Increased all-cause mortality among patients diagnosed with warm autoimmune haemolytic anaemia compared to the general population: a nationwide register study in Sweden

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Key Takeaways

- **All-cause mortality was significantly increased for patients with wAIHA compared to the general population. Patients with primary or secondary wAIHA had a 2.2-fold or 3.9-fold higher mortality risk, respectively. Excess risk was highest among patients diagnosed at younger ages (<60 years).**
- **Up to 30% of the 5-year all-cause mortality was associated with autoimmune haemolytic anaemia (11%) and potential complications of the disease and its treatment (infections and cardiovascular events; 19%).**
- **Persistent, increased mortality confirms an ongoing need for the development of safer and more effective treatments to improve survival outcomes in patients with wAIHA.**

Background

Warm autoimmune haemolytic anaemia (wAIHA) is the most common form of autoimmune haemolytic anaemia (AIHA); a severe condition with high morbidity and mortality [1].

Patients with wAIHA, regardless if primary or secondary wAIHA, have poor overall survival [2,3,4].

Comprehensive, nationwide studies on patient survival, particularly in comparison to the general population, remain limited [4].

Objectives

To assess all-cause mortality and cause of death among patients with wAIHA in Sweden and compare mortality with the Swedish general population.

Methods

Data Sources

- Linked Swedish population-based healthcare registries provided data on patients with wAIHA: National Patient Register (NPR) and Cause of Death Register.
- WHO mortality database [5] provided data on the general population in Sweden.

Study Population

- Inclusion of all adult patients diagnosed with wAIHA between 1st July 2005 and 31st December 2022 (requirement: wAIHA-specific ICD-10-SE code D59.1B as primary diagnosis in NPR; D59.1B code has been in use since 1994).
- Exclusion of patients with Evans Syndrome based on records of immune thrombocytopenia (±180 days from wAIHA diagnosis).
- Classification as primary or secondary based on records of associated underlying diseases (haematologic malignancies, autoimmune diseases, primary immunodeficiencies, chronic viral infections, or bone marrow/pancreas transplantations) within ±180 days of wAIHA diagnosis.

Study Outcomes

- **Overall survival (OS)** across subgroups (sex, age at diagnosis and diagnosis period)
  Defined as time from wAIHA diagnosis to death from any cause or censoring (emigration or end of follow-up, i.e., 31st December 2022), whichever occurred first.
- **Cumulative incidence of cause-specific mortality**
  Deaths due to AIHA, solid malignant neoplasms, haematologic malignancies, infections, and cardiovascular diseases (myocardial infarction, cardiac arrhythmias, cerebrovascular diseases) were assessed.
- **Standardized mortality ratios (SMRs)**
  - Calculated by comparing observed all-cause deaths among patients with wAIHA to expected deaths in the Swedish general population.
  - Sex-, age-, and calendar year-stratified mortality rates for the general Swedish population were used.
  - Poisson regression was performed to compare SMR trends across subgroups.

Results

5-year overall survival rates were 70.3% and 44.8% for patients with primary and secondary wAIHA, respectively.

- 401 adult patients diagnosed with wAIHA between 2005 and 2022 in Sweden were identified, including 264 patients with primary wAIHA (median follow-up time of 3.4 years) and 137 patients with secondary wAIHA (median follow-up time of 2.4 years).
- Patients with secondary wAIHA had significantly worse overall survival (OS) than those with primary wAIHA, with a median OS of 11.4 years for primary wAIHA and 4.2 years for secondary wAIHA.
- Crude OS did not differ significantly by sex or diagnosis period but was impacted by age at diagnosis in both primary and secondary wAIHA (median OS in primary wAIHA: 2.5y for ≥80y vs. 10y for 60-79y vs. not reached for <60y; median OS in secondary wAIHA: 2.2y for ≥80y vs. 5y for 60-79y vs. 11.8y for <60y).

Autoimmune haemolytic anaemia contributed to mortality in primary wAIHA.

- Among patients with primary wAIHA, the 5-year cumulative all-cause mortality was 29.7%. 11% of this mortality was attributed to AIHA, 14% to myocardial infarction/ cerebrovascular diseases/ cardiac arrhythmias, 5% to infections, and 70% to other causes. Notably, cardiovascular events and infections (together accounting for approx. 19% of the 5-year all-cause mortality) are both known potential complications of wAIHA or its treatment [6,7].
- Among patients with secondary wAIHA, the 5-year cumulative all-cause mortality was 55.2%. 6% of this mortality was attributed to myocardial infarction/cardiac arrhythmias, 4% to infections, 64% to solid cancers and haematological malignancies, and 26% to other causes.

