Cumulative Effect of Abnormal Biomarkers on the Risk of Mortality and Thromboembolic Events in Patients with Cold Agglutinin Disease

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INTRODUCTION

- Cold agglutinin disease (CAD) is a rare autoimmune haemolytic anaemia (AIHA) characterised by classical complement activation resulting in haemolysis.[1]
- Published evidence suggests that patients with CAD are twice as likely to die or experience thromboembolic events (TE) than matched non-CAD referents.[2]
- Moreover, increased risks of mortality and TE were observed in patients with CAD with abnormal levels of disease biomarkers.[3]
- However, there is a paucity of data on how the cumulative abnormal biomarkers affect mortality and TE in the CAD population.

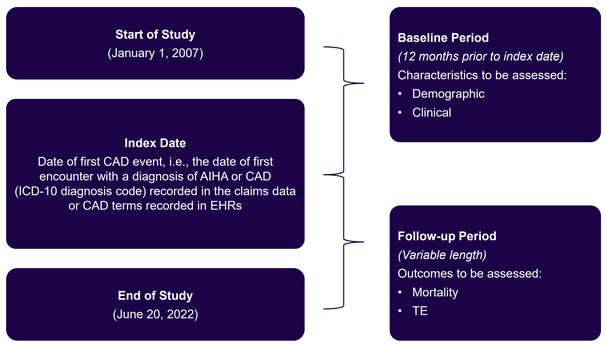
AIMS

- To assess the cumulative effect of abnormal values of haemoglobin (Hb), bilirubin, and lactate dehydrogenase (LDH) on the risk of mortality and first TE in patients with CAD.

METHODS

- A retrospective cohort study was conducted using the US Optum's Market Clarity de-identified electronic health records (EHRs) and claims data from 2007 to 2022 (**Figure 1**).

Figure 1. Study design



AIHA, autoimmune haemolytic anaemia; CAD, cold agglutinin disease; CM, Cox proportional hazards models; ICD-10, International Classification of Disease, Tenth revision; JM, shared random-effects joint models; TDCM, Cox models with time-dependent covariates; TE, thromboembolic events.

- Patients entered the CAD cohort on the date of their first encounter with:
  - ICD-10 diagnosis code for CAD or AIHA as recorded in the claims data.
  - CAD terms ('cold agglutinin disease', 'cold autoimmune haemolytic anaemia', or 'cold agglutinin haemoglobinuria') recorded in EHRs.
- Patients were excluded if:
  - Aged < 18 years at index date.
  - Prior diagnosis of mycoplasma, cytomegalo virus, Epstein-Barr virus, lymphoma, mucosa-associated lymphoid tissue lymphoma, chronic lymphoid leukaemia, Waldenström's macroglobulinemia, or myeloma.
  - No continuous medical activity during the reporting period.
- Two metrics were built to estimate the cumulative extent of abnormal biomarkers:
  - Metric 1 (M1): frequency of abnormal biomarker values over the duration of follow-up, i.e., the number of abnormal values per day.
  - Metric 2 (M2): proportion of abnormal biomarker values among all available laboratory measures of biomarkers, i.e., the proportion of abnormal values across all results (**Figure 2**).
- Abnormal biomarker levels were defined as <10 g/dL for Hb (frontier between mild and moderate anaemia), >1.2 mg/dL (upper limit of normal [ULN]) for bilirubin, and >250 U/L (ULN) for LDH.

Figure 2. Example of metrics (M1 and M2) established to estimate the cumulative extent of abnormal biomarkers

$$\text{Metric 1} = \frac{(Number\ of\ abnormal\ values\ \Delta t)}{(Number\ of\ days\ past\ \Delta t)} \qquad \text{Metric 2} = \frac{(Number\ of\ abnormal\ values\ \Delta t)}{(Number\ of\ recorded\ values\ \Delta t)}$$

Days	1	2	3	4	5	6	7	8	9	10
Biomarker record	Abnormal value	-	Abnormal value	-	Normal value	Normal value	-	Abnormal value	-	Outcome event
Value of **Metric 1**	$\frac{1}{1}$	-	$\frac{2}{3}$	-	$\frac{2}{5}$	$\frac{2}{6}$	-	$\frac{3}{8}$	-	$\frac{3}{10}$
Value of **Metric 2**	$\frac{1}{1}$	-	$\frac{2}{2}$	-	$\frac{2}{3}$	$\frac{2}{4}$	-	$\frac{3}{5}$	-	$\frac{3}{5}$

In this example, values were not observed on Days 2, 4, 7, and 9.

