

Validation of a Claims-Based Algorithm for Myocarditis/Pericarditis and Assessment of the Impact of Outcome Misclassification in a US Postapproval study of COVID-19 Vaccine Safety

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Background

- Myocarditis/Pericarditis (m/p) is a potential safety concern after mRNA COVID-19 vaccination.
- Data are lacking on the validity of claims-based algorithms for m/p.
- As part of a US postapproval study of the original monovalent Pfizer BioNTech COVID-19 vaccine (BNT162b2), we validated an ICD-10-CM code algorithm for m/p (EUPAS43468).

Objective

- To estimate the positive predictive value (PPV) of a claims-based m/p algorithm in a population of BNT162b2 vaccinees and matched unvaccinated individuals, and to conduct quantitative bias analyses (QBA) examining the potential for outcome misclassification in the final study results.

Methods

Population

- Administrative claims data were drawn from five insurers participating in the US Sentinel System; eligible individuals were aged ≥12 years.
- Potential m/p cases were identified using an ICD-10-CM diagnosis code algorithm among BNT162b2 vaccinees (December 2020-April 2023) and matched unvaccinated comparators, within a 21-day risk window after the index date (vaccination or cohort entry date).
- Medical record validation was performed in a sample of algorithm-identified cases with a recorded m/p diagnosis at one participating insurer.

Claims-based algorithm

- Algorithm** based on COVID-19 Safety Surveillance by the FDA's BEST Initiative.
- First recorded diagnosis** of m/p in any care setting in the 21-day risk window
- Washout window:** Relative to the index date in days [−365, 0].

Medical Record Review

- Two clinicians blinded to vaccination status independently reviewed medical records and classified each potential case.
- Cases were adjudicated using Brighton Collaboration adapted definitions.
 - Primary** clinical definition included definitive/probable cases
 - Secondary** clinical definition included definitive/probable or clinician diagnosed cases

Statistical Analyses

- PPV** was calculated as the proportion of medical record-confirmed cases among algorithm-identified cases; estimates were reported overall, by care setting, and by exposure status and used two denominators:
 - PPV1:** All reviewed cases.
 - PPV2:** Cases with sufficient information to confirm case status.
- QBA** was conducted as a sensitivity analysis, applying exposure-specific PPVs to calculate corrected incidence rate ratios (IRRs) for the overall study.
 - QBA** assumed algorithm sensitivity was 5–20% higher in vaccinated than unvaccinated individuals, with sensitivity in the vaccinated set at 80% or 100%.

