# Validation of Algorithms to Identify Cardiac-Related Deaths in Population-Based Studies Using a Claims Database

EPH115

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## CONCLUSIONS

- With high specificity and NPV and moderate sensitivity and PPV, the claims-based CRD definition at any diagnosis within 7 days of death (algorithm C) had the highest Cohen κ in identifying CRD
- Increasing the identification window did not improve algorithm accuracy
- These findings may help to inform definitions of CRD for future claims database research

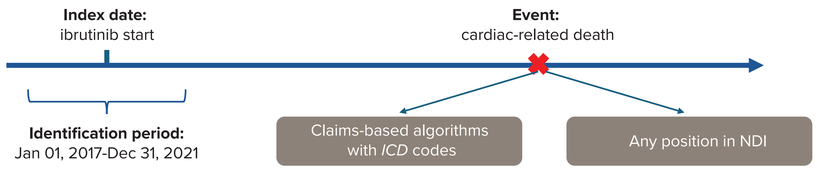
## BACKGROUND

- Cardiovascular diseases are the second most prevalent cause of mortality in patients with cancer[1]
- Cardiovascular toxicity of oncology treatments is a major concern for patients and clinicians[2]
- Cardiac-related death (CRD) is a cause-specific outcome of interest in assessing the safety and effectiveness of new treatments
- While mortality data can be captured in claims-based studies via linkage to other sources, cause of death is often not available and must be derived with additional algorithms
- This study aimed to assess claims-based algorithms to identify CRD using a large US administrative claims database

## METHODS

- This was a retrospective cohort study using the US Medicare Fee-For-Service database
- The study population included patients with indolent B-cell malignancies (chronic lymphocytic leukemia/small lymphocytic lymphoma [CLL/SLL], follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma, or Waldenström macroglobulinemia) who started ibrutinib between January 1, 2017, and December 31, 2021 (**Figure 1**)
- Patients were followed up from ibrutinib start (index date) until the earliest of ibrutinib discontinuation, death, disenrollment, or study end (end of follow up)
- CRD was defined as a death due to cardiac arrest/sudden cardiac death, atrial fibrillation or flutter, heart failure, myocardial infarction, ventricular fibrillation or flutter, ventricular tachycardia, sudden death, or ischemic stroke. Deaths with trauma-related claims (defined via *International Classification of Diseases, 10th Revision, Clinical Modification [ICD-10-CM]* codes) within 14 days prior were not counted as cardiac-related deaths
  - Four algorithms were evaluated using prespecified *ICD-10-CM* codes for cardiac-related events at primary diagnosis within (A) 7 or (B) 30 days and any diagnosis (primary or secondary in the claim) within (C) 7 or (D) 30 days of death
  - The National Death Index (NDI) was used as the reference
- Performance metrics, including accuracy, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and Cohen κ, were calculated

### Figure 1. Study Design Scheme and Algorithms




| Algorithm | Position | Time window |
|---|---|---|
| A | Primary | Within 7 days |
| B | Primary | Within 30 days |
| C | Any | Within 7 days |
| D | Any | Within 30 days |

**Abbreviations**: *ICD, International Classification of Diseases*; NDI, National Death Index.

## RESULTS

### Baseline Characteristics and CRD Incidence Using the NDI

- In total, 13,241 patients were included (male, 57.7%; median age, 77.2 years; non-Hispanic White, 90.7%; CLL/SLL alone, 78.9%) (**Table 1**)
- Using the NDI, 568 CRD events (4.3%) were identified, with an incidence rate of 35.2 per 1000 person-years