- The potential impact of these metrics on the risk of mortality and first TE (utilising diagnostic codes used in the analyses performed by Broome et.al[2]) was evaluated using three different models:
  - Cox proportional hazards models (CM)
  - Cox models with time-dependent covariates (TDCM)
  - Shared random-effects joint models (JM)
- TDCM and JM considered values of biomarkers since index date throughout the follow-up period, while CM considered the cumulative abnormal values of biomarkers during baseline (one year) period.
- Age at index date, sex, history of TE, smoking status, index season, and Charlson Comorbidity Index score were used as covariates in all three models.

RESULTS

Baseline characteristics

- The study included 876 patients with primary CAD (**Table 1**).
  - Majority of patients were females (63.50%).

Table 1. Baseline characteristics

Parameters	CAD (N = 876)
Age at index date (years)*	
Mean (SD)	66.75 (14.84)
Race, n (%)	
African American	61 (7.03)
Caucasian	740 (84.54)
Other/unknown	75 (8.61)
History of TE#, n (%)	
No	769 (87.85)
Yes	107 (12.21)
Smoking status#, n (%)	
Current smoker	68 (7.82)
Non-smoker	302 (34.54)
Other/unknown/missing	287 (32.82)
Past smoker	219 (25.00)
CCI score#	
Mean (SD)	1.93 (2.58)
Median [Q1, Q3]	1.00 [0.00, 3.00]

*The index date was the date of first CAD event i.e., the date of first encounter with a diagnosis of AIHA or CAD (ICD-10 diagnosis code) recorded in the claims or CAD terms recorded in EHRs. #Variables measured during the baseline period.
AIHA, autoimmune haemolytic anaemia; CAD, cold agglutinin disease; CCI, Charlson Comorbidity Index; SD, standard deviation; TE, thromboembolic events.

- The mean (standard deviation) follow-up duration, i.e., the number of months from the index date (inclusive) until the end of medical activity, study period, or death, whichever occurred first, was 43.25 (35.80) months.

Evaluation of mortality risk using M1 and M2

Using M1

- Increase in the proportion of cumulative abnormal values of Hb increased the risk of mortality (HR [95% CI]) with CM (1.02 [1.01–1.04]) and TDCM (2.89 [1.77–4.73]), and numerically increased with JM (1.92 [0.95–3.90]).
- Increase in the proportion of cumulative abnormal values of bilirubin also increased the risk of mortality (HR [95% CI]) with TDCM (1.93 [1.13–3.29]).
- The risk of mortality was not increased with cumulative abnormal values of LDH with TDCM and CM, while non-convergence was observed with JM (**Figure 3**).

Using M2

- Increase in the proportion of cumulative abnormal values of Hb increased the risk of mortality (HR [95% CI]) across all models: CM (3.21 [2.00–5.14]), TDCM (6.87 [3.99–11.85]), and JM (6.05 [3.61–10.16]).
- Increase in the proportion of cumulative abnormal values of bilirubin also increased the risk of mortality (HR [95% CI]) with TDCM (1.46 [1.02–2.08]).
- Increase in the proportion of cumulative abnormal values of LDH increased the risk of mortality (HR [95% CI]) with JM (1.50 [1.01–2.22]) and numerically increased with TDCM (1.46 [0.98–2.18], **Figure 3**).

Evaluation of the risk of first TE using M1 and M2

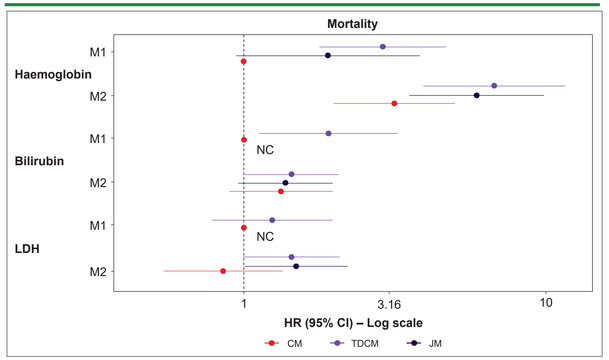
Using M1

- The risk of first TE increased with JM (2.09 [1.02–4.30]) and numerically increased with TDCM (1.56 [0.93–2.62]) for increase in the proportion of cumulative abnormal values of Hb.
- The risk of first TE was not increased with cumulative abnormal values of bilirubin and LDH with TDCM and CM, while non-convergence was observed with JM (**Figure 4**).