Results

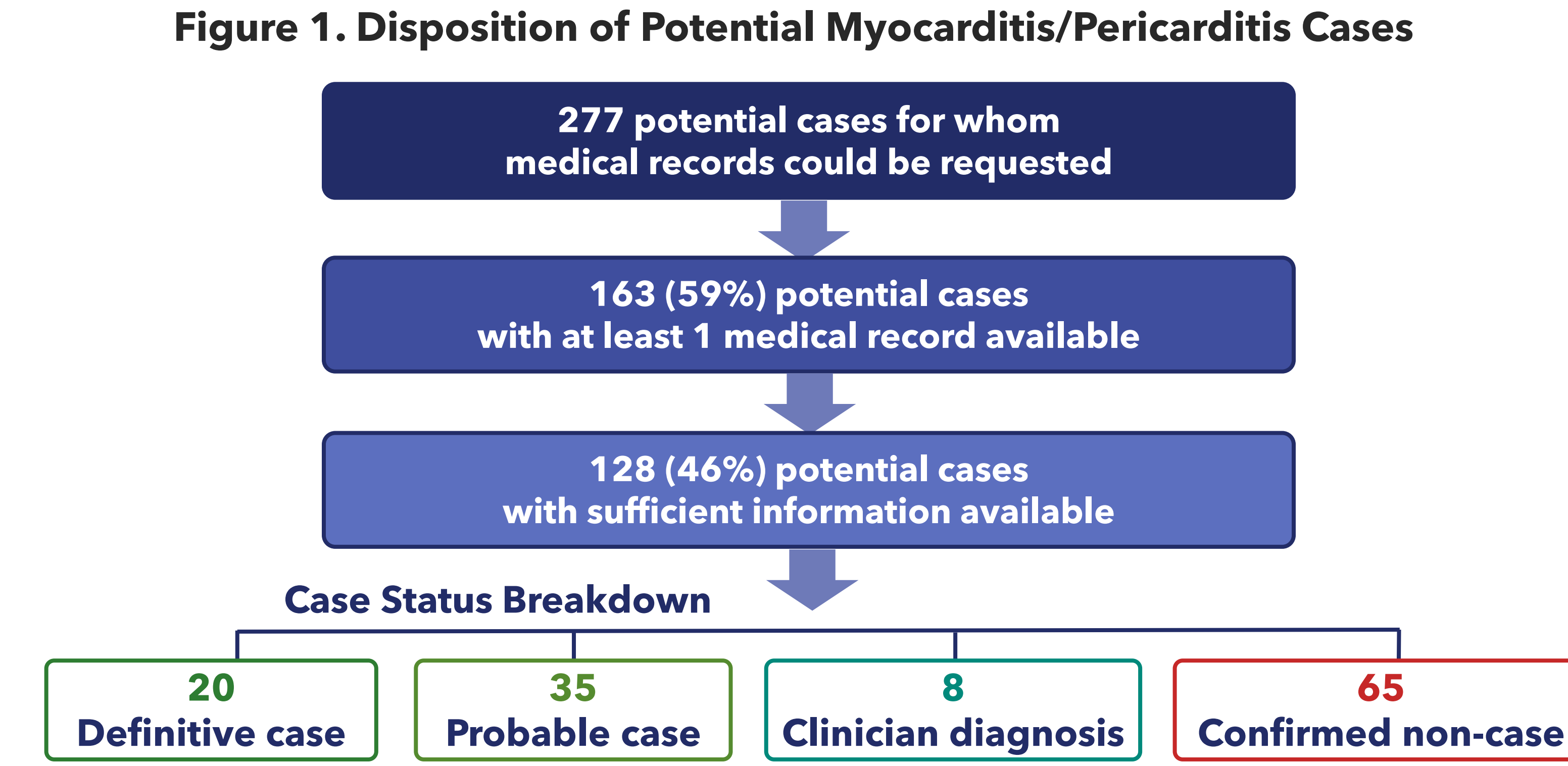


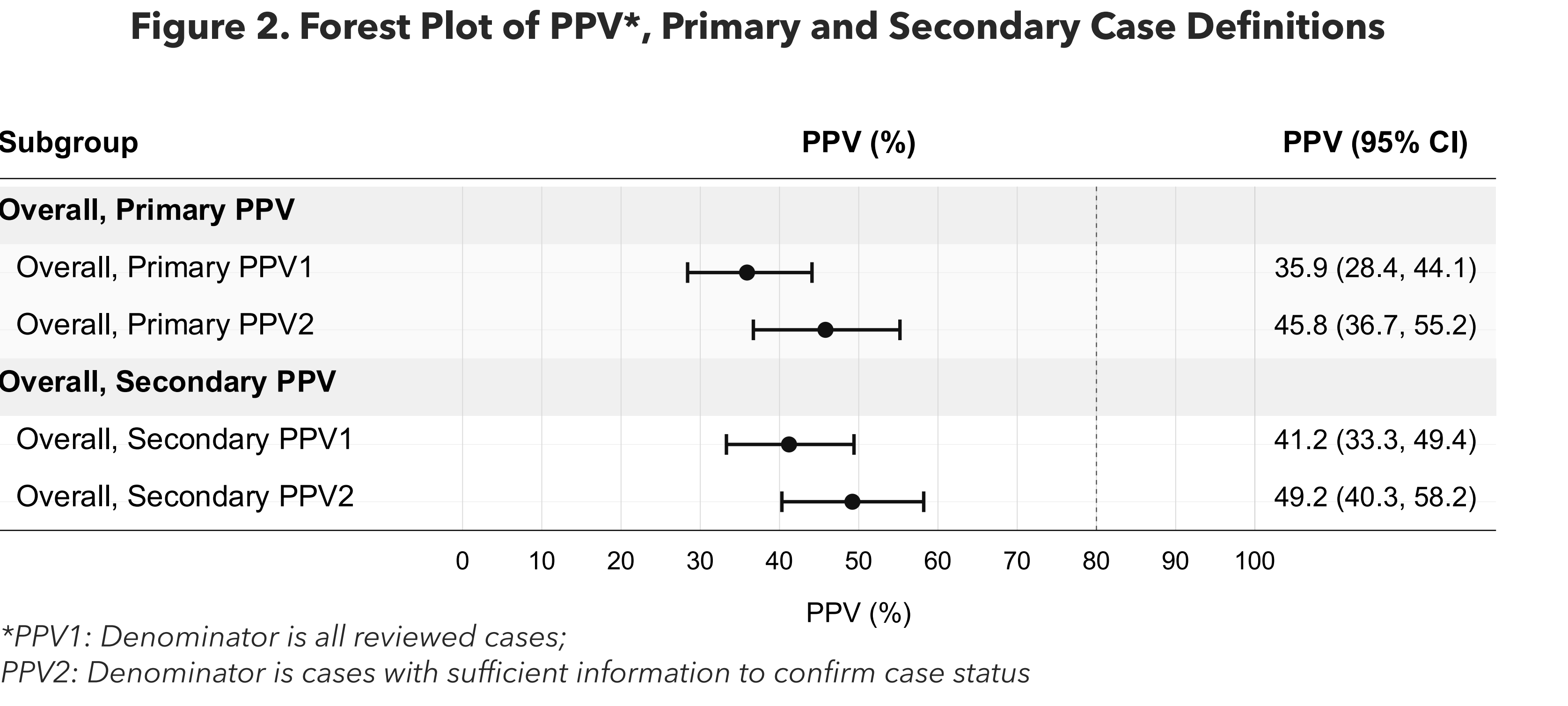
Table 1. Descriptive Characteristics of Potential Myocarditis/Pericarditis Cases ≥12 Years in the Validation and Final Analysis Cohorts

