Received: 3 February 2022 | Revised: 5 March 2022 | Accepted: 7 March 2022

DOI: 10.1111/ejh.13764

ORIGINAL ARTICLE

European Journal of Haematology WILEY

Survival in autoimmune hemolytic anemia remains poor, results from a nationwide cohort with 37 years of follow-up

Dennis Lund Hansen[1,2] | Sören Möller[2,3] | Henrik Frederiksen[1,2]

[1]Department of Hematology, Odense University Hospital, Odense, Denmark

[2]Department of Clinical Research, University of Southern Denmark, Odense, Denmark

[3]OPEN, Odense University Hospital, Odense, Denmark

Correspondence
Dennis Lund Hansen, Department of Hematology, Odense University Hospital, Kloevervaenget 10, 12th floor, Odense C 5000, Denmark.
Email: dlh@dadlnet.dk

Abstract

Introduction: Autoimmune hemolytic anemia (AIHA) is considered a chronic disease, with an overall good prognosis. However, recent reports indicate pre-mature mortality. Causes of death have not been evaluated previously.

Methods: In a nationwide setting, we identified all patients with warm type AIHA or cold agglutinin disease (CAD), and age–sex-matched comparators from Denmark, 1980–2016. We estimated overall survival and cause-specific mortality from anemia, infection, cardiovascular causes, hematological or solid cancer, bleeding, or other causes, using cumulative incidence proportions.

Results: We identified 1460 patients with primary AIHA, 1078 with secondary AIHA, 112 with CAD, and 130 801 comparators. One-year survival and median survival were, 82.7% and 9.8 years for primary AIHA, 69.1% and 3.3 years for secondary AIHA, and 85.5% and 8.8 years for CAD. Prognosis was comparable to the general population only in patients with primary AIHA below 30 years. In all other age and subgroups, the difference was considerable. Cumulated cause-specific mortality at 1 year was increased among patients versus comparators.

Discussion: All groups of autoimmune hemolytic anemia are associated with increased overall and cause-specific mortality compared to the general population. This probably reflects unmet needs in both treatment and follow-up programs.

KEYWORDS
autoimmune hemolytic anemia, survival analysis, cause of death, cohort analysis, cold agglutinins, cold agglutinin disease, survival rate

1 | INTRODUCTION

Autoimmune hemolytic anemia (AIHA) is a heterogeneous autoimmune disease where autoantibodies of cold type, warm type, or mixed types target red blood cell (RBC) surface antigens and evoke hemolysis.[1,2] Warm type AIHA may be primary without associated explanatory diseases or secondary AIHA where an underlying disease, most frequently systemic lupus erythematosus or lymphoproliferative disorders initiate the autoimmune RBC reaction.[3] Cold type AIHA encompass different clinical phenotypes of which the predominant form is cold agglutinin disease (CAD) a monoclonal disease arising from clonal lymphoproliferative cells in the bone marrow.[4,5] The difference in etiology gives rise to differences in treatment.[1]AIHA has been associated with increased morbidity, especially thromboses, malignancies and connective tissue diseases,[6–15] and in addition, mortality among patients with AIHA is

increased.[2,14,16] Most recently, a French study found that the 1-year survival was 79.5% among 9663 patients with AIHA[14]—lower than indicated by prior reports where survival at later time points was 79%–96%.[9,12,13,17] Patients with secondary AIHA are an even more vulnerable group with a 1-year survival as low as 52%.[14–16,18,19] The combined body of evidence indicates that the prognosis is dismal. However, only the French study above has studied survival among patients with AIHA in a nationwide cohort and compared it with the general population, and as such, these results warrant support from other population-based longitudinal cohorts to inform on the prognosis and possible temporal changes.[14] Furthermore, causes of death have been reported from less than 100 patients and without general population comparison.[12,13,20]

In this study, we report on prognosis and death among patients with all types of AIHA in Denmark, 1980–2016, focusing on temporal changes in survival rates and causes of death.

2 | METHODS

The source population was the Danish population from January 1, 1980, to December 31, 2016, the population increased from 5.1 to 5.7 million in this period.[21,22] The database population was the Danish National Patient Register (Patient Register) containing registered diagnoses from all hospitalizations since 1977 and since 1994 also including hospital outpatient and emergency room visits. The few private hospitals in Denmark are not engaged in diagnosing or treatment of red blood cell disorders. During 1977–1994, diagnoses were registered using the International Classification of Diseases, version 8 (ICD-8) and since 1994 according to ICD-10.[23,24] We used this data source to construct the Danish Hemolysis Cohort, including approximately 15 000 persons diagnosed with acquired or congenital hemolytic disorders.[2,25] In an earlier study, we validated the diagnoses of hemolytic disorders and found them to be valid, with a conservative estimated positive predictive value of 78.4% for an AIHA diagnosis registration.[26] The central person registration number is assigned to all citizens of Denmark upon birth or immigration and uniquely and consistently identifies inhabitants through all public registers. We used this key to link information from the Patient Register, the Central Person Register, the Causes of Death Register, and the Danish Prescription Database for all patients and comparators.[22,23,27,28]

The study was registered at the Region of Southern Denmark (reference 17/10885). According to Danish law, register-based research without patient contact does not require ethical approval.

2.1 | Patients and comparators

For this study, we focused on patients with a first registered diagnosis of AIHA or cold agglutinin disease (CAD) in the Danish Hemolysis Cohort 1980–2016.[2] Patients were identified using the International Classification of Diseases (ICD) codes from version 8: 28309, 28390, and 28391, and version 10: D591 and D591A, where the A suffix is a Danish addition distinguishing CAD from AIHA.[2,23,26] We disaggregated patients with the AIHA diagnosis into primary and secondary types based on specified diagnoses, such as chronic lymphocytic leukemia or systemic lupus erythematosus, as described previously.[3] A patient qualified as having secondary AIHA diagnosis if a defining associated diagnosis was identified in the Patient Register before or up to 30 days following the first diagnosis registration of AIHA (Table S1). However, due to limitations in diagnosis registrations, it was not possible to disentangle cold agglutinin syndrome from CAD, and therefore we classified all these as CAD.[29]

Comorbidity assessment was based on registrations of specified diagnoses in the Patient Register. We combined these with information on prescriptions for selected drugs, such as antidiabetics to identify comorbid conditions, which are diagnosed in general practice and followed without hospital referral (Table S2).[28] Date of migration or death, and cause of death were obtained from the Central Person Register and the Cause of Death Register.[22,23,27]

On the date of AIHA or CAD diagnosis, each patient was matched (on age and sex) with 50 comparators from the general population, and we followed these individuals from this index date to death, emigration, or December 31, 2016, whichever occurred first. We obtained information on comorbidities, death, and causes of death, as described for the index patients.

Our primary objective was to study all-cause mortality as well as cause-specific mortality and mortality rates in patients with AIHA and to compare these with age–sex-matched general population comparators.

