Hemolytic markers, mortality, and thromboembolic events in CAD: risk assessment by time period since diagnosis

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BACKGROUND:

- Cold agglutinin disease (CAD) is a rare autoimmune hemolytic anemia (AIHA) characterized by classical complement pathway-mediated hemolysis.[1]
- Although there is consensus on an increased risk of thromboembolic events (TEs) in patients with CAD than those without CAD[2], the evidence on mortality is mixed.
- The association of mortality and TE risks with time since CAD diagnosis and biomarker levels has been rarely assessed.

AIMS:

Aim 1: To evaluate whether patients with CAD have higher risk of mortality and TEs compared with a matched non-CAD population at various time periods since CAD diagnosis.

Aim 2: To determine the association between hemolytic biomarker levels (hemoglobin [Hb], bilirubin, and lactate dehydrogenase [LDH]) and the risk of mortality and TEs in patients with CAD.

METHODS:

Study design and participants

- This was a retrospective, cohort study of patients with CAD and exact-matched patients without CAD in the US, identified using the OPTUM® de-identified Electronic Health Record dataset (2007–2021).
- Patients with cold agglutinin syndrome were excluded.

Assessment of mortality, TEs, and biomarkers

- Mortality and TEs were assessed over the full follow-up period (from index date [first CAD mention] till the end of medical activity, study period, or death) and at pre-defined time periods (100 days, 1-, 2-, 3-, 5-, and 10-years) from CAD diagnosis.
- Biomarker levels were assessed at baseline and during follow-up, and categorized as follows:
  - Bilirubin: Severely elevated, >2.4 mg/dL; moderately elevated, >1.2–≤2.4 mg/dL; normal, ≤1.2 mg/dL.
  - LDH: Severely elevated, >500 U/L; moderately elevated, >250–≤500 U/L; normal, ≤250 U/L.
  - Hb: No anemia, Hb ≥12 g/dL; mild, Hb ≥10–<12 g/dL; moderate, Hb ≥8–<10 g/dL; and severe, Hb <8 g/dL.

Statistical analyses

- Adjusted ratios account for age, sex, smoking, comorbidities (Charlson Comorbidity Index), past TEs, and index season.

Aim 1: Mortality or TE risk in CAD versus non-CAD patients from the time period since CAD diagnosis

- Adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) were obtained for the pre-defined time periods using multivariate Cox proportional hazard regression analyses.
- Probabilities of survival and remaining TE-free were assessed using Kaplan–Meier (KM) analysis with log rank test.

Aim 2: Association between biomarkers and the risk of mortality and TEs in patients with CAD

- Time-varying Cox regression was used in the CAD cohort to analyze the association between biomarkers (all observations until event) and the risk of mortality and TEs.

RESULTS:

Baseline characteristics

- Overall, 457 patients with CAD and 2285 exact-matched non-CAD patients were included (**Table 1**).

Table 1. Baseline demographics and clinical characteristics of patients with and without CAD in the US

Characteristic	CAD cohort (N=457)	Non-CAD cohort (N=2285)	*P*-value
Mean age at index date (SD), years	66.82 (16.16)	66.82 (16.15)	1.000
Female, n (%)	286 (63)	1430 (63)	1.000
Medical history, n (%)			
Any TE	67 (14.7)	104 (4.6)	<0.001
Received blood transfusion	67 (14.7)	<11 (<1.0)	<0.001
CCI, n (%)			
0	174 (38.1)	1525 (66.7)	<0.001
1	89 (19.5)	281 (12.3)	
2	61 (13.3)	181 (7.9)	
≥3	133 (29.1)	298 (13.0)	

Exact matching was used to generate a sample of non-CAD patients that were matched to the patients with CAD on key characteristics (age, sex, race, geographic region, and index year).
CAD, cold agglutinin disease; CCI, charlson comorbidity index; n, number; SD, standard deviation; TE, thromboembolic event

***Mortality or TE risk in patients with CAD compared with matched non-CAD cohort* at various time periods**

- Mortality risk was particularly higher in patients with CAD compared with non-CAD cohorts during the first 100 days following CAD diagnosis (aHR [95% CI]: 16.36 [6.83–39.19]; *P*<0.001) versus at 10 years (aHR [95% CI]: 2.26 [1.84–2.77]; *P*<0.001) (**Table 2**).
- Mortality risk in CAD vs non-CAD cohorts demonstrated a decreasing trend from 100 days since diagnosis until 3-year follow-up and then stabilized at over two at 5- and 10 year follow-ups (*P*<0.001) (**Table 2**).
- Consistent with mortality risk, the risk of TEs in patients with CAD was significantly higher compared with the non-CAD cohort, particularly in the early periods after diagnosis (e.g., 100 days aHR [95% CI]: 4.92 [3.22–7.45]; *P*<0.001) than in the later periods (e.g., 10 years aHR [95% CI]: 2.08 [1.71–2.53]; *P*<0.001) (**Table 2**).