Patients with wAIHA experienced significantly higher mortality compared to the Swedish general population.

- Patients with primary wAIHA experienced higher mortality than the Swedish general population (SMR: 2.2; 95% CI: 1.8-2.7). This is particularly noteworthy since patients with primary wAIHA lack underlying diseases, which are commonly associated with excess mortality in secondary wAIHA (e.g. haematologic malignancies).
- Patients with secondary wAIHA experienced an even higher increase in mortality compared to the Swedish general population (SMR: 3.9; 95%CI, 3.1-4.9).
- This excess mortality risk holds for all analysed patient subgroups.
- SMR was the highest for patients diagnosed with wAIHA at younger ages, i.e., patients diagnosed at age <60 years (*p*-value for SMR trend = 0.022 and 0.001 for primary and secondary wAIHA, respectively).

FIGURE 1. Kaplan-Meier plots of OS among patients diagnosed with primary or secondary wAIHA in Sweden 2005-2022, shown overall (a) and stratified by sex (b), age at diagnosis (c), and calendar period of diagnosis (d)

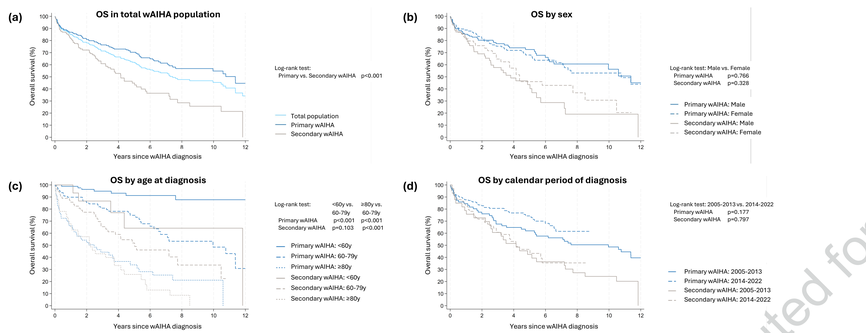


TABLE 1. OS among patients diagnosed with primary or secondary wAIHA in Sweden 2005-2022, presented overall and stratified by sex, age at diagnosis, and calendar period of diagnosis

	Primary wAIHA						Secondary wAIHA					
	Patients at risk, n	Deaths, n	OS rate, %			Median OS in years (95% CI)	Patients at risk, n	Deaths, n	OS rate, %			Median OS in years (95% CI)
			1y	5y	10y				1y	5y	10y	
Total	264	87	86.8	70.3	54.8	11.4 (7.6-NE)	137	69	82.0	44.8	25.8	4.2 (3.2-5.7)
Sex												
Male	137	43	85.2	72.5	56.4	11.4 (6.5-NE)	72	39	82.4	43.5	19.1	3.8 (2.5-5.4)
Female	127	44	88.7	68.1	53.3	10.8 (7.1-NE)	65	30	81.5	45.8	30.6	4.4 (3.2-8.5)
Age at diagnosis												
<60 years	87	7	98.8	91.2	87.7	NR	17	5	100.0	63.0	63.0	11.8 (4.4-NE)
60-79 years	111	37	89.8	74.9	48.7	10.0 (6.5-11.4)	78	32	85.7	51.9	33.9	5.0 (3.3-10.5)
≥80 years	66	43	65.9	33.8	21.1	2.5 (1.2-3.7)	42	32	68.1	25.9	NR	2.2 (1.1-3.7)
Calendar period of diagnosis												
2005-2013	71	40	84.5	62.0	48.6	10.0 (5.3-NE)	33	27	78.8	42.4	24.2	4.2 (2.6-7.2)
2014-2022	193	47	87.7	74.3	NR	NR	104	42	83.2	46.5	NR	4.2 (2.9-NE)

FIGURE 2. Cumulative cause-specific mortality over follow-up time among patients with wAIHA

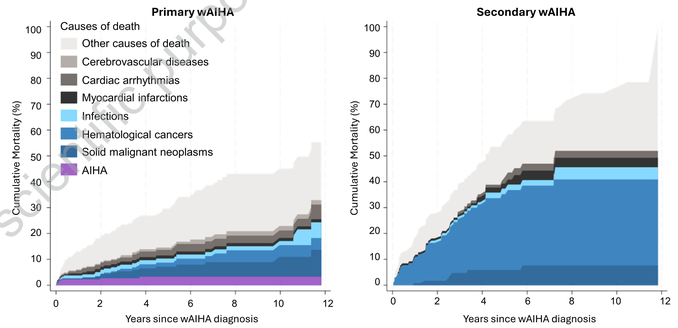


TABLE 2. 1- and 5-year cumulative cause-specific mortality among patients with wAIHA