2.2 | Statistical analysis

At the beginning of follow-up, we computed descriptive statistics of age at diagnosis, and distribution according to sex, proportion with secondary AIHA, period of diagnosis, and comorbidities.

We evaluated all-cause mortality using the Kaplan–Meier estimator, comparing overall survival between patients and comparators, and subdivided by sex, age, and year of diagnosis (1980–1999 and 2000–2016). Survival was also assessed using Cox proportional hazard regression to obtain unadjusted and adjusted hazard ratios between patients and comparators. We adjusted for sex, age at diagnosis, year of diagnosis, splenectomy, and comorbidities. We applied splenectomy status and comorbidities as time varying covariates, which were either present at AIHA diagnosis or registered later. We further introduced time split in the regressions at 100 days, and 1 and 5 years after AIHA diagnosis to adjust for time varying hazard ratios of the exposure, that is, AIHA and CAD.

Cause-specific mortality was evaluated using nonparametric cumulative mortality functions comparing patients and comparators, treating all other causes of death and migration as competing risks.[30,31] We aggregated causes of death into anemia, cardiovascular disease, bleeding, hematological cancer, infection, solid cancer, and other causes of death (Table S3). We further used cause-specific Cox

proportional hazard regression to obtain unadjusted and adjusted cause-specific hazard ratios between patients and comparators.[32,33]

We estimated mortality rates and median survival in consecutive 5-year intervals from 1980 to 2014, applying both full observation time and censoring 5 years after diagnosis to counteract bias of unequal observation time.

Proportionality assumptions were assessed visually using log–log plots, and goodness of fit was assured using Nelson–Aalen plots.

2.3 | Data management and analysis

We performed all data management and analyses using Stata 16.1 with built-in commands and the community-provided commands, *stcompet* and *stcomlist*.[30,34]

3 | RESULTS

We included 2650 patients with AIHA or CAD and 130 801 matched comparators, giving a mean match ratio of 49.4. Primary AIHA comprised 1460 patients with a comparator cohort of 72 124 persons, and secondary AIHA comprised 1078 patients with a comparator cohort of 53 511 persons. CAD was registered in 112 patients who were assigned 5166 comparators.

A total risk time of 1 269 955 person-years was available with a mean risk time of 9.5 person-years. Patients with primary AIHA contributed 11 728 person-years with a mean risk time of 8.0 person-years, and patients with secondary AIHA contributed 4640 person-years with a mean risk time of 4.3 person years. Patients with CAD contributed 447 person-years, and a mean risk time of 4.0 person-years.

Baseline characteristics are presented in Table 1. Patients with primary AIHA were younger at diagnosis, mean age 59.1 years, than secondary AIHA, mean age 68.4 years, and among patients with primary AIHA, a larger proportion were women, 59.2%, compared to 51.5% among secondary AIHA. Secondary AIHA and CAD had comparable age and sex distribution, Table 1. By definition, secondary AIHA patients had a higher prevalence of comorbidities at diagnosis compared to primary AIHA, Table 1.

3.1 | Overall survival

Kaplan–Meier curves of overall survival are depicted in Figure 1. Primary AIHA had a median survival of 9.8 years [95% CI: 8.73; 10.94] after diagnosis—much longer than secondary AIHA, where median survival was 3.3 years [95% CI: 2.93; 3.87]. In CAD, median survival was 8.8 years [95% CI: 5.43; n/a]. Survival was best among women and younger persons (Figure 1 - second and third row), and among patients with primary AIHA aged <30 years, survival was comparable to age–sex-matched general population comparators. However, the gap between patients with AIHA or CAD and their corresponding comparisons was considerable in all other age and subgroups (Figure 1, third row).

Overall survival and the median survival in particular improved during the study period as depicted in Figure 1, fourth row, and Table S4. Median survival among patients with primary AIHA was 8.18 [95% CI: 6.15; 10.23] years in 1980–1989, 8.26 years [95% CI: 6.38; 9.95] in 1990–1999, and 12.60 years [95% CI: 9.89; -] after 2000. A similar trend was seen in patients with secondary AIHA, where median survival increased from 1.12 years [95% CI: 0.56; 2.49] in 1980–1989, via 3.00 years [95% CI: 2.24; 4.48] in 1990–1999, to 3.89 years [95% CI: 3.25; 4.74] after year 2000.

Mortality rates did not significantly improve after 2000 in any of the included diseases, as presented in Table S4.

Unadjusted and adjusted Cox proportional hazard ratios derived from the time split model are presented in Table 2 and Table S5. The first 100 days after diagnosis conferred the highest mortality risk in all three diseases. The adjusted hazard ratios during the first 100 days were comparable between patients with primary (50.6) and patients with secondary (46.2) AIHA, Table 2. The hazard ratio (HR) for death in primary AIHA remained significantly elevated through the entire study period. Although the magnitude decreased with time, the HR remained elevated to 1.4 [95% CI: 1.2; 1.6] even 10 years after diagnosis, Table 2 and Table S5. A comparable time-dependent decrease in the hazard ratio for death was seen for secondary AIHA, where the HR was 1.5 [95% CI: 1.3; 1.7] 5 years after diagnosis, but had decreased to 1.1 ten years after diagnosis (Table 3 and Table S6). The point estimate of the HR for death in CAD versus comparators was elevated until 5 years after diagnosis, but due to small samples, estimates were generally imprecise.

3.2 | Causes of death

Causes of death are presented in Table 3 and Table S6, and depicted in Figure 2. Within the first 100 days, 2.8% of patients with primary AIHA had died from cardiovascular causes, and 8.0% of patients with secondary AIHA had died from hematological cancers.

Cumulated cause-specific mortality at 1 year was elevated among patients versus comparators, Table 3. Among patients classified as primary AIHA, 1% had died from hematological cancers within the first year after diagnosis, yielding an adjusted cause-specific hazard ratio of 10.1, Table 3. Death attributed to infections had a cumulative mortality of 1.5% after 1 year among primary AIHA, and 0.9% among patients with secondary AIHA. Corresponding adjusted cause-specific HR was 9.3 in the primary AIHA patient-comparator-set and 5.9 in the secondary AIHA patient-comparator-set. Death due to bleeding was prevailing in both primary and secondary AIHA compared with the general population with adjusted cause-specific HR of 9.0 and 8.1, respectively.