**Table 1. Baseline Characteristics**

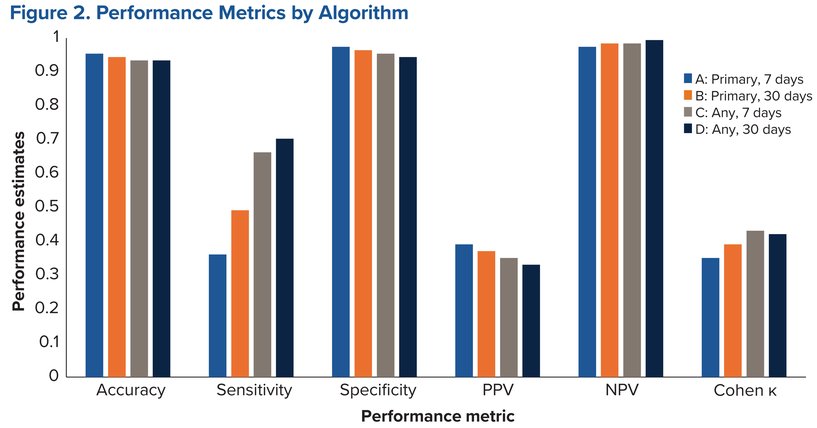
| | Overall N=13,241 | Single B-cell malignancy, CLL/SLL[a] n=10,449 | Single B-cell malignancy, non-CLL[a] n=2622 | Multiple B-cell malignancies[a] n=170 |
|---|---|---|---|---|
| **Age at index, median (Q1-Q3), years** | 77.2 (72.2-82.8) | 77.1 (72.1-82.7) | 77.7 (72.5-83.0) | 77.2 (71.1-84.6) |
| **Age group at index, n (%)** | | | | |
| 65-69 years | 1979 (14.9) | 1596 (15.3) | 352 (13.4) | 31 (18.2) |
| 70-74 years | 3144 (23.7) | 2501 (23.9) | 609 (23.2) | 34 (20.0) |
| 75-79 years | 3277 (24.7) | 2569 (24.6) | 670 (25.6) | 38 (22.4) |
| 80-84 years | 2590 (19.6) | 2043 (19.6) | 520 (19.8) | 27 (15.9) |
| ≥85 years | 2251 (17.0) | 1740 (16.7) | 471 (18.0) | 40 (23.5) |
| **Calendar year at index, n (%)** | | | | |
| 2017 | 3010 (22.7) | 2341 (22.4) | 638 (24.3) | 31 (18.2) |
| 2018 | 3008 (22.7) | 2391 (22.9) | 590 (22.5) | 27 (15.9) |
| 2019 | 3035 (22.9) | 2542 (24.3) | 456 (17.4) | 37 (21.8) |
| 2020 | 2466 (18.6) | 1894 (18.1) | 525 (20.0) | 47 (27.6) |
| 2021 | 1722 (13.0) | 1281 (12.3) | 413 (15.8) | 28 (16.5) |
| **Sex, n (%)** | | | | |
| Female | 5597 (42.3) | 4426 (42.4) | 1097 (41.8) | 74 (43.5) |
| Male | 7644 (57.7) | 6023 (57.6) | 1525 (58.2) | 96 (56.5) |
| **Race and ethnicity (self-reported), n (%)** | | | | |
| Non-Hispanic White | 12,010 (90.7) | 9470 (90.6) | 2387 (91.0) | 153 (90.0) |
| Black/African American | 614 (4.6) | 536 (5.1) | >67 (2.6) | n<11 |
| Asian/Pacific Islander | 112 (0.8) | 81 (0.8) | >22 (>0.8) | n<11 |
| Hispanic | 84 (0.6) | >52 (>0.5) | 30 (1.1) | n<11 |
| American Indian/Alaska Native | 18 (0.1) | >11 (>0.1) | n<11 | 0 |
| Other | 117 (0.9) | 71 (0.7) | >35 (1.3) | n<11 |
| Unknown | 286 (2.2) | 223 (2.1) | >52 (2.0) | n<11 |
| **Region, n (%)[b]** | | | | |
| Northeast | 2673 (20.2) | 2068 (19.8) | 567 (21.6) | 38 (22.4) |
| Midwest | 3358 (25.4) | 2718 (26.0) | 599 (22.8) | 41 (24.1) |
| South | 4732 (35.7) | 3762 (36.0) | 910 (34.7) | 60 (35.3) |
| West | 2464 (18.6) | >1890 (>18.0) | >535 (>20.4) | 31 (18.2) |
| **Dual eligibility, n (%)** | | | | |
| Yes | 1161 (8.8) | 913 (8.7) | >237 (9.0) | n<11 |
| Full dual eligibility | 816 (6.2) | 651 (6.2) | >154 (5.9) | n<11 |
| Partial dual eligibility | 345 (2.6) | 262 (2.5) | >72 (2.7) | n<11 |
| No | 12,080 (91.2) | 9536 (91.3) | >2380 (90.8) | >159 (>93.5) |

[a]Groups are mutually exclusive. [b]Remaining patients are from outlying areas under US sovereignty.
**Abbreviations:** CLL, chronic lymphocytic leukemia; Q, quartile; SLL, small lymphocytic lymphoma.

