SEASONALITY OF HEALTHCARE RESOURCE UTILIZATION AMONG COLD AGGLUTININ DISEASE PATIENTS IN DENMARK: A RETROSPECTIVE ANALYSIS

J. FRYZEK[1], N. HOODA[1], B. ESEN[2], T. SOURDILLE[3], E. HORVÁTH-PUHÓ[2], E. VAGO[2], C. BROOME[4], A. RÖTH[5]

[1] EpidStrategies, a Division of ToxStrategies, Inc., Rockville, MD, [2] Department of Clinical Epidemiology, Aarhus University, Aarhus, Denmark, [3] Sanofi, Cambridge, MA, [4] Division of Hematology, MedStar Georgetown University Hospital, Washington, DC, USA, [5] Department of Hematology and Stem Cell Transplantation, West German Cancer Center, University Hospital Essen, University of Duisburg-Essen, Essen, Germany

INTRODUCTION

- Cold agglutinin disease (CAD) is a serious and rare form of autoimmune hemolytic anemia (AIHA) characterized by monoclonal autoantibodies targeting red blood cell (RBC) surface structures, preferentially at lower temperatures.[1] This results in both agglutination of RBCs and complement-mediated hemolysis
- Symptoms of CAD include chronic anemia, profound fatigue, weakness and acute hemolytic crisis,[2–4] which can be debilitating for patients
- CAD is associated with substantial economic burden and consumption of healthcare resources, notably via need for blood transfusions, hospitalization, and outpatient and emergency room visits[5,6]
- Patients with CAD were previously shown to have a greater healthcare utilization compared to the general population[7]
- Considering exposure to cold temperatures may precipitate both the circulatory symptoms of CAD and hemolysis,[4] understanding seasonal variation of CAD manifestations may be important to guide nonpharmacological management strategies and prophylactic recommendations[8,9]
- A previous retrospective cohort in the United States demonstrated persistent hemolysis independent of the season with disease manifestations, as evaluated by healthcare resource utilization (HRU)[2]

OBJECTIVE

To elucidate the effects of seasonal temperature on the HRU of CAD patients in Denmark and a matched comparison cohort from the general population by comparing fall (September-November), winter (December-February), spring (March-May), and summer (June-August) values for inpatient hospital admissions and outpatient visits for the first year after index date as well as for the entire follow-up period

METHOD

- Data sources for this population-based cohort study were the Danish National Patient Registry (covering all hospitalizations, emergency room visits, and outpatient clinic visits), the Danish Civil Registration System (a national population registry), and the Danish National Prescription Registry (covering all reimbursed prescriptions)
- Denmark has a universal tax-supported health care system, and administrative and medical registries that provide complete follow-up information for all citizens, allowing for highly accurate disease and mortality ascertainment[11]
- Patients with CAD diagnosed between 1999–2013 were identified retrospectively using the Danish version of the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) code D591A, which is specific to cold agglutinin–mediated AIHA and excludes warm and mixed AIHAs since 1999
- Study index date for CAD patients was the date of the first inpatient or outpatient visit. Patients were followed until death, emigration or through 2013. Study index date for comparison patients was the same as the matched CAD patient's index date
- Each patient was matched based on age, sex, and region of residence, to 10 comparison individuals from the general population who were alive and without a CAD diagnosis on the matched CAD patient's index date
- Crude numbers of HRU were determined by the number of inpatient admissions and outpatient visits in the first year after index date and for the entire follow-up period for each season
- Hospital visits with ICD-10 codes D591, D649, D594, and D599 either as a primary or secondary diagnosis were classified as CAD-related visits

RESULTS

Study cohorts

- We identified 72 patients diagnosed with CAD between 1999 and 2013 and a matched comparison cohort of 720 individuals (**Table 1**)
- Mean age at CAD diagnosis was 68.5 years and 58% of patients were female. Patient demographics for both the CAD patient and the matched cohort are shown in **Table 1**. Mean follow-up duration was 3.4 years for patients with CAD and 3.8 years for matched comparisons
- Twenty-four percent of patients with CAD had a Carlson Comorbidity Index score of ≥3 at baseline, compared to 9% in the matched comparison cohort (**Table 1**)