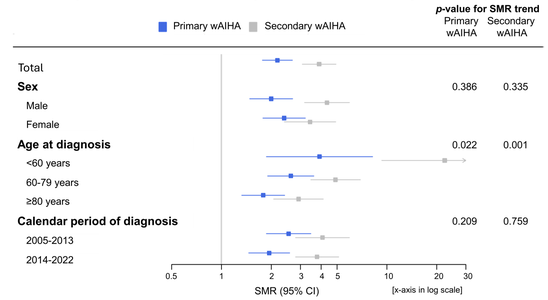
	Primary wAIHA		Secondary wAIHA	
	At the end of 1st year	At the end of 5th year	At the end of 1st year	At the end of 5th year
Cumulative cause-specific mortality, % (95% CI)				
AIHA	2.3 (0.9-4.7)	3.3 (1.5-6.2)	0 (0-0)	0 (0-0)
Solid malignant neoplasms	0.4 (0.0-2.0)	3.9 (1.8-7.3)	0.9 (0.1-4.2)	5.9 (2.4-11.7)
Haematologic malignancies	0 (0-0)	1.6 (0.4-4.2)	9.4 (5.1-15.2)	29.5 (20.8-38.6)
Infections	1.2 (0.3-3.1)	1.6 (0.5-3.8)	0 (0-0)	2.2 (0.4-7.0)
Myocardial infarction	0.8 (0.2-2.6)	1.2 (0.3-3.2)	0.8 (0.1-3.9)	2.0 (0.4-6.4)
Cardiac arrhythmias	1.2 (0.3-3.2)	2.2 (0.8-4.7)	0 (0-0)	1.1 (0.1-5.4)
Cerebrovascular diseases	0.4 (0.0-2.0)	0.9 (0.2-3.0)	0 (0-0)	0 (0-0)
Other causes of death	7.0 (4.3-10.6)	15.1 (10.7-20.2)	7.1 (3.5-12.4)	14.5 (8.6-22.0)
Cumulative all-cause mortality, % (95% CI)	13.2 (9.6-17.9)	29.7 (24.0-36.4)	18.0 (12.3-25.9)	55.2 (45.5-65.6)

TABLE 3. Standardized mortality ratios (SMRs) for all-cause mortality comparing patients with wAIHA to the general population in Sweden, presented overall and stratified by sex, age at diagnosis, and calendar period of diagnosis

	Primary wAIHA				Secondary wAIHA			
	Observed deaths, n	Expected deaths, n	SMR (95% CI)	AEM[a]	Observed deaths, n	Expected deaths, n	SMR (95% CI)	AEM[a]
Total	87	39.9	2.18 (1.77-2.69)	40.0	69	17.7	3.90 (3.08-4.93)	122.5
Sex								
Male	43	21.5	2.00 (1.48-2.69)	35.6	39	9.0	4.35 (3.17-5.95)	144.5
Female	44	18.4	2.39 (1.78-3.22)	44.6	30	8.7	3.43 (2.40-4.91)	100.8
Age at diagnosis								
<60 years	7	1.8	3.92 (1.87-8.22)	10.1	5	0.2	22.34 (9.30-53.67)	62.5
60-79 years	37	14.1	2.63 (1.90-3.62)	46.4	32	6.5	4.89 (3.46-6.92)	104.8
≥80 years	43	24.0	1.79 (1.33-2.41)	115.1	32	10.9	2.92 (2.07-4.13)	211.9
Calendar period of diagnosis								
2005-2013	40	15.7	2.55 (1.87-3.47)	46.9	27	6.6	4.08 (2.80-5.95)	123.8
2014-2022	47	24.2	1.94 (1.46-2.58)	34.6	42	11.1	3.78 (2.80-5.12)	121.6

[a] AEM indicates absolute excess deaths per 1,000 patient-years

FIGURE 3. Forest plot showing increased all-cause mortality among Swedish patients with wAIHA compared to the Swedish general population



Limitations

- Cause-specific mortality reporting was limited to selected key causes of death since not all causes of death were available in the current dataset due to data minimization requirements.
- Use of publicly available, aggregated mortality data for the general population enables adjustment for key risk factors such as sex, age, and diagnosis period, but not for more detailed patient-level information, such as comorbidities.
- The limited number of patients with secondary wAIHA prohibited mortality analysis stratified by underlying diseases.

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