After 5 years, cardiovascular death was still more common in primary AIHA than among the general population comparators with cumulative mortalities of 10% versus 6.3%, Table 3. Within the first year from diagnosis, cardiovascular disease was also a common

TABLE 1 Characterization at diagnosis of patients with autoimmune hemolytic anemia (AIHA) or cold agglutinin disease (CAD), and matched comparators from the general population

	Primary AIHA, *n* = 1460	Primary AIHA, Comparators, *n* = 72 124	Secondary AIHA, n = 1078	Secondary AIHA, Comparators, *n* = 53 511	CAD, *n* = 112	CAD, Comparators, *n* = 5166
Women	59.2 [56.6; 61.7]	59.1 [58.8; 59.5]	51.5 [48.5; 54.5]	51.5 [51.1; 51.9]	51.8 [42.1; 61.3]	52.3 [50.9; 53.6]
Age at diagnosis, years (mean)	59.1 [57.9; 60.4]	58.9 [58.7; 59.1]	68.4 [67.4; 69.3]	68.3 [68.2; 68.4]	68.6 [65.8; 71.3]	67.6 [67.2; 68.0]
Year of diagnosis						
1980–1999	45.5 [42.9; 48.1]	45.3 [45.0; 45.7]	29.7 [27.0; 32.5]	29.7 [29.3; 30.1]	0.9 [0.0; 4.9]	1.0 [0.7; 1.3]
2000–2016	54.5 [51.9; 57.1]	54.7 [54.3; 55.0]	70.3 [67.5; 73.0]	70.3 [69.9; 70.7]	99.1 [95.1; 100.0]	99.0 [98.7; 99.3]
Comorbidities						
Alcohol-related diagnosis	4.5 [3.5; 5.7]	2.0 [1.9; 2.1]	3.8 [2.7; 5.1]	2.7 [2.5; 2.8]	6.3 [2.5; 12.5]	3.9 [3.3; 4.4]
Atrial fibrillation	7.8 [6.5; 9.3]	4.1 [4.0; 4.2]	9.1 [7.4; 11.0]	5.5 [5.3; 5.7]	6.3 [2.5; 12.5]	4.3 [3.8; 4.9]
Chronic pulmonary disease	20.3 [18.3; 22.5]	17.7 [17.4; 18.0]	25.0 [22.5; 27.7]	20.5 [20.1; 20.8]	26.8 [18.9; 36.0]	26.9 [25.7; 28.1]
Congestive heart failure	8.9 [7.5; 10.5]	3.1 [3.0; 3.3]	8.3 [6.7; 10.1]	4.3 [4.1; 4.5]	7.1 [3.1; 13.6]	4.1 [3.6; 4.7]
Connective tissue disease	3.1 [2.3; 4.1]	2.7 [2.6; 2.8]	16.1 [14.0; 18.5]	3.5 [3.3; 3.7]	11.6 [6.3; 19.0]	3.8 [3.3; 4.4]
Diabetes unspecified	9.8 [8.3; 11.4]	5.4 [5.3; 5.6]	11.0 [9.2; 13.1]	7.9 [7.7; 8.1]	13.4 [7.7; 21.1]	10.1 [9.3; 11.0]
Dyslipidemia	12.0 [10.4; 13.8]	10.4 [10.1; 10.6]	17.6 [15.4; 20.0]	18.7 [18.4; 19.1]	30.4 [22.0; 39.8]	30.8 [29.5; 32.0]
Hypertension	31.8 [29.5; 34.3]	25.7 [25.4; 26.0]	44.7 [41.7; 47.7]	38.6 [38.2; 39.0]	57.1 [47.4; 66.5]	50.5 [49.1; 51.9]
Ischemic heart disease	15.8 [13.9; 17.7]	10.4 [10.2; 10.6]	20.0 [17.7; 22.6]	15.2 [14.9; 15.5]	20.5 [13.5; 29.2]	18.3 [17.2; 19.3]
Liver disease	4.3 [3.3; 5.5]	0.6 [0.5; 0.6]	5.1 [3.9; 6.6]	0.7 [0.6; 0.8]	2.7 [0.6; 7.6]	1.2 [0.9; 1.5]
Moderate to severe renal disease	5.1 [4.1; 6.4]	1.2 [1.1; 1.3]	7.4 [5.9; 9.2]	1.7 [1.6; 1.8]	3.6 [1.0; 8.9]	2.5 [2.1; 3.0]
Obesity	5.0 [3.9; 6.2]	2.3 [2.2; 2.4]	3.8 [2.7; 5.1]	2.8 [2.6; 2.9]	2.7 [0.6; 7.6]	4.0 [3.5; 4.6]
Peripheral artery disease	3.0 [2.2; 4.0]	1.7 [1.7; 1.8]	3.4 [2.4; 4.7]	2.7 [2.6; 2.8]	7.1 [3.1; 13.6]	3.3 [2.8; 3.8]
Venous thromboembolism	4.5 [3.5; 5.7]	2.1 [2.0; 2.2]	6.3 [4.9; 7.9]	2.9 [2.8; 3.0]	6.3 [2.5; 12.5]	3.4 [3.0; 4.0]
Solid cancer	1.0 [0.6; 1.7]	8.5 [8.3; 8.7]	34.1 [31.3; 37.1]	12.0 [11.8; 12.3]	20.5 [13.5; 29.2]	13.8 [12.9; 14.8]
Metastatic solid cancer	0.4 [0.2; 0.9]	0.7 [0.6; 0.7]	6.7 [5.3; 8.3]	0.9 [0.9; 1.0]	2.7 [0.6; 7.6]	1.4 [1.1; 1.7]
Hematological cancer	1.8 [1.2; 2.7]	1.2 [1.1; 1.2]	54.0 [51.0; 57.0]	1.7 [1.6; 1.8]	28.6 [20.4; 37.9]	2.4 [2.0; 2.9]

Note: Comorbidities were present before diagnosis and up to 30 days after. Numbers are percentages if not otherwise indicated, and 95% confidence intervals are given in brackets.

Abbreviations: AIHA, autoimmune hemolytic anemia; CAD, Cold agglutinin disease; csHR, cause-specific hazard ratios; HR, Cox proportional hazard ratios.