Table 1 | *Clinical characteristics and demographics of patients with CAD and the matched comparison cohort*

	Patients with CAD (N=72)	Matched comparison (N=720)
Sex, n (%)		
Female	42 (58)	420 (58)
Male	30 (42)	300 (42)
Age at index date (years), n (%)		
19–59	17 (24)	170 (24)
60–69	13 (18)	130 (18)
70–79	27 (38)	276 (38)
80–89	15 (21)	144 (20)
Age at index date (years)		
Mean (SD)	68.5 (14.9)	68.5 (14.7)
Median (range)	72.2 (20.3–89.6)	72.2 (19.8–89.9)
Year of diagnosis/index date, n (%)		
1999–2003	5 (7)	50 (7)
2004–2008	22 (31)	220 (31)
2009–2013	45 (63)	450 (63)
Region of residence at index date, n (%)		
North Denmark Region	5 (7)	50 (7)
Central Denmark Region	13 (18)	130 (18)
Region of Southern Denmark	19 (26)	190 (26)
Capital Region of Denmark	26 (36)	260 (36)
Region Zealand	9 (13)	90 (13)
Charlson Comorbidity Index score, n (%)		
0	25 (35)	447 (62)
1–2	30 (42)	205 (28)
≥3	17 (24)	68 (9)
Duration of follow-up (years)		
Mean (SD)	3.4 (2.9)	3.8 (3.1)
Median (range)	3.1 (0.0–14.3)	2.9 (0.0–14.3)

RESULTS

HRU: Inpatient stays

First year after index date

- During the first year after index date, the proportion of patients with CAD-related inpatient stays were: spring, 20.8%; summer, 19.4%; fall, 19.4% and winter, 23.6%, for patients with CAD. Rates for the matched comparisons were: spring, 1.8%; summer, 2.1%; fall, 2.5% and winter, 3.3% (**Figure 1a**). All HRU inpatient stays during this time followed a similar pattern (**Figure 1b**)
- During the first year after index date, mean CAD-related inpatient stays (per patient per season) for patients with CAD and their matched comparisons for all seasons were: spring: 1.4 and 1.1, summer: 1.3 and 1.1, fall: 2.4 and 1.3, and winter: 2.1 and 1.5, respectively (**Table 2**) All HRU inpatient stays during this time are shown in **Table 2**

Entire follow-up duration

- The proportion of patients with CAD-related inpatient stays during the entire duration of follow-up were: spring, 40.3%; summer, 31.9%; fall, 36.1% and winter, 36.1%, for patients with CAD. Proportions for the matched comparisons were: spring, 9.0%; summer, 8.1%; fall, 9.4% and winter, 9.2% (**Figure 2a**). All HRU inpatient stays during this time followed a similar pattern (**Figure 2b**)
- During the entire follow-up duration, mean CAD-related inpatient stays (per patient per season) for patients with CAD and their matched comparisons for all seasons were: spring: 1.7 and 1.2, summer: 1.6 and 1.4, fall: 2.3 and 1.6, and winter: 2.5 and 1.4, respectively (**Table 2**). All HRU inpatient stays during this time are shown in **Table 2**

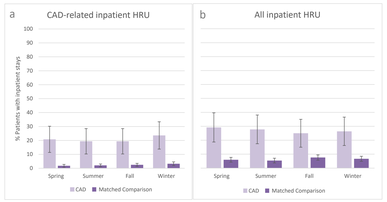

Figure 1 | *CAD-related inpatient stays (**a**) and all inpatient stays (**b**) during the first year after index date by season (% patients with at least one inpatient stay ± 95% confidence intervals)*

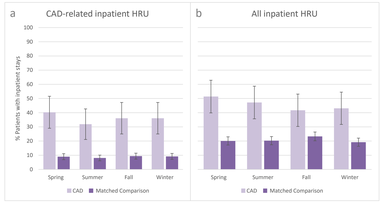

Figure 2 | *CAD-related inpatient stays (**a**) and all inpatient stays (**b**) during entire follow-up period: 1999-2013 (% patients with at least one inpatient stay ± 95% confidence intervals)*

