# Mortality Associated with Warm Autoimmune Hemolytic Anemia Among Medicare Beneficiaries

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## Key Takeaways

- **Patients with wAIHA face a significantly higher risk of death after their initial diagnosis than their matched non-AIHA counterparts, including in cases of primary wAIHA without the comorbidities typically associated with secondary disease**
- **Results highlight possible gaps in early diagnosis and effective management of the disease, which may contribute to increased mortality**
- **Future research should aim to identify patient-specific factors contributing to elevated mortality risk**

## Background

Warm autoimmune hemolytic anemia (wAIHA) is a disorder in which autoantibodies bind to red blood cells at body temperature, leading to premature destruction;[1] it is the most common type of autoimmune hemolytic anemia (AIHA)[1]

wAIHA is associated with clinical complications such as venous thromboembolism, severe infection, and premature death[2,3]

In European studies, both primary and secondary AIHA have been associated with increased mortality relative to the general population, even after adjusting for comorbidities[4,5]

Real-world mortality assessments among patients with wAIHA relative to patients without AIHA in the United States are lacking

## Objective

**To estimate mortality associated with wAIHA by comparing Medicare beneficiaries with wAIHA and those without AIHA**

## Methods

### Data Source and Study Design

- This was a retrospective, observational cohort study of Medicare beneficiaries from the 100% Medicare Fee-for-Service database for the period from October 1, 2019, to December 31, 2023
- Study cohorts included patients with wAIHA (index date was the first qualifying wAIHA diagnosis) and a comparison cohort of those without AIHA (index date was random during continuous Medicare eligibility)
- The baseline period was defined as 12 months before the index date
- The follow-up period spanned the index date until the earliest of death, end of continuous Medicare eligibility, or end of data

### Patient Selection Criteria

- ≥18 years old on the index date
- 12 months of continuous Medicare Part A, B, and D eligibility before the index date (i.e., baseline period)
- Additionally for patients with wAIHA:
  - Evidence of wAIHA defined as one of the following:
    - A diagnosis of wAIHA (International Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10-CM] code D59.11) in the primary position during an inpatient setting
    - ≥2 diagnoses of wAIHA in any position (i.e., primary or secondary) or setting ≥30 days apart, with the second diagnosis considered wAIHA-qualifying
    - A diagnosis of wAIHA in any position or setting preceded by ≥30 days by any diagnosis of AIHA (ICD-10-CM codes D59.10, D59.19, D59.8, and D59.9)
  - No diagnoses of cold or mixed-type AIHA (ICD-10-CM codes D59.12 and D59.13) during the baseline period or on the index date
- Additionally for patients without AIHA
  - No diagnoses for any AIHA during the study period
- Patients in the non-AIHA cohort were matched 10:1 to the wAIHA cohort based on age on the index date

### Statistical Analysis and Outcomes

- Overlap weighting was used to further balance baseline confounders between cohorts
  - Baseline confounders included demographic characteristics, dual Medicare/Medicaid eligibility, index year, and mortality-related comorbidities (coronary artery disease, renal failure, valvular disease, liver disease, and pulmonary circulation disorder), excluding conditions related to secondary wAIHA and secondary wAIHA-adjusted Quan-Charlson Comorbidity Index
- Mortality during the follow-up period was evaluated between the weighted cohorts using Kaplan–Meier analysis and the Cox proportional hazards model; patients without observed death were censored at the end of follow-up
- A sensitivity analysis for the primary wAIHA subgroup was conducted by excluding patients with conditions for secondary wAIHA during the baseline period or on the index date from both cohorts
  - Conditions for secondary wAIHA included hematologic or lymphoproliferative disorders, solid tumors, autoimmune or inflammatory diseases, viral or bacterial infections, and primary immunodeficiencies
- In the sensitivity analysis, cohorts were not re-weighted, and weights from the main analysis were used; characteristics that remained unbalanced were included as covariates in the Cox proportional hazards model