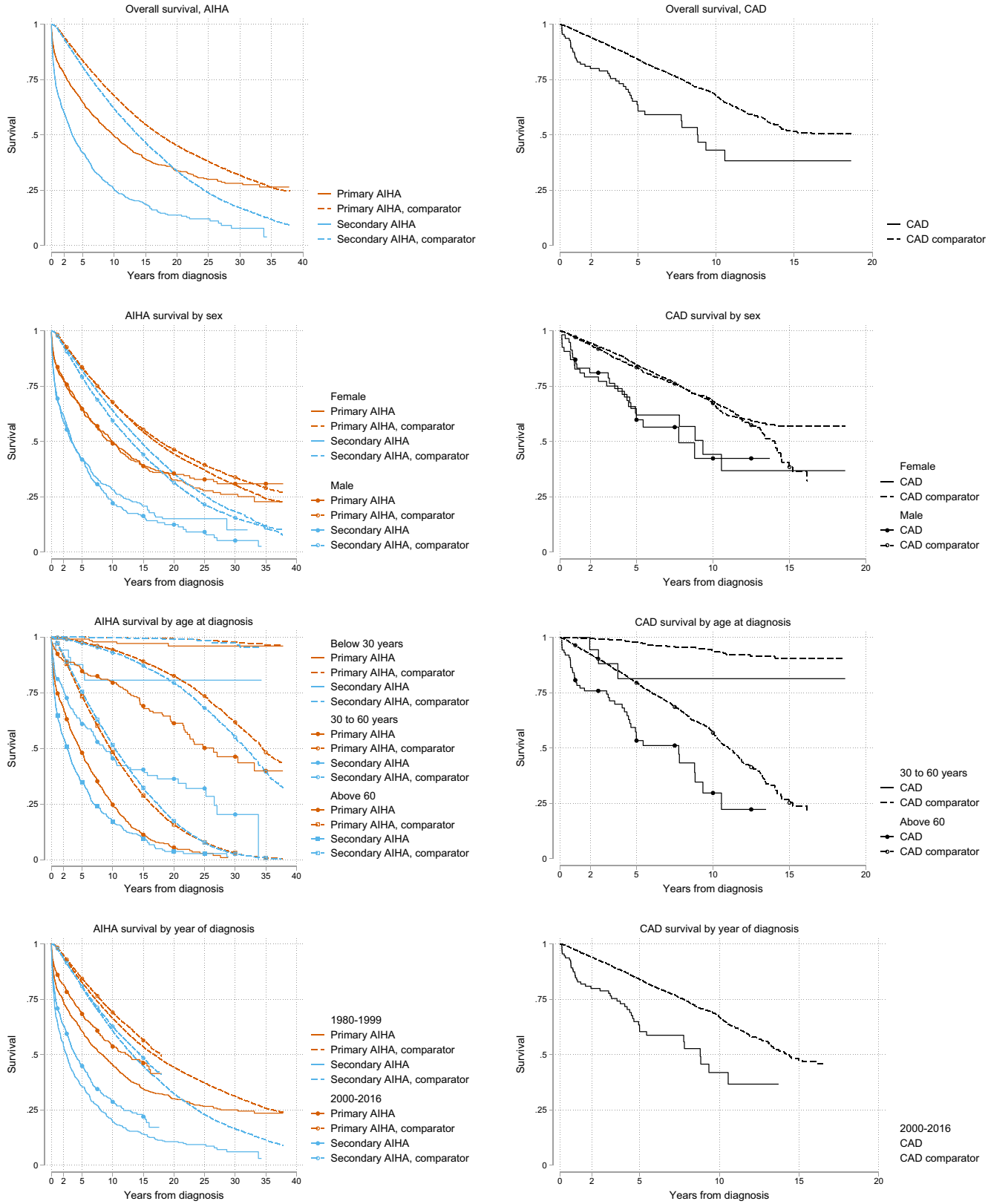

FIGURE 1 Kaplan–Meier plots for overall survival among patients with primary autoimmune hemolytic anemia (AIHA), secondary AIHA or cold agglutinin disease (CAD) and their respective comparators from the general population. Solid lines represent patients with hemolysis and punctured lines comparators, likewise hollow circles or squares represent comparators

TABLE 2 Overall survival and corresponding Cox proportional hazard ratios (HR) among patients with primary autoimmune hemolytic anemia (AIHA), secondary AIHA or cold agglutinin disease (CAD), and comparators from the general population

	Primary AIHA, $n = 1460$	Primary AIHA, Comparators, $n = 72\,124$	Primary AIHA, adjusted HR	Secondary AIHA, $n = 1078$	Secondary AIHA, Comparators, $n = 53\,511$	Secondary AIHA, adjusted HR	CAD, $n = 12$	CAD, Comparators, $n = 5166$	CAD, adjusted HR
Overall survival at									
100 days	90.7 [89.1;92.1]	99.8 [99.8;99.8]	50.6 [39.9;64.2]	83.3 [80.9;85.4]	99.8 [99.8;99.8]	46.2 [36.1;59.1]	95.4 [89.3;98.1]	99.6 [99.3;99.7]	7.4 [2.8;19.7]
1 year	82.7 [80.6;84.5]	98.2 [98.1;98.3]	6.5 [5.4;7.9]	69.1 [66.2;71.8]	97.8 [97.7;97.9]	4.9 [4.1;5.9]	85.5 [77.1;91.0]	97.3 [96.8;97.7]	3.2 [1.6;6.1]
5 years	64.6 [62.0;67.1]	83.4 [83.1;83.7]	1.6 [1.4;1.9]	42.2 [39.0;45.3]	80.7 [80.3;81.1]	1.5 [1.3;1.7]	63.5 [51.5;73.2]	84.3 [83.0;85.4]	1.1 [0.7;1.9]
10 years	49.4 [46.5;52.2]	67.5 [67.1;67.9]	1.4 [1.2;1.6]	25.4 [22.3;28.5]	61.8 [61.3;62.3]	1.1 [0.9;1.4]	41.6 [25.2;57.2]	68.1 [65.9;70.3]	0.6 [0.3;1.5]

Note: Ninety-five percent confidence intervals are given in brackets.

cause of death among patients with secondary AIHA, but the risk decreased with time, and after 5 years, it was equal among patients and comparators. This decrease in risk is also reflected in the cause-specific hazard ratios, which became insignificant after 5 years, Table 3 and Table S6).

Infections and hematological cancer were common causes of death after 5 years in all three diseases (Table 2, Table S6, and Figure 2). Beyond 10 years, cardiovascular cause of death was still more common among patients with primary AIHA or cold agglutinin disease than in comparators. Similarly, infections remained a more common cause of death in all three diseases than among comparators (Table 2, Table S6, and Figure 2).

4 | DISCUSSION

Both primary and secondary AIHA as well as CAD conferred reduced survival compared to age–sex-matched comparators from the general population, even when adjusted for comorbidities. Prognosis was poor and improved only modestly during our 37 years of observation time. The only exception was patients with primary AIHA below 30 years of age at diagnosis, where survival approximated comparators. For all subtypes, the first year after diagnosis of AIHA was associated with the highest mortality. Leading causes of death in primary AIHA were cardiovascular disease, anemia, and infections. For secondary AIHA patients, solid cancer, hematological cancer, and cardiovascular diseases were the most commonly registered causes of death.

Previously, few studies have reported on overall survival in AIHA, and only one compared patients with the general population.[8,9,14,20]

In our study, 1-year and 5-year survival in patients with primary AIHA were 82.7% and 64.6%, respectively. This high risk of death within the first years after diagnosis is in line with previous reports and is further comparable to that seen in Evans syndrome.[8,9,20,35,36] However, our 1- and 5-year survival are lower than previous reports from small cohorts; for example, 5-year survival was 84%–85% in two studies that included 101 and 53 patients, respectively.[9,20] Contrasting these small studies, our results are highly comparable to what has recently been reported from the French nationwide study, where 1-year survival was 82.1% and 5-year survival was 65.2% among patients with primary AIHA.[14] Combined, the French study and our results report on 3000 patients with primary AIHA, and the highly comparable results could indicate that the more optimistic prognosis in smaller cohorts arises from sampling bias.

