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# Mortality in cold agglutinin disease shows seasonal pattern

We have with great interest read the recent publication by Röth et al. illustrating that patients with cold agglutinin disease (CAD) have persistent biochemical hemolysis all year round.[1] The study supports that anemia, hemolysis, and directly related symptoms like fatigue persist through seasons. Despite these findings, we have recently shown a remarkable seasonal variation in the incidence of CAD diagnosis in Norway, Denmark, and Italy indicating that symptoms may be aggravated and become clinically overt during colder months.[2] We, therefore, speculated whether mortality in cold agglutinin disease likewise shows seasonal variation, not seen in other acquired hemolytic diseases.

In order to address this we used our cohort including all patients diagnosed in Denmark with CAD or autoimmune hemolytic anemia (AIHA), and for each patient in the two categories up to 50 age-sex-matched comparators from the general population.[3] Denmark has nationwide health registers deriving from a universal, tax-funded health system providing a complete inclusion and minimal loss to follow up.[4] We included patients diagnosed from 1980 to 2016 for AIHA and 1994 to 2016 for CAD. A Danish adaptation of the International Classification of Diseases revision 10 in 1994, allows the separation of CAD (D591A) from unspecified AIHA (D591) in the Danish National Patient Register.[3–5] The unspecified AIHA category consists of warm-type AIHA and less frequently mixed-type AIHA.[2,3,5] Follow-up started on the date of diagnosis of either CAD or AIHA, the same start date was allotted to the corresponding comparators, and continued to the first of death, emigration, or December 31, 2017.

The main outcome was the date of death, grouped into the calendar seasons: *Spring* (March, April, May), *Summer* (June, July, August), *Autumn* (September, October, November), and Winter (December, January, February). The rarity of CAD made it impossible to analyze by month or assess seasonal patterns in causes of death.

We used Cox proportional hazard regression to estimate the risk of death in each disease or comparator group with respect to calendar season. We estimated unadjusted hazard ratios (HR) in a combined model including all diseases and comparator groups, applying interaction between each group and season, with the groups of comparators for the patients with CAD as a global reference, and summer as a local reference for mortality within each of the three remaining groups (CAD, AIHA, and AIHA comparators). Subsequently, adjusted HRs were estimated, including age at diagnosis, sex, and year of diagnosis in the model.

We identified 114 patients with CAD and 5311 comparators, who accumulated 45 and 1074 fatalities, respectively. In addition, we identified 2889 patients with AIHA and 143,269 comparators, experiencing 1809 and 64,954 fatalities. The two groups of patients with CAD and AIHA differed in mean age at diagnosis and sex distribution, but patient groups and corresponding comparator groups were similar by study design, Table S1.

Adjusted estimates are depicted in Figure 1, all adjusted and unadjusted HRs are presented in Table S2. When comparing patients with CAD to their age-sex-matched comparators there was no significant difference in the risk of death during spring and autumn. However, winter was associated with a 4.5 (95% confidence interval [CI] 2.00; 10.08) times increased risk of death, adjusted for age, sex, and year of diagnosis, Table S2. The unadjusted risk of death during winter was 3.2 (95% CI 1.43; 7.18). Amongst patients with AIHA or corresponding comparators, no significant seasonal effect was observed, Table S2.

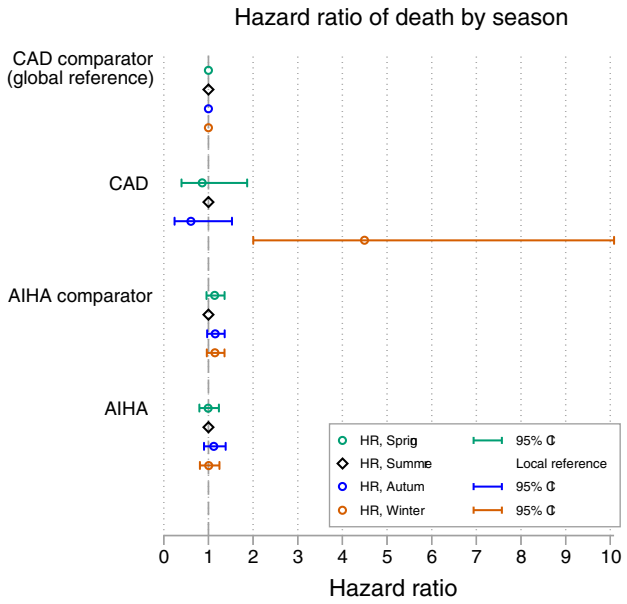


**FIGURE 1** Risk of death by season amongst patients with cold agglutinin disease, autoimmune hemolytic anemia, or comparators [Color figure can be viewed at wileyonlinelibrary.com]

Our results indicate that CAD is associated with an increased risk of death during the colder months. However, our observational data does not allow for a direct causal inference. Especially, as biochemical data are not available to us we cannot directly address the issue of seasonal independent constant hemolysis in CAD, raised by Röth et al.[1] If seasonal independent hemolysis is the norm in CAD the increased risk of death during winter could arise from general frailty in the mostly elderly patients with CAD, where perhaps short term increases in hemolysis or impaired microcirculation could be an aggravating factor adding to effects of comorbidity, further, infections is also a leading cause of death and may be aggravated by both season and immunosuppressive treatment.[6] Of note, the increased risk of death was not seen amongst patients with AIHA or their comparators. Even though the effect is large (HR 4.5) and statistically significant, it lacked precision due to the limited number of patients. Consequently, these findings should seek confirmations in other cohorts and preferably other climatic areas, as this could potentially inflict on results.[1,2]

## CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest with this study. Outside of the study DLH: research grants from Alexion and Novartis, conference fee from EUSA Pharma. SM: None. 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. SB: Advisory board/consultancy honoraria from Annexon, Apellis, Bioverativ, Momenta Pharmaceuticals, Sanofi-Genzyme, and SOBI: lecture honoraria from Apellis, Janssen-Cilag, and Sanofi-Genzyme.

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