## Results

### Baseline Patient Characteristics

**Table 1.** ***Baseline characteristics of the weighted cohorts***

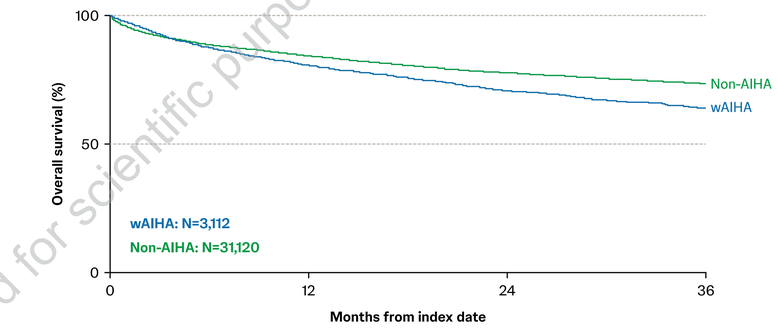
| Characteristic[a] | Main Analysis: wAIHA Cohort N=3,112 | Main Analysis: Non-AIHA Cohort N=31,120 | Std. diff. | Sensitivity Analysis: Primary wAIHA Subgroup N=1,442 | Sensitivity Analysis: Non-AIHA Subgroup N=23,966 | Std. diff. |
|---|---|---|---|---|---|---|
| **Age at index date,** years | 74.4 ± 11.6 [75.0] | 74.6 ± 11.2 [75.0] | 2.3 | 74.9 ± 11.6 [75.0] | 74.2 ± 11.4 [75.0] | 5.8 |
| **Sex, female** | 1,747 (56.1) | 17,468 (56.1) | 0.0 | 875 (60.7) | 13,671 (57.0) | 7.4 |
| **Race/ethnicity** | | | | | | |
| Non-Hispanic White | 2,634 (84.6) | 26,334 (84.6) | 0.1 | 1,245 (86.4) | 20,226 (84.4) | 5.6 |
| Black | 178 (5.7) | 1,786 (5.7) | 0.0 | 69 (4.8) | 1,368 (5.7) | 4.1 |
| Hispanic | 130 (4.2) | 1,307 (4.2) | 0.1 | 59 (4.1) | 1,037 (4.3) | 1.0 |
| Asian | 77 (2.5) | 768 (2.5) | 0.0 | 35 (2.4) | 615 (2.6) | 0.9 |
| Multiple or other | 29 (0.9) | 294 (0.9) | 0.0 | 12 (0.8) | 225 (0.9) | 1.4 |
| Unknown | 63 (2.0) | 631 (2.0) | 0.0 | 22 (1.5) | 496 (2.1) | 4.4 |
| **Geographic region** | | | | | | |
| South | 983 (31.6) | 9,843 (31.6) | 0.1 | 462 (32.1) | 7,508 (31.3) | 1.6 |
| Midwest | 849 (27.3) | 8,479 (27.2) | 0.1 | 425 (29.5) | 6,660 (27.8) | 3.8 |
| Northeast | 696 (22.4) | 6,951 (22.3) | 0.0 | 296 (20.5) | 5,201 (21.7) | 2.8 |
| West | >585 (-)[b] | 5,836 (18.8) | 0.0 | >257 (-)[b] | >4,589 (-)[b] | 3.4 |
| Other and unknown | <11 (-)[b] | 11 (0.0) | 0.1 | <11 (-)[b] | <11 (-)[b] | 1.7 |
| **Medicaid and Medicare dual eligibility** | 616 (19.8) | 6,171 (19.8) | 0.1 | 302 (20.9) | 4,989 (20.8) | 0.3 |
| **Year of index date** | | | | | | |
| 2020 | 423 (13.6) | 4,233 (13.6) | 0.0 | 213 (14.8) | 3,198 (13.3) | 4.1 |
| 2021 | 1,070 (34.4) | 10,691 (34.4) | 0.0 | 513 (35.6) | 8,298 (34.6) | 2.0 |
| 2022 | 900 (28.9) | 8,997 (28.9) | 0.0 | 409 (28.4) | 6,959 (29.0) | 1.5 |
| 2023 | 719 (23.1) | 7,200 (23.1) | 0.1 | 307 (21.3) | 5,511 (23.0) | 4.2 |
| **Secondary wAIHA** | 1,670 (53.7) | – | – | – | – | – |
| **Conditions leading to secondary wAIHA** | | | | | | |
| Autoimmune and inflammatory diseases | 865 (27.8) | 3,417 (11.0) | 42.6* | – | – | – |
| Hematologic disorders and lymphoproliferative diseases | 742 (23.8) | 393 (1.3) | 68.2* | – | – | – |
| Solid tumors | 524 (16.8) | 3,920 (12.6) | 11.9* | – | – | – |
| Primary immunodeficiencies | 38 (1.2) | 28 (0.1) | 14.1* | – | – | – |
| Viral infections | 36 (1.2) | 234 (0.8) | 4.3 | – | – | – |
| **Other comorbidities related to mortality** | | | | | | |
| Coronary artery disease | 1,154 (37.1) | 11,536 (37.1) | 0.1 | 527 (36.5) | 8,144 (34.0) | 5.3 |
| Renal failure | 993 (31.9) | 9,918 (31.9) | 0.1 | 435 (30.2) | 6,979 (29.1) | 2.3 |
| Chronic pulmonary disease | 992 (31.9) | 8,766 (28.2) | 8.1 | 452 (31.4) | 6,106 (25.5) | 13.1* |
| Valvular disease | 893 (28.7) | 8,919 (28.7) | 0.1 | 387 (26.8) | 6,191 (25.8) | 2.3 |
| Liver disease | 509 (16.4) | 5,083 (16.3) | 0.0 | 189 (13.1) | 3,103 (12.9) | 0.4 |
| Pulmonary circulation disorder | 436 (14.0) | 4,351 (14.0) | 0.0 | 188 (13.1) | 2,846 (11.9) | 3.6 |
| **Quan-CCI excluding conditions leading to secondary wAIHA** | 1.9 ± 2.0 [1.0] | 1.9 ± 2.1 [1.0] | 0.1 | 1.9 ± 1.9 [1.0] | 1.7 ± 1.9 [1.0] | 6.6 |

