding errors[3,4]
- The Standardized Data Collection for Cardiovascular Trials Initiative (SCTI) and the US Food and Drug Administration (FDA) have proposed a set of objective criteria for defining MI in the clinical trial (CT) setting[2]
- The aim of this study was to develop and validate algorithms for identifying MI using pooled CT data by adapting the clinical rules suggested by SCTI and FDA, which can be extended to RWD for use in research and in pragmatic clinical trials

METHODS

Data Source and Pooled Database

- Anonymized, historical pooled CT data was sourced from the Medidata Enterprise Data Store, comprising more than 31,000 historical CTs with 9 million patients in around 100 countries over 20 years[5]
- For this investigation, Phase 3 cardiovascular outcome trials for cardiovascular and metabolic syndrome-related indications where algorithm inputs had been captured were standardized into a common data model and pooled
- The pooled CT study database contained patient demographics, medical history, medications, longitudinal treatments and procedures, clinical assessments (i.e., labs, vital signs, etc.), adverse clinical events, and death details

Study Population

- This study included patients from the study database who were assigned to either a treatment or placebo arm and were 40 years of age or older at the start of study treatment

Study Design

- *Index Date:* The date of the start of study treatment within each respective CT
- *Follow-up Period:* Index date until death or the end trial participation
- *Algorithms:* Seven rule-based algorithms to identify and date MI events were developed. Algorithms were adapted from clinical rules in the literature and utilized only information readily available in administrative claims databases (**Figure 1**)
- *Algorithm Validation and Performance:* All pooled CTs included flags for Clinical Events Committee (CEC) adjudicated nonfatal MI events that were used as the source of truth for algorithm validation. If the algorithm-identified MI event occurred within +/- 15 days of the CEC adjudicated MI event, then the event was considered a True Positive (**Figure 2**). Algorithm performance was assessed using sensitivity and positive predictive value (PPV)

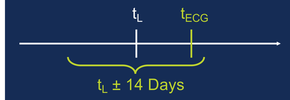
Figure 1. Rule-Based MI Identification Algorithms

For all algorithms, the date of the algorithm-assigned MI event was defined as the date of the cardiac biomarker test (t_L)

Algorithm 1 (A1): Cardiac Biomarkers

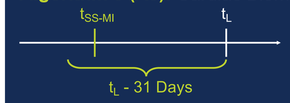
MI Definition: If a patient had a cardiac biomarker lab test (t_L) then the algorithm assigned the event as an MI
Cardiac Biomarker Lab Tests included Troponin, Troponin I, Troponin T, and CK-MB

Algorithm 2 (A2): Cardiac Biomarkers AND Electrocardiogram (ECG)



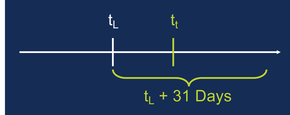
MI Definition: If a patient had a cardiac biomarker lab test (t_L) **AND** within 14 days prior to or following the lab test had an ECG (t_{ECG}), then the algorithm assigned the event as an MI

Algorithm 3 (A3): Cardiac Biomarkers AND Signs and Symptoms of MI



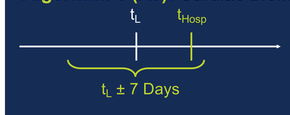
MI Definition: If a patient had a cardiac biomarker lab test (t_L) **AND** within 31 days prior to the lab test had documented signs/symptoms of MI (t_{SS-M}), then the algorithm assigned the event as an MI
Signs and symptoms included chest pain, chest discomfort, chest pressure, shoulder pain, palpitations, upper back pain, arm pain, indigestion, and nausea[6]

Algorithm 4 (A4): Cardiac Biomarkers AND Treatment



MI Definition: If a patient had a cardiac biomarker lab test (t_L) **AND** within 31 days following the lab test (t_L) had an MI-related treatment (t_t), including either a new prescription for an MI-related medication or an MI-related procedure, then the algorithm assigned the event as an MI
MI Medications included aspirin, thrombolytic agents, and anticoagulants
MI Procedures included coronary angioplasty and stenting (percutaneous coronary intervention) and coronary artery bypass surgery

Algorithm 5 (A5): Cardiac Biomarkers AND Hospitalization



MI Definition: If a patient had a cardiac biomarker lab test (t_L) **AND** within 7 days prior to or following the lab test was hospitalized for any reason (t_{hosp}), then the algorithm assigned the event as an MI