Characteristic	Potential cases in the validation cohort (n=277) ^a	Potential cases with retrievable records and sufficient information (n=128) ^b
Sex		
Male	175 (63.2%)	82 (64.1%)
Female	102 (36.8%)	46 (35.9%)
Age at index date		
12–24 years	66 (23.8%)	35 (27.3%)
25–39 years	43 (15.5%)	16 (12.5%)
40–64 years	115 (41.5%)	51 (39.8%)
≥65 years	53 (19.1%)	26 (20.3%)
Medical care setting of m/p diagnosis^c		
Inpatient	104 (37.5%)	48 (37.5%)
Emergency department	30 (10.8%)	16 (12.5%)
Ambulatory care	143 (51.6%)	64 (50.0%)

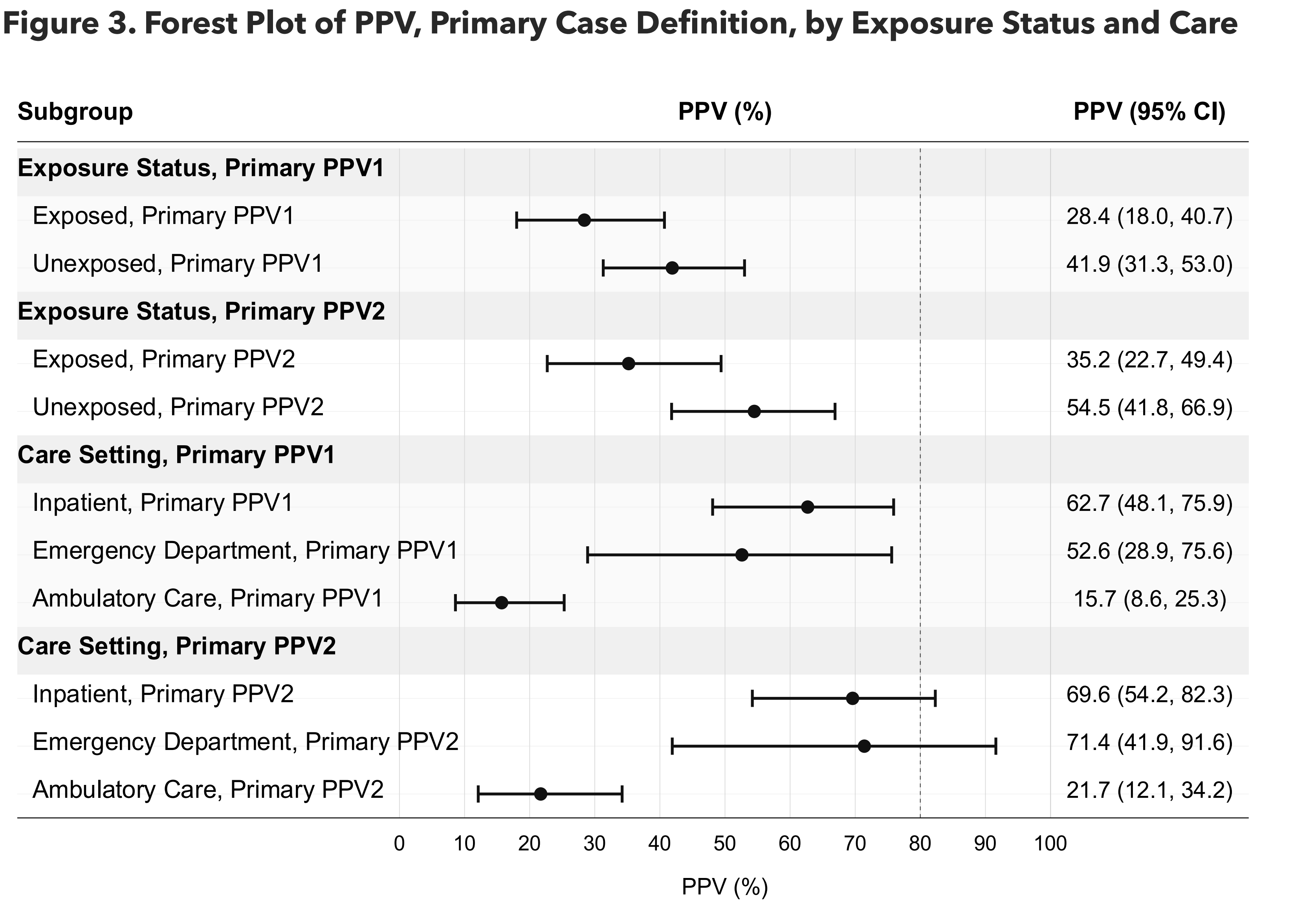
^a Potential cases eligible for medical record review at one Research Partner (excludes those not eligible to have medical records used for research studies).
^b Excludes cases without sufficient information in record. These were used to calculate PPV2 estimates.
^c If more than one medical care setting for the potential case of myocarditis/pericarditis was observed in electronic data, setting was assigned according to the following hierarchy: inpatient>emergency department>ambulatory care.