*Values are presented as mean ± SD [median] or n (%). [b]Values were suppressed per CMS privacy policy. *Denotes >10%, indicating imbalance.
***AIHA***=autoimmune hemolytic anemia, ***CMS***=Centers for Medicare & Medicaid Services, ***Quan-CCI***=Quan-Charlson Comorbidity index, ***SD***=standard deviation, ***Std. diff.***=standardized difference, ***wAIHA***=warm autoimmune hemolytic anemia.

### Mortality

- Mean follow-up time was 17.2 months (standard deviation [SD] 11.7) and 14.9 months (SD 11.4) in the wAIHA and non-AIHA cohorts, respectively
- Survival rates in the wAIHA versus non-AIHA cohort remained significantly lower during follow-up: 80.3% versus 84.0% at 12 months, 70.7% versus 77.6% at 24 months, and 63.7% versus 73.1% at 36 months (all $p<0.001$)
- Patients with wAIHA were at 20%, 27%, and 30% higher risk of death at 12, 24, and 36 months, respectively, compared to those without AIHA (**Figure 1**)
- In the sensitivity analysis excluding patients with conditions for secondary wAIHA, findings remained consistent: patients with primary wAIHA were at 26%, 30%, and 34% higher risk of death at 12, 24, and 36 months, respectively, compared to those without AIHA (all $p<0.001$; **Figure 2**)