During the study period, median survival in primary AIHA improved from 8.2 years to 12.6 years, an increase above increasing life expectancy in the general population. Our data do not include granular information on treatment of the disease, but this improvement could possibly be attributed to improved management possibilities, such as the introduction of rituximab.[37–39]

Previously, younger age at chronic disease diagnosis has been associated with a favorable prognosis, especially in children; however,

TABLE 3 Cumulative cause-specific mortality and adjusted cause-specific hazard ratios (csHR) among patients with primary autoimmune hemolytic anemia (AIHA), secondary AIHA or cold agglutinin disease (CAD), and comparators from the general population

	Primary AIHA, *n* = 1460	Primary AIHA, Comparators, *n* = 72124	Primary AIHA, adjusted csHR	Secondary AIHA, *n* = 1078	Secondary AIHA, Comparators, *n* = 53 511	Secondary AIHA, adjusted csHR	CAD, *n* = 112	CAD, Comparators, *n* = 5166	CAD, adjusted csHR
Cumulative cause-specific mortality at									
End of 100 days									
Anemia	3.0 [2.2;3.9]	n/a	n/a	1.4 [0.8;2.2]	n/a	n/a	2.8 [0.7;7.2]	n/a	n/a
Infection	0.8 [0.4;1.3]	0.0 [0.0;0.0]	65.4 [26.3;162.8]	0.5 [0.2;1.0]	0.0 [0.0;0.0]	92.0 [21.7;388.9]	n/a	n/a	n/a
Cardiovascular	2.8 [2.0;3.7]	0.1 [0.1;0.1]	34.2 [22.6;51.9]	1.7 [1.0;2.6]	0.1 [0.0;0.1]	n/a	n/a	0.1 [0.0;0.2]	n/a
Cancer, hematological	0.4 [0.2;0.9]	0.0 [0.0;0.0]	28.5 [9.1;88.8]	8.0 [6.5;9.7]	0.0 [0.0;0.0]	68.1 [16.7;277.3]	0.9 [0.1;4.5]	0.0 [0.0;0.1]	3.9 [0.2;66.8]
Cancer, solid	0.3 [0.1;0.8]	0.0 [0.0;0.1]	29.7 [11.5;76.5]	2.7 [1.9;3.8]	0.0 [0.0;0.1]	16.2 [9.5;27.5]	n/a	0.1 [0.0;0.2]	n/a
Bleeding	0.2 [0.1;0.6]	0.0 [0.0;0.0]	73.8 [12.3;442.4]	0.2 [0.0;0.6]	0.0 [0.0;0.0]	22.9 [4.6;114.6]	n/a	n/a	n/a
Other or unspecified	1.9 [1.3;2.7]	0.1 [0.0;0.1]	30.0 [18.5;48.7]	2.2 [1.5;3.3]	0.1 [0.0;0.1]	39.9 [23.2;68.7]	n/a	0.2 [0.1;0.4]	4.0 [0.5;30.9]
End of first year									
Anemia	4.5 [3.5;5.7]	0.0 [0.0;0.0]	441.3 [131.6;1480.1]	1.9 [1.2;2.8]	0.0 [0.0;0.0]	78.2 [21.3;287.0]	3.7 [1.2;8.6]	0.0 [0.0;0.1]	173.2 [8.5;3522.5]
Infection	1.5 [0.9;2.2]	0.1 [0.1;0.1]	9.3 [4.8;18.2]	0.9 [0.5;1.7]	0.1 [0.1;0.2]	5.9 [2.4;15.0]	n/a	0.1 [0.0;0.2]	n/a
Cardiovascular	5.1 [4.1;6.4]	0.7 [0.6;0.7]	4.2 [2.9;5.9]	3.5 [2.5;4.7]	0.7 [0.7;0.8]	4.0 [2.5;6.5]	1.9 [0.4;6.2]	0.7 [0.5;1.0]	2.6 [0.6;11.1]
Cancer, hematological	1.0 [0.6;1.6]	0.0 [0.0;0.1]	10.1 [4.4;23.3]	14.3 [12.3;16.5]	0.1 [0.0;0.1]	4.6 [2.9;7.3]	3.9 [1.3;8.9]	0.0 [0.0;0.1]	7.3 [0.7;80.9]
Cancer, solid	1.1 [0.6;1.7]	0.4 [0.3;0.4]	7.9 [4.2;15.0]	5.6 [4.3;7.1]	0.5 [0.4;0.5]	2.5 [1.7;3.6]	2.0 [0.4;6.3]	0.7 [0.5;1.0]	2.6 [0.6;11.2]
Bleeding	0.7 [0.4;1.2]	0.1 [0.0;0.1]	9.0 [4.1;20.0]	0.5 [0.2;1.1]	0.1 [0.1;0.1]	8.1 [2.4;26.7]	n/a	0.0 [0.0;0.1]	n/a
Other or unspecified	3.5 [2.7;4.6]	0.5 [0.5;0.6]	4.3 [2.8;6.5]	4.2 [3.1;5.5]	0.7 [0.6;0.8]	4.1 [2.6;6.5]	2.9 [0.8;7.6]	1.1 [0.8;1.4]	2.2 [0.5;9.2]
End of 5th year									
Anemia	6.7 [5.4;8.1]	0.0 [0.0;0.1]	64.3 [37.8;109.3]	2.4 [1.6;3.5]	0.1 [0.0;0.1]	21.2 [7.3;61.4]	6.5 [2.6;13.0]	0.1 [0.0;0.2]	163.5 [12.9;2069.1]
Infection	2.7 [1.9;3.6]	1.1 [1.0;1.2]	1.7 [1.0;2.8]	2.2 [1.5;3.3]	1.4 [1.3;1.5]	2.2 [1.2;4.0]	5.0 [1.6;11.5]	0.9 [0.6;1.2]	9.7 [3.2;29.5]
Cardiovascular	10.0 [8.5;11.7]	6.3 [6.1;6.5]	1.0 [0.8;1.3]	6.0 [4.6;7.6]	6.4 [6.2;6.6]	0.9 [0.6;1.3]	6.6 [2.3;14.1]	3.9 [3.3;4.6]	1.0 [0.3;3.4]
Cancer, hematological	3.3 [2.4;4.3]	0.3 [0.3;0.4]	3.0 [2.0;4.5]	28.2 [25.4;31.0]	0.4 [0.4;0.5]	2.3 [1.8;2.9]	5.2 [1.9;10.9]	0.4 [0.2;0.7]	0.2 [0.0;1.7]
Cancer, solid	2.9 [2.1;3.9]	3.3 [3.1;3.4]	1.8 [1.2;2.7]	9.3 [7.6;11.2]	4.3 [4.1;4.5]	0.5 [0.4;0.7]	6.6 [2.3;14.0]	4.2 [3.6;4.9]	0.8 [0.3;2.7]
Bleeding	1.1 [0.6;1.8]	0.7 [0.6;0.7]	0.8 [0.3;2.0]	1.0 [0.5;1.8]	0.7 [0.6;0.8]	2.1 [0.9;5.3]	n/a	0.5 [0.3;0.8]	n/a
Other or unspecified	8.8 [7.4;10.4]	4.9 [4.7;5.1]	1.6 [1.2;2.0]	8.7 [7.0;10.5]	6.1 [5.9;6.3]	0.5 [1.1;2.1]	6.6 [2.7; 13.0]	5.7 [5.0;6.5]	0.8 [0.2;2.6]

Note: Ninety-five percent % confidence intervals are given in brackets.

n/a: not applicable, statistics could not be estimated, due to the absence of events.