Using M2

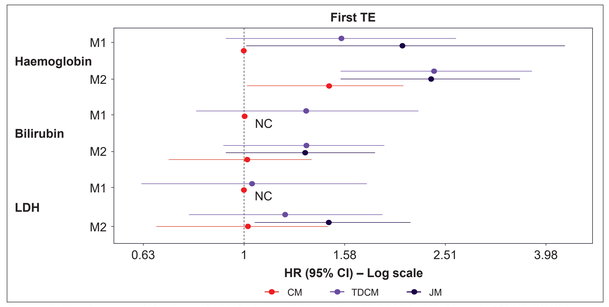
- The risk of first TE (HR [95% CI]) increased with CM (1.46 [1.03–2.08]), TDCM (2.41 [1.57–3.69]) and JM (2.37 [1.57–3.57]) for increase in the proportion of cumulative abnormal values of Hb.
- The risk of first TE (HR [95% CI]) numerically increased with cumulative abnormal values of bilirubin with TDCM (1.32 [0.92–1.91]) and JM (1.32 [0.94–1.84]).
- The risk of first TE increased with cumulative abnormal values of LDH with JM (1.49 [1.03–2.15]; **Figure 4**).

Figure 3. Analyses of the cumulative effect of abnormal values of biomarkers on mortality according to Metrics 1 and 2 using three different models



Abnormal biomarkers were defined as <10 g/dL for haemoglobin, >1.2 mg/dL(ULN) for bilirubin and >250 U/L (ULN) for LDH.
CI, confidence interval; CM, Cox proportional hazards models; HR, hazard ratio; JM, shared random-effects joint models; LDH, lactate dehydrogenase; M1, metric 1; M2, metric 2; NC, non-convergence; TDCM, Cox models with time-dependent covariates; ULN, upper limits of normal.

Figure 4. Analyses of the cumulative effect of abnormal values of biomarkers on first TE according to Metrics 1 and 2 using three different models



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CI, confidence interval; CM, Cox proportional hazards models; HR, hazard ratio; JM, shared random-effects joint models; LDH, lactate dehydrogenase; M1, metric 1; M2, metric 2; NC, non-convergence; TDCM, Cox models with time-dependent covariates; TE, thromboembolic events; ULN, upper limits of normal.

DISCUSSION

- In addition to the classic CM model, two more complex models (TDCM and JM) were used to consider specificity of the data and increase robustness of the results (**Table 2**).
- Limitations of the study:
  - Inability of the metrics to differentiate patients who had several abnormal values within a short period from patients who had the same number of abnormal values over a longer duration.
  - JM when applied to bilirubin and LDH failed to converge for the risk of mortality and TE when using M1. This could be attributed to a higher proportion of patients in the CAD cohort (N = 876) with missing laboratory data during follow-up (bilirubin: 19% and 31%; LDH: 50% and 59.5% for mortality and first TE analyses, respectively). In addition, the trajectory of M1 tends faster and sooner to zero than M2, leading to non-convergence.

Table 2. Comparisons between the three models used in the study

Models	Advantages	Disadvantages
Cox proportional hazards models (CM)	• Short time of computing • Easy to implement • The use of metrics avoids making assumptions related to the distribution of biomarker values between timepoints	• Do not handle time-varying (exogenous AND endogenous) covariates • Do not capture cumulative effects
Cox models with time-dependent covariates (TDCM)	• Handle time-varying covariates (exogenous) • Short time of computing • Easy to implement • The use of metrics avoids making assumptions related to the distribution of biomarker values between timepoints	• Do not handle endogenous covariates • Do not capture cumulative effects but instantaneous hazards
Shared random-effects joint models (JM)	• Handle time-varying covariates (endogenous) • The use of metrics avoids making assumptions related to the distribution of biomarker values between timepoints	• Need more computational time • May not converge, especially where data are sparse • Do not capture cumulative effects but instantaneous hazards

CONCLUSIONS

- **Increase in cumulative abnormal values of Hb increased the risks of mortality and first TE in patients with CAD throughout three models and two metrics.**
- **Increase in the proportion of cumulative abnormal values of bilirubin and LDH increased the risk of mortality; however, less marked effects were observed on the risk of first TE.**
- **Early and chronic control of complement pathway activation and the resulting haemolysis in patients with CAD may therefore help manage the risk of mortality and TE.**

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