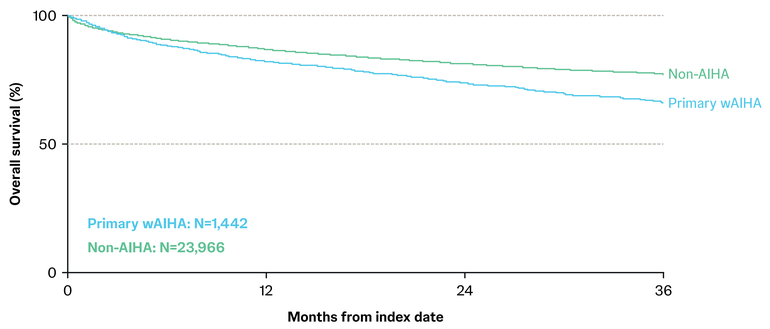
**Figure 1.** ***Overall survival among weighted wAIHA and non-AIHA cohorts (main analysis)***




| | 12 Months | 24 Months | 36 Months |
|---|---|---|---|
| **Patients at risk, n (%)** | | | |
| **wAIHA** | 1,833 (58.9) | 981 (31.5) | 242 (7.8) |
| **Non-AIHA** | 16,636 (53.5) | 7,807 (25.1) | 1,291 (4.1) |
| **Kaplan–Meier rate (95% CI)** | | | |
| **wAIHA** | 80.3 (78.8–81.8) | 70.7 (68.8–72.5) | 63.7 (61.3–66.2) |
| **Non-AIHA** | 84.0 (83.5–84.5) | 77.6 (76.9–78.2) | 73.1 (72.2–74.1) |
| **Hazard ratio (95% CI),[a] *p*-value** | | | |
| **wAIHA vs non-AIHA** | 1.20 (1.10–1.32), $p<0.001$ | 1.27 (1.18–1.38), $p<0.001$ | 1.30 (1.21–1.40), $p<0.001$ |

[a]*Hazard ratio of >1 indicates a higher mortality rate among the wAIHA cohort compared to the non-AIHA cohort.*
***AIHA***=autoimmune hemolytic anemia, ***CI***=confidence interval, ***wAIHA***=warm autoimmune hemolytic anemia.

**Figure 2.** ***Overall survival among weighted primary wAIHA and non-AIHA subgroups (sensitivity analysis)***




| | 12 Months | 24 Months | 36 Months |
|---|---|---|---|
| **Patients at risk, n (%)** | | | |
| **Primary wAIHA** | 886 (61.9) | 495 (34.6) | 120 (8.4) |
| **Non-AIHA** | 13,158 (52.4) | 6,245 (24.9) | 991 (3.9) |
| **Kaplan–Meier rate (95% CI)** | | | |
| **Primary wAIHA** | 82.1 (80.0–84.2) | 73.6 (71.0–76.3) | 65.7 (62.0–69.4) |
| **Non-AIHA** | 86.7 (86.2–87.3) | 81.2 (80.5–81.9) | 77.0 (76.0–78.0) |
| **Hazard ratio (95% CI),[a] *p*-value** | | | |
| **Primary wAIHA vs non-AIHA** | 1.35 (1.18–1.54), $p<0.001$ | 1.40 (1.24–1.57), $p<0.001$ | 1.44 (1.29–1.61), $p<0.001$ |
| **Primary wAIHA vs non-AIHA (doubly robust)[b]** | 1.26 (1.10–1.44), $p<0.001$ | 1.30 (1.16–1.46), $p<0.001$ | 1.34 (1.20–1.50), $p<0.001$ |

[a]*Hazard ratio of >1 indicates a higher mortality rate among the primary wAIHA subgroup compared to the non-AIHA subgroup.* [b]*Chronic pulmonary disease (yes/no) was included as a covariate in the outcome model.*
***AIHA***=autoimmune hemolytic anemia, ***CI***=confidence interval, ***wAIHA***=warm autoimmune hemolytic anemia.



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