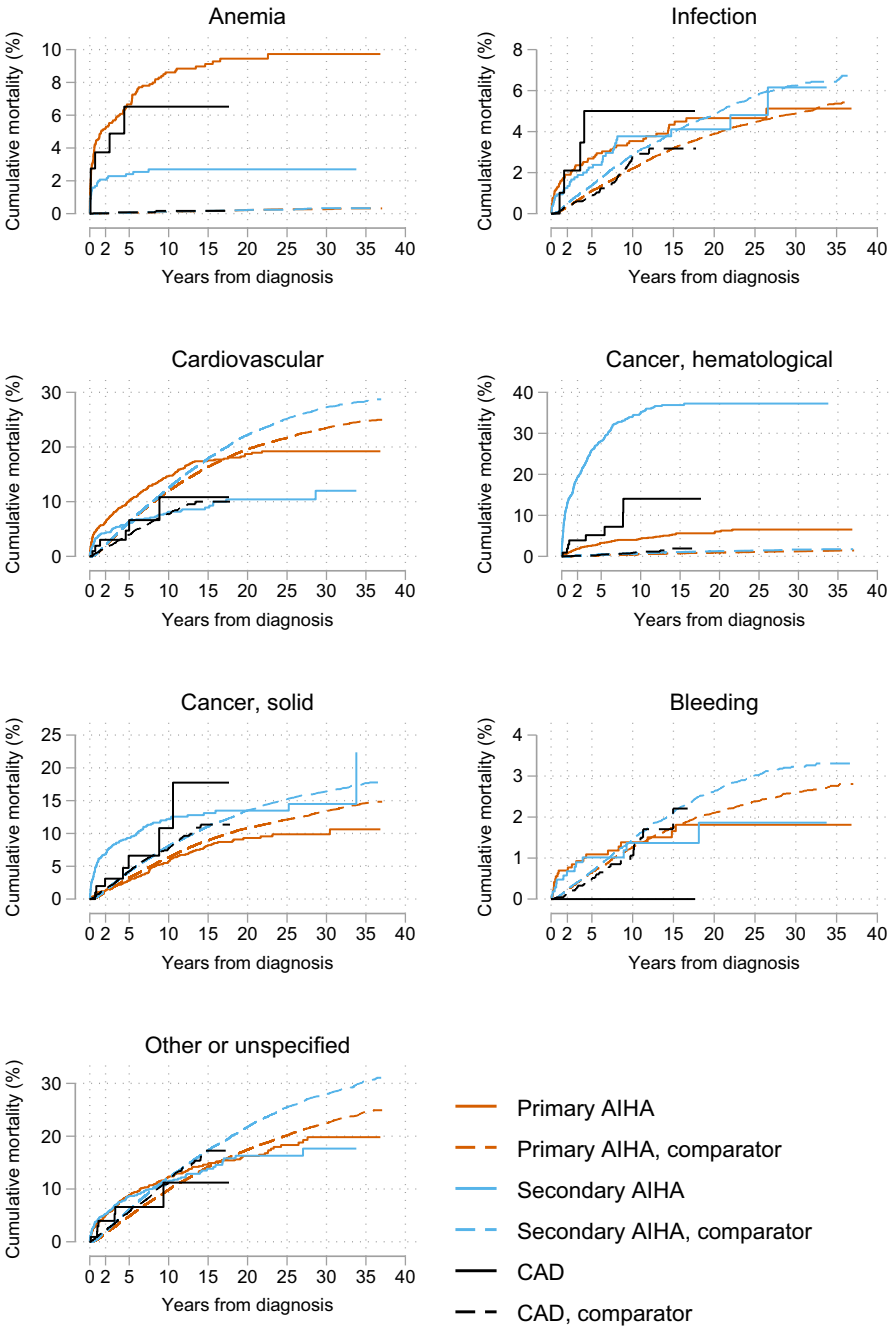

FIGURE 2 Cumulative incidence of specific causes of death among patients with primary autoimmune hemolytic anemia (AIHA), secondary AIHA or cold agglutinin disease (CAD), and general population comparators. Solid lines represent patients, and punctured lines comparators. Note that the y-axes vary between graphs

lower age has also been associated with increased severity and risk of relapse.[8,9,12,17] Our estimates of survival with primary AIHA among patients less than 30 years at diagnosis indicate that in this subgroup, prognosis is good. However, in all other age groups, AIHA is associated with reduced survival.

The median survival among patients with secondary autoimmune hemolysis showed much poorer results and a lower increase from 3.0 to 3.9 years before and after the year 2000. Again, this increase could be related to improved treatment options, improved supportive care, and advances in the management of underlying conditions. Of note, the 1-year survival among patients with secondary AIHA was only 69.1%, in line with the French results, where 1-year survival of secondary AIHA ranged 71.6%–85.7%.[14]

Survival in CAD has been estimated in very few studies and only one with a comparator population.[4,40] Median survival in our study was 8.8 years and almost identical to the study by Bylsma et al.[40] of 8.5 years, estimated in an overlapping patient population from Denmark. However, Berentsen and coworkers reported a much better prognosis with a median survival of 16 years in an international cohort.[4] Our 5-year survival of 63.5% is also much lower than the 83% reported by this group. Despite a comparable age at diagnosis, the difference could reflect the higher proportion of women in their population, and comorbidities could be more pronounced in our cohort.[4] Furthermore, the cohort is a combined Norwegian and Italian cohort, and climatic differences may impact survival differently in the two countries, since exposure to lower temperatures can aggravates hemolysis.[4,41]

Cardiovascular disease as well as cancer and infection were prominent causes of death within the first year, where cardiovascular-related death was the most frequent cause among patients with primary AIHA, both 1 year and 5 years after diagnosis, 5.1% and 10.0%, respectively. The risk of death attributed to infection remained elevated for up to 10 years but decreased with time and normalized to the risk among comparators 15 years following diagnosis. Previously, increased risks of sepsis and infections have been reported. A study from Thailand found that infections were the cause of death in approximately 5% of patients with AIHA during a median observation time of 4.5 years.[9] In California, USA, the cumulative incidence of sepsis 1 year after diagnosis of AIHA ranged 4.3%–6.7%.[8] Furthermore, 22.9% of the patients with AIHA from France had been hospitalized with infection during the first year of diagnosis of AIHA.[14] The same pattern was also seen in CAD, where 5-year cumulative mortality from infections was 5% versus 0.9% in patients versus comparators.