### Performance Metrics by Algorithm

- Algorithms using any diagnosis had higher sensitivity (C: 0.66; 95% CI, 0.62-0.70; D: 0.70; 95% CI, 0.66-0.74) than those using primary diagnosis only (A: 0.36; 95% CI, 0.32-0.40; B: 0.49; 95% CI, 0.45-0.53) (**Figure 2**)
- Specificities and NPVs were similar across algorithms (specificity range, 0.94-0.97; NPV range, 0.97-0.99)
- PPVs were slightly higher using primary diagnosis (A: 0.39; 95% CI, 0.35-0.43; B: 0.37; 95% CI, 0.34-0.41) vs any diagnosis (C: 0.35; 95% CI, 0.33-0.38; D: 0.33; 95% CI, 0.31-0.36)
- Algorithm C had the highest Cohen κ (0.43; 95% CI, 0.40-0.46)

### Figure 2. Performance Metrics by Algorithm




| Metrics (95% CI) | Algorithms A: Primary, 7 days | B: Primary, 30 days | C: Any, 7 days | D: Any, 30 days |
|---|---|---|---|---|
| **Accuracy** | 0.95 (0.94-0.95) | 0.94 (0.94-0.95) | 0.93 (0.93-0.94) | 0.93 (0.92-0.93) |
| **Sensitivity** | 0.36 (0.32-0.40) | 0.49 (0.45-0.53) | 0.66 (0.62-0.70) | 0.70 (0.66-0.74) |
| **Specificity** | 0.97 (0.97-0.98) | 0.96 (0.96-0.97) | 0.95 (0.94-0.95) | 0.94 (0.93-0.94) |
| **PPV** | 0.39 (0.35-0.43) | 0.37 (0.34-0.41) | 0.35 (0.33-0.38) | 0.33 (0.31-0.36) |
| **NPV** | 0.97 (0.97-0.97) | 0.98 (0.97-0.98) | 0.98 (0.98-0.99) | 0.99 (0.98-0.99) |
| **Cohen κ** | 0.35 (0.31-0.39) | 0.39 (0.36-0.43) | 0.43 (0.40-0.46) | 0.42 (0.39-0.45) |

**Abbreviations:** NPV, negative predictive value; PPV, positive predictive value.

## Strengths and Limitations

- This study leveraged Medicare Fee-for-Service, a large closed claims database with well-documented mortality data
- Cause of death, which is not usually available for claims-based analysis, was documented in the NDI and linked to the study population, allowing for this validation exercise
- Limitations include possible variation in documentation of cause of death due to physician, location, and other factors that have not been measured and lack of data from more recent years due to limited availability of NDI data

## REFERENCES

1. Okwuosa TM, et al. *J Am Coll Cardiol*. 2018;72(2):228-232.
2. Albini A, et al. *J Natl Cancer Inst*. 2010;102(1):14-25.

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## DISCLOSURES

**RJ**: Honoraria: Secura Bio; Consulting or advisory role: AbbVie, AstraZeneca, Genentech, BeOne Medicines, Ltd, Genmab, Lilly; Speakers bureau and travel, accommodations, expenses: AbbVie, Adaptive, BeOne Medicines, Ltd, AstraZeneca. **AF**: Consulting or advisory role: Janssen, AstraZeneca, BeOne Medicines, Ltd, Genentech; Research funding: Genmab, Genetech, Lilly. **XW**: Employment: BeOne Medicines, Ltd (current), Flatiron Health (former); Stock or other ownership: BeOne Medicines, Ltd, Roche. **QF**: Employment and stock: BeOne Medicines, Ltd (self), AbbVie (spouse). **AB, NL, YZ, JA**: Employment: Genesis Research Group; Consulting or advisory role and research funding: BeOne Medicines, Ltd (payable to institution). **DvB**: Employment: BeOne Medicines, Ltd; Stock or other ownership: BeOne Medicines, Ltd, Pfizer, GSK, Nurix. **AKA**: Employment and owns stock: BeOne Medicines, Ltd. **MF**: Honoraria: Zoll; Consulting or advisory role: AstraZeneca, AbbVie, Janssen, Pfizer; Research funding: Medtronic, AstraZeneca.

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