Health care resource	Season	Population	Number of CAD-related inpatient visits			Number of all inpatient visits		
			Mean	Median	Range	Mean	Median	Range
First year after index date	Spring	CAD	1.4	1	1-2	1.6	2	1-3
		Matched Comparison	1.1	1	1-2	1.3	1	1-4
	Summer	CAD	1.3	1	1-3	1.3	1	1-3
		Matched Comparison	1.1	1	1-2	1.2	1	1-2
	Fall	CAD	2.4	1	1-7	2.5	1.5	1-7
		Matched Comparison	1.3	1	1-2	1.4	1	1-4
	Winter	CAD	2.1	1	1-6	2.2	1	1-7
		Matched Comparison	1.5	1	1-4	1.5	1	1-4
Entire follow-up period	Spring	CAD	1.7	1	1-3	2.0	2	1-4
		Matched Comparison	1.2	1	1-3	1.5	1	1-6
	Summer	CAD	1.6	1	1-4	1.8	1	1-5
		Matched Comparison	1.4	1	1-3	1.6	1	1-8
	Fall	CAD	2.3	1	1-8	2.8	2	1-9
		Matched Comparison	1.6	1	1-4	1.8	1	1-9
	Winter	CAD	2.5	1	1-8	2.9	2	1-10
		Matched Comparison	1.4	1	1-4	1.7	1	1-6

Table 2 | *Number of all inpatient, and CAD-related inpatient, stays by season (per patient per season) during the first year after index date, and during the entire follow-up period (1999–2013), for CAD patients and their matched comparisons*

HRU: Outpatient visits

First year after index date

- During the first year after index date, the proportion of patients with CAD-related outpatient visits were: spring, 62.5%; summer, 63.9%; fall, 62.5% and winter, 63.9%, for patients with CAD. Proportions for the matched comparisons were: spring, 2.8%; summer, 2.6%; fall, 3.3% and winter, 3.3% (**Figure 3a**). All HRU outpatient visits during this time followed a similar pattern (**Figure 3b**)
- During the first year after index date, mean CAD-related outpatient visits (per patient per season) for patients with CAD and their matched comparisons for all seasons were: spring: 6 and 3, summer: 4 and 4, fall: 5 and 3, and winter: 6 and 2, respectively (**Table 3**) All HRU outpatient visits during this time are shown in **Table 3**

Entire follow-up duration

- The proportion of patients with CAD-related outpatient visits during the entire duration of follow-up were: spring, 72.2%; summer, 70.8%; fall, 77.8% and winter, 73.6%, for patients with CAD. Proportions for the matched comparisons were: spring, 9.0%; summer, 7.8%; fall, 10.1% and winter, 9.0% (**Figure 4a**). All HRU outpatient visits during this time are shown in **Figure 4b**
- During the entire follow-up period mean CAD-related inpatient stays (per patient per season) for patients with CAD and their matched comparisons for all seasons were: spring: 12 and 5, summer: 11 and 6, fall: 12 and 6, and winter: 12 and 5, respectively (**Table 3**). All HRU outpatient visits during this time are shown in **Table 3**

RESULTS

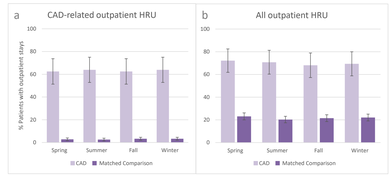

Figure 3 | *CAD-related outpatient visits (**a**) and all outpatient visits (**b**) during the first year after diagnosis or cohort entry by season (% patients with at least one outpatient visit ± 95% confidence intervals)*

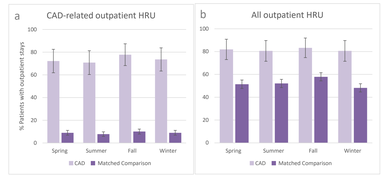

Figure 4 | *CAD-related outpatient visits (**a**) and all outpatient visits (**b**) during entire follow-up period: 1999–2013 (% patients with at least one outpatient visit ± 95% confidence intervals)*