We found that risk of cardiovascular death was increased even 20 years after diagnosis among patients with primary AIHA. The risk of death from cardiovascular causes has not been assessed neither in patients with hemolysis nor in comparison to the general population risk, but cardiovascular related deaths have been reported before, as well as an increased risk of both thromboembolism and cardiovascular problems.[12–14,42,43] This association could reflect an overall increased thromboembolic risk in AIHA or the complex pathophysiology including vascular wall dysfunction damage, hemolysis, and perhaps treatment side effects.[6,13,44] This finding emphasizes that management of comorbidity and acknowledgement of late effects may lead to survival benefits in these patients.

Hematological cancer contributed substantially to mortality, and this risk remained elevated in line with other reports and could be either a causal relationship or a simple correlation.[9] If the relationship is causal, hematological cancer could be an undiagnosed cause of AIHA and promote a more therapy-resistant form of AIHA. Cancer could also be a side effect to immunosuppressive treatments used to treat AIHA.[1]

Despite the nationwide cohort with complete inclusion and follow-up, and unprecedented long follow-up, our study has limitations. The positive predictive value of AIHA or CAD is not 100%, and hence some of the patients included as AIHA or CAD will probably be erroneously included. Based on our prior validation study, we increased precision, by excluding patients not diagnosed at departments of pediatrics, internal medicine, or hematology.[2,26] However, only in case where a more severe disease systematically was misclassified as AIHA would it increase the difference between patients and comparators, inducing a falsely increased association. Effects of the reduced precision in diagnosis would lead to a non-differential misclassification, thereby decreasing the difference between patients and comparators and an underestimation of the association. Furthermore, information on causes of death from death certificates may not be accurate.[45] Enhancing this problem, autopsy rates have declined since the beginning of the observation period.[27,45–47] This will affect both patients and comparators and can distort the generalizability of the reported causes of death, even though the relative distribution between patients and comparators may be reliable within the cohort.

5 | CONCLUSION

In this study, we show that mortality in AIHA is considerable, especially within the first year, and does not normalize for most patients. Among patients with primary AIHA, survival has improved modestly, whereas patients with secondary AIHA had nearly unchanged prognosis during the observation period.

Hematological cancer was consistently a more prevailing cause of death among patients with any type of AIHA or CAD than among comparators. Cardiovascular disease and infections were likewise frequent causes of death among patients with any type of immune hemolysis.

Taken together, our results emphasize an unmet need in management of patients with AIHA and CAD.

ACKNOWLEDGEMENTS

The authors thank Cathrine Fox Maule and Marianne Andresen at Statistics Denmark for help with defining and hosting data.

CONFLICT OF INTEREST

DLH: research grants from Alexion and Novartis, conference fee from EUSA Pharma. HF: project grants from Novartis, Alexion, Sanofi, and Gilead for research unrelated to this study, and honoraria from Sanofi and Alexion for lectures on thrombotic microangiopathies. SM: No conflict of interest.

AUTHOR CONTRIBUTIONS

DLH and HF conceived the study. All authors planned the analyses. DLH performed the analyses. DLH wrote the first draft, and all authors improved on subsequent versions and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

All data were stored and analyzed on a secure server platform at Statistics Denmark. These patient data cannot be made publicly available.

ORCID

Dennis Lund Hansen https://orcid.org/0000-0002-4478-1297
Sören Möller https://orcid.org/0000-0003-0858-4269
Henrik Frederiksen https://orcid.org/0000-0001-8905-0220

REFERENCES

1. Jager U, Barcellini W, Broome CM, et al. Diagnosis and treatment of autoimmune hemolytic anemia in adults: recommendations from the First International Consensus Meeting. *Blood Rev*. 2020;41:100648. doi:10.1016/j.blre.2019.100648. Epub 2019 Dec 5. PMID: 31839434.