Algorithm 6 (A6): Cardiac Biomarkers AND ECG AND Hospitalization

MI Definition: If a patient had a cardiac biomarker lab test (t_L) **AND** within 14 days prior to or following the lab test had an ECG (t_{ECG}) **AND** within 7 days prior to or following the lab test was hospitalized for any reason (t_{hosp}), then the algorithm assigned the event as an MI

Algorithm 7 (A7): Cardiac Biomarkers AND ECG AND Treatment

MI Definition: If a patient had a cardiac biomarker lab test (t_L) **AND** within 14 days prior to or following the lab test had an ECG (t_{ECG}) **AND** within 31 days following the lab test had an MI-related treatment (t_t) then the algorithm assigned the event as an MI

Figure 2. Cross Tabulation of Adjudicated Occurrence and Date of Occurrence of MI Versus Rule-based Algorithm to Identify and Date the Occurrence of MI

Adjudicated MI► / Rule-Based MI▼	Occurrence and Date of Occurrence of MI	No Occurrence of MI
Classification of MI (±15 days)	True Positive	False Positive
No Occurrence of MI	False Negative	—

MI, myocardial infarction.

RESULTS

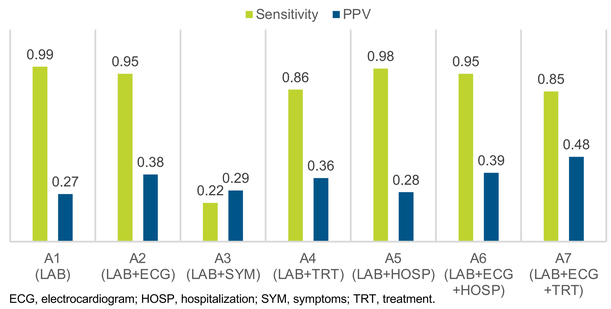
- A total of **40,866** patients met the study inclusion criteria and were followed for a median follow-up time of 1.6 years (IQR: 3.7 years). Baseline characteristics are shown in **Table 1**
- Among these patients, **1,133** CEC adjudicated nonfatal MI events occurred during the follow-up period
- The algorithm with only cardiac biomarkers (A1) had the highest sensitivity (99%) for identifying MI, but a low PPV (27%) (**Figure 3**)
- The algorithm that combined cardiac biomarkers with all-cause hospitalizations (A5) had similar performance to cardiac biomarkers alone, with a sensitivity of 98% and a PPV of 28%
- The algorithm including signs and symptoms of MI (A3) had the lowest sensitivity (22%), without meaningful gains in PPV (29%)
- Combining cardiac biomarkers with ECG (A2) improved algorithm PPV to 38% with a slight reduction to sensitivity (95%)
- Combining cardiac biomarkers with both ECG and MI-related treatment (A7) produced the largest PPV of all algorithms (48%) and a sensitivity of 85%

Table 1. Baseline Characteristics of the Study Cohort (N=40,866)

Clinical or Demographic Characteristic	N (%)
Age, mean years (SD)	65.7 (9.0)
Age, median years (25th-75th percentile)	65.0 (60.0-72.0)
Male	24,244 (59.3)
Hypertension	34,995 (85.6)
Type II Diabetes Mellitus	30,929 (75.7)
Chronic Kidney Disease	11,371 (27.8)
Heart Failure	5,014 (12.3)

SD, standard deviation.

Figure 3. Performance of Rule-based MI Identification Algorithms



ECG, electrocardiogram; HOSP, hospitalization; SYM, symptoms; TRT, treatment.

CONCLUSIONS

- In this study, we developed MI identification algorithms based on clinical rules in the literature and validated those algorithms in a large, diverse pooled CT database
- We found that algorithm sensitivity for MI was high when relying on cardiac biomarker assessments alone, but PPV was low. Low algorithm PPV was likely an artifact of not including test results, which may have increased PPV but would have limited algorithm utility in administrative claims data
- The incorporation of signs and symptoms of MI in an algorithm resulted in both low sensitivity and PPV. Since MI symptoms are reimbursable, they are likely more accurately documented in RWD than in CT data. Therefore, this algorithm may exhibit improved performance in real-world (RW) databases
- Combining cardiac biomarkers with ECGs, hospitalizations, and MI-related treatments improved algorithm PPV
- Hospital discharge diagnosis codes were not available in the CT data. Selecting only hospitalizations with discharge diagnosis codes indicative of MI would likely improve algorithm PPV in RW databases
- The findings of this study may be used to augment existing algorithms to identify MI in RW retrospective studies or prospectively in pragmatic trials

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