Health care resource	Season	Population	Number of CAD-related outpatient visits			Number of all outpatient visits		
			Mean	Median	Range	Mean	Median	Range
First year after index date	Spring	CAD	6	4	1–16	7	5	1–27
		Matched Comparison	3	2	1–11	3	2	1–28
	Summer	CAD	4	3	1–13	5	4	1–15
		Matched Comparison	4	2	1–16	3	2	1–25
	Fall	CAD	5	3	1–17	6	4	1–17
		Matched Comparison	3	2	1–10	3	2	1–27
	Winter	CAD	6	3	1–22	7	4	1–22
		Matched Comparison	2	1	1–15	3	2	1–26
Entire follow-up period	Spring	CAD	12	10	1–76	15	11	1–86
		Matched Comparison	5	2	1–52	5	3	1–80
	Summer	CAD	11	7	1–75	13	10	1–86
		Matched Comparison	6	3	1–60	5	3	1–109
	Fall	CAD	12	9	1–97	15	10	1–108
		Matched Comparison	6	3	1–45	6	4	1–96
	Winter	CAD	12	9	1–85	15	11	1–94
		Matched Comparison	5	2	1–40	5	3	1–80

Table 3 | *Number of all outpatient, and CAD-related outpatient, visits by season (per patient per season) during the first year after index date, and during the entire follow-up period (1999–2013), for CAD patients and their matched comparisons*

CONCLUSIONS

- Patients with CAD in this cohort had evidence of persistent HRU independent of the season. This included all inpatient and all outpatient HRU, in addition to CAD-related inpatient and outpatient HRU
- Overall, patients with CAD had a higher level of both inpatient and outpatient HRU, compared with the matched comparison group independent of season
- These data do not support perceptions of CAD as a seasonal disorder; recommendations such as moving to regions with warmer climates may not provide meaningful clinical benefit
- The lack of seasonal variability in this cohort suggests that treatment considerations for patients with CAD should be season-independent

ABBREVIATIONS AND REFERENCES

AIHA, autoimmune hemolytic anemia; CAD, cold agglutinin disease; HRU, healthcare resource utilization; ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th Revision; RBC, red blood cell; SD, standard deviation.

1. Berentsen S, et al. *Hematol Oncol Clin North Am*. 2015;29(3):455–71; 2. Röth A, et al. *Transfusion*. 2022;62(1):51–9; 3. Swiecicki PL, et al. *Blood* 2013;122:1114–21; 4. Berentsen S. *Br J Haematol* 2018;181:320–30; 5. Mullins M, et al. *Blood Adv.* 2017;1:839–48; 6. Su J, et al. *J Med Econ* 2019;23:902–7; 7. Vágó EK, et al. *Curr Med Res Opin*. 2021;37(10):1829–35; 8. Lyckholm LJ and Edmond MB. *N Engl J Med*. 1996;334(7):437; 9. Berentsen S, et al. *Hematology*. 2007; 12(5):361–70; 10. Bylsma LC, et al. *Blood Adv.* 2019;3(20):2980–5; 11. Schmidt M, et al. Clin Epidemiol. 2019;11:563-591

ACKNOWLEDGEMENTS

Medical writing and editing support were provided by Emma East of Lucid Group Communications Ltd., and was funded by Sanofi.

DISCLOSURES

This work was funded by Sanofi. The Department of Clinical Epidemiology, Aarhus University, Aarhus, Denmark, was supported by EpidStrategies who, in turn, was funded by Sanofi. Sanofi reviewed and provided feedback on the presentation. The authors had full editorial control of the presentation and provided their final approval of all content. **JF** and **NH** are employees of EpidStrategies. **BOE**, **EHP** and **EKV** have no disclosures. **TS** is an employee of Sanofi and may hold shares and/or stock options. **CMB** has received honoraria/consulting fees from Alexion, Argenx, Annexon, Incyte and Sanofi. **AR** has as received research support from Roche, and honoraria/consulting fees from Alexion, Bioverativ, a Sanofi company, Novartis, Roche and Sanofi.