2. Hansen DL, Moller S, Andersen K, Gaist D, Frederiksen H. Increasing incidence and prevalence of acquired hemolytic anemias in Denmark, 1980–2016. *Clin Epidemiol*. 2020;12:497-508.
3. Tranekær S, Hansen DL, Frederiksen H. Epidemiology of secondary warm autoimmune haemolytic anaemia-A systematic review and meta-analysis. *J Clin Med*. 2021;10(6):1244.
4. Berentsen S, Barcellini W, D'Sa S, et al. Cold agglutinin disease revisited: a multinational, observational study of 232 patients. *Blood*. 2020;136(4):480-488.
5. Berentsen S. New insights in the pathogenesis and therapy of cold agglutinin-mediated autoimmune hemolytic anemia. *Front Immunol*. 2020;11:590.
6. Audia S, Bach B, Samson M, et al. Venous thromboembolic events during warm autoimmune hemolytic anemia. *PLoS One*. 2018;13(11):e0207218.
7. Baek SW, Lee MW, Ryu HW, et al. Clinical features and outcomes of autoimmune hemolytic anemia: a retrospective analysis of 32 cases. *Korean J Hematol*. 2011;46(2):111-117.
8. Ho G, Brunson A, Keegan THM, Wun T. Splenectomy and the incidence of venous thromboembolism and sepsis in patients with autoimmune hemolytic anemia. *Blood Cells Mol Dis*. 2020;81:102388.
9. Rattarittamrong E, Eiamprapai P, Tantiworawit A, et al. Clinical characteristics and long-term outcomes of warm-type autoimmune hemolytic anemia. *Hematology*. 2016;21(6):368-374.
10. Sokol RJ, Hewitt S, Stamps BK. Autoimmune haemolysis: an 18-year study of 865 cases referred to a regional transfusion centre. *BMJ*. 1981;282(6281):2023-2027.
11. Sokol RJ, Booker DJ, Stamps R. The pathology of autoimmune haemolytic anaemia. *J Clin Pathol*. 1992;45(12):1047-1052.
12. Barcellini W, Fattizzo B, Zaninoni A, et al. Clinical heterogeneity and predictors of outcome in primary autoimmune hemolytic anemia: a GIMEMA study of 308 patients. *Blood*. 2014;124(19):2930-2936.
13. Roumier M, Loustau V, Guillaud C, et al. Characteristics and outcome of warm autoimmune hemolytic anemia in adults: New insights based on a single-center experience with 60 patients. *Am J Hematol*. 2014;89(9):E150-E155.
14. Maquet J, Lafaurie M, Walter O, et al. Epidemiology of autoimmune hemolytic anemia: a nationwide population-based study in France. *Am J Hematol*. 2021;96(8):E291-E293.
15. Zhou JC, Wu MQ, Peng ZM, Zhao WH, Bai ZJ. Clinical analysis of 20 patients with non-Hodgkin lymphoma and autoimmune hemolytic anemia: a retrospective study. *Medicine*. 2020;99(7):e19015.
16. Hansen DL, Möller S, Frederiksen H. Survival in autoimmune hemolytic anemia remains poor. 25th EHA Annual Congress; 2020; VIRTUAL - Frankfurt, Tyskland.
17. Aladjidi N, Leverger G, Leblanc T, et al. New insights into childhood autoimmune hemolytic anemia: a French national observational study of 265 children. *Haematologica*. 2011;96(5):655-663.
18. Quinquenel A, Al Nawakil C, Baran-Marszak F, et al. Old DAT and new data: positive direct antiglobulin test identifies a subgroup with poor outcome among chronic lymphocytic leukemia stage A patients. *Am J Hematol*. 2015;90(1):E5-E8.
19. Wang M, Wang W, Abeywardane A, et al. Autoimmune hemolytic anemia after allogeneic hematopoietic stem cell transplantation: analysis of 533 adult patients who underwent transplantation at King's College Hospital. *Biol Blood Marrow Transplant*. 2015;21(1):60-66.
20. Nakasone H, Kako S, Endo H, et al. Diabetes mellitus is associated with high early-mortality and poor prognosis in patients with autoimmune hemolytic anemia. *Hematology*. 2009;14(6):361-365.
21. Benchimol EI, Smeeth L, Guttmann A, et al. The REporting of studies conducted using observational routinely-collected health Data (RECORD) statement. *PLoS Med*. 2015;12(10):e1001885.
22. Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol*. 2014;29(8):541-549.
23. Schmidt M, Schmidt SAJ, Adelborg K, et al. The Danish health care system and epidemiological research: from health care contacts to database records. *Clin Epidemiol*. 2019;11:563-591.
24. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449-490.
25. Hansen DL, Glenthoj A, Moller S, et al. Prevalence of congenital hemolytic disorders in Denmark, 2000–2016. *Clin Epidemiol*. 2020;12:485-495.
26. Hansen DL, Overgaard UM, Pedersen L, Frederiksen H. Positive predictive value of diagnosis coding for hemolytic anemias in the Danish National Patient Register. *Clin Epidemiol*. 2016;8:241-252.
27. Helweg-Larsen K. The Danish Register of causes of death. *Scand J Public Health*. 2011;39(7 Suppl):26-29.
28. Kildemoes HW, Sorensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health*. 2011;39(7 Suppl):38-41.
29. Berentsen S. Role of complement in autoimmune hemolytic anemia. *Transf Med Hemother*. 2015;42(5):303-310.
30. Coviello V, Boggess M. Cumulative incidence estimation in the presence of competing risks. *Stata J*. 2004;4(2):103-112.
31. Lacny S, Wilson T, Clement F, et al. Kaplan-Meier survival analysis overestimates cumulative incidence of health-related events in competing risk settings: a meta-analysis. *J Clin Epidemiol*. 2018;93:25-35.
32. Andersen PK, Geskus RB, de Witte T, Putter H. Competing risks in epidemiology: possibilities and pitfalls. *Int J Epidemiol*. 2012;41(3):861-870.
33. Latouche A, Allignol A, Beyersmann J, Labopin M, Fine JP. A competing risks analysis should report results on all cause-specific hazards and cumulative incidence functions. *J Clin Epidemiol*. 2013;66(6):648-653.
34. Stata Statistical Software. *Release 16* [computer program]. StataCorp LLC.; 2019.
35. Hansen DL, Moller S, Andersen K, Gaist D, Frederiksen H. Evans syndrome in adults - incidence, prevalence, and survival in a nationwide cohort. *Am J Hematol*. 2019;94(10):1081-1090.
36. Mannering N, Hansen DL, Frederiksen H. Evans syndrome in children below 13 years of age – A nationwide population-based cohort study. *PLoS One*. 2020;15(4):e0231284.
37. Gupta N, Kavuru S, Patel D, et al. Rituximab-based chemotherapy for steroid-refractory autoimmune hemolytic anemia of chronic lymphocytic leukemia. *Leukemia*. 2002;16(10):2092-2095.
38. Perrotta S, Locatelli F, La Manna A, Cennamo L, De Stefano P, Nobili B. Anti-CD20 monoclonal antibody (Rituximab) for life-threatening autoimmune haemolytic anaemia in a patient with systemic lupus erythematosus. *Br J Haematol*. 2002;116(2):465-467.
39. Zecca M, Nobili B, Ramenghi U, et al. Rituximab for the treatment of refractory autoimmune hemolytic anemia in children. *Blood*. 2003;101(10):3857-3861.
40. Bylsma LC, Gulbech Ording A, Rosenthal A, et al. Occurrence, thromboembolic risk, and mortality in Danish patients with cold agglutinin disease. *Blood Adv*. 2019;3(20):2980-2985.
41. Hansen DL, Berentsen S, Fattizzo B, Hansen PL, Barcellini W, Frederiksen H. Seasonal variation in the incidence of cold agglutinin disease in Norway, Denmark, and Italy. *Am J Hematol*. 2021;96(7):E262-E265.
42. Zoller B, Li X, Sundquist J, Sundquist K. Risk of subsequent ischemic and hemorrhagic stroke in patients hospitalized for immune-mediated diseases: a nationwide follow-up study from Sweden. *BMC Neurol*. 2012;12:41.

43. Ungprasert P, Tanratana P, Srivali N. Autoimmune hemolytic anemia and venous thromboembolism: a systematic review and meta-analysis. *Thromb Res*. 2015;136(5):1013-1017.
44. L'Acqua C, Hod E. New perspectives on the thrombotic complications of haemolysis. *Br J Haematol*. 2015;168(2):175-185.
45. Lu TH. Using ACME (Automatic Classification of Medical Entry) software to monitor and improve the quality of cause of death statistics. *J Epidemiol Community Health*. 2003;57(6):470-471.
46. Burton JL, Underwood J. Clinical, educational, and epidemiological value of autopsy. *Lancet*. 2007;369(9571):1471-1480.
47. PETRI CNA. Decrease in the frequency of autopsies in Denmark after the introduction of a New Autopsy Act. *Int J Qual Health Care*. 1993;5(4):315-318.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Hansen DL, Möller S, Frederiksen H. Survival in autoimmune hemolytic anemia remains poor, results from a nationwide cohort with 37 years of follow-up. *Eur J Haematol*. 2022;109:10–20. https://doi.org/10.1111/ejh.13764