Disclosure Statement: Some co-authors are or were employed at nonprofit organizations (RTI Health Solutions, Harvard Pilgrim Health Care Institute and IU School of Medicine/Indiana University Health) which conduct work for government and private organizations, including pharmaceutical companies. Some authors are employees at Carelon Research, Inc. and may own stock in Elevance Health. Some authors are employees and stockholders of Pfizer Inc., the company that produced the vaccine being evaluated. SCC was employed at IU School of Medicine/Indiana University Health at time of this study and is currently at Elli Lilly.

Acknowledgements: HPHCI: Maria Michaelidis, Andrew Simon



- Overall PPVs were 36%/46% for the primary definition and 41%/49% for the secondary definition (PPV1/PPV2)**



- PPVs were highest in inpatient (63%/71%) and emergency settings (53%/75%), and lowest in ambulatory settings (16%/27%) [Primary/Secondary Case Definitions]**

- PPVs were lower among exposed (28%/39%) than unexposed individuals (42%/58%) [Primary/Secondary Case Definitions]**

Table 2. Corrected Incidence Rate Ratios (IRR) Assuming Differential Outcome Sensitivity by Exposure Group

Primary series analysis		
Number of events per PY in matched cohorts		
Exposed cohort	443 per 664,175.47	
Unexposed/comparator cohort	724 per 1,238,551.34	
Observed IRR^a	1.14	
Corrected IRRs^b, with the following assumptions		
Sensitivity is 20% higher in exposed compared to unexposed cohort		
E ⁺ vs. E ⁻ : 100% vs. 80%	0.59	
E ⁺ vs. E ⁻ : 80% vs. 60%	0.55	
Sensitivity is 10% higher in exposed compared to unexposed cohort		
E ⁺ vs. E ⁻ : 100% vs. 90%	0.66	
E ⁺ vs. E ⁻ : 80% vs. 70%	0.64	
Sensitivity is 5% higher in exposed compared to unexposed cohort		
E ⁺ vs. E ⁻ : 100% vs. 95%	0.70	
E ⁺ vs. E ⁻ : 80% vs. 75%	0.69	

E⁺ is exposed cohort; E⁻ is unexposed/comparator cohort
^a The observed IRR was calculated by dividing the IR in the matched, exposed cohort by the IR in the matched, unexposed cohort in all 5 RPs, with IRs calculated as the number of events in each exposure cohort divided by the total person-time in each exposure cohort.
^b Corrected IRRs were calculated as IRR^c = IRR₀ * (PPV₁/PPV₀) * (Se₀/Se₁). IRR₀ denotes the observed IRR. PPV₁ and PPV₀ denote the positive predictive value estimates among the exposed and unexposed cohorts, respectively; Se₁ and Se₀ denote sensitivity estimates in the exposed and unexposed cohorts, respectively. Under all quantitative bias analysis scenarios, the PPV in the exposed cohort was assumed to be 35.2% and the PPV in the unexposed cohort was assumed to be 54.5%, based on the results of medical record validation performed for this study.

- The observed primary series IRR in the final analysis was 1.14, whereas the corrected IRRs for m/p ranged from 0.55 - 0.70.**

Conclusions

- The PPV of the m/p algorithm was <50%, but increased when restricted to inpatient or emergency department events.
- In QBA, the corrected IRR was attenuated to below the null, suggesting that the IRR observed in main study was not underestimated relative to the true IRR due to outcome misclassification.