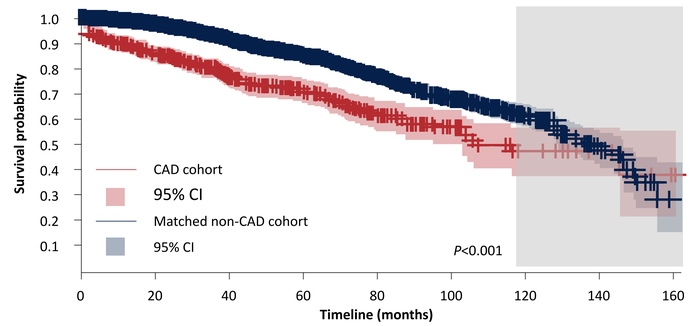
Table 2. aHR (CAD vs matched non-CAD cohorts) for time to first death/TE by pre-defined time periods

Time from CAD diagnosis		CAD cohort (N=457) Patients with event, n (%)	Non-CAD (N=2285) Patients with event, n (%)	aHR* [95% CI]	*P*-value
100 days	Death	26 (5.69)	7 (0.31)	16.36 [6.83–39.19]	<0.001
	TE	63 (13.79)	42 (1.84)	4.92 [3.22–7.45]	<0.001
1 year	Death	48 (10.50)	25 (1.09)	8.68 [5.18–14.54]	<0.001
	TE	97 (21.23)	124 (5.43)	2.97 [2.24–3.95]	<0.001
2 years	Death	67 (14.66)	66 (2.89)	4.99 [3.48–7.17]	<0.001
	TE	117 (25.60)	202 (8.84)	2.51 [1.97–3.20]	<0.001
3 years	Death	85 (18.60)	126 (5.51)	3.53 [2.64– 4.71]	<0.001
	TE	129 (28.23)	254 (11.12)	2.38 [1.90–2.98]	<0.001
5 years	Death	108 (23.63)	227 (9.93)	2.66 [2.10–3.38]	<0.001
	TE	143 (31.29)	331 (14.49)	2.23 [1.81–2.74]	<0.001
10 years	Death	136 (29.76)	362 (15.84)	2.26 [1.84–2.77]	<0.001
	TE	152 (33.26)	407 (17.81)	2.08 [1.71–2.53]	<0.001
Full follow-up	Death	137 (29.98)	386 (16.89)	2.16 [1.76–2.65]	<0.001
	TE	153 (33.48)	411 (17.99)	2.07 [1.70–2.51]	<0.001

*Multivariate cox regression adjusted on age, sex, smoking status, comorbidities, index season, and history of TEs
aHR, adjusted hazard ratio; CAD, cold agglutinin disease; CI, confidence interval; LDH, lactate dehydrogenase; TE, thromboembolic event.

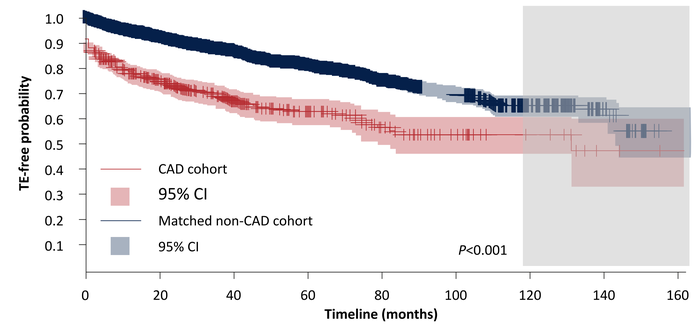
- Overall, survival probability and probability to remain TE-free were significantly lower in the CAD cohort than in the non-CAD cohort during full follow-up as shown by the KM survival chart (**Figure 1**) and KM TE-free probability chart (**Figure 2**).

Figure 1. Survival curve for patients with CAD compared with a matched cohort of patients without CAD



P-values were assessed using the log-rank test. Survival probability after 120 months is unreliable due to low patient numbers.
CAD, cold agglutinin disease; CI, confidence interval

Figure 2. Probability to remain TE-free curve for patients with CAD compared with a matched cohort of patients without CAD



P-values were assessed using the log-rank test. Survival probability after 120 months is unreliable due to low patient numbers.
CAD, cold agglutinin disease; CI, confidence interval; TE, thromboembolic event

Association between biomarkers and the risk of mortality and TEs in patients with CAD

- In the CAD cohort, patients with mild (aHR [95% CI]: 2.55 [1.40–4.65]; *P*=0.002), moderate (aHR [95% CI]: 7.00 [4.00–12.23]; *P*=0.001), or severe anemia (aHR [95% CI]: 16.70 [9.14–30.34]; *P*=0.001) had significantly higher risk of mortality than those without anemia (**Table 3**).
- Moderate (aHR [95% CI]: 2.16 [1.28–3.64]; *P*=0.004) and severe anemia (aHR [95% CI]: 3.37 [1.81–6.26]; *P*=0.001) were also correlated with higher risk of TEs compared with no anemia (**Table 3**).
- Severely elevated bilirubin (aHR [95% CI]: 3.03 [1.98–4.64]; *P*=0.001) and severely elevated LDH levels (aHR [95% CI]: 2.31 [1.29–4.13]; *P*=0.005) were associated with increased risk of mortality compared with normal levels (**Table 3**).

Table 3. Mortality and TEs by biomarker state in the CAD cohort

Biomarker state (compared with normal levels)	Mortality aHR* [95% CI]	Mortality *P*-value	TE aHR* [95% CI]	TE *P*-value
Mild anemia	2.55 [1.40–4.65]	0.002	1.40 [0.85–2.31]	0.193
Moderate anemia	7.00 [4.00–12.23]	0.001	2.16 [1.28–3.64]	0.004
Severe anemia	16.70 [9.14–30.34]	0.001	3.37 [1.81–6.26]	0.001
Moderately elevated bilirubin	0.98 [0.61–1.58]	0.938	1.45 [0.88–2.37]	0.145
Severely elevated bilirubin	3.03 [1.98–4.64]	0.001	1.15 [0.64–2.04]	0.645
Moderately elevated LDH	1.26 [0.81–1.96]	0.300	1.08 [0.64–1.81]	0.782
Severely elevated LDH	2.31 [1.29–4.13]	0.005	1.58 [0.76–3.28]	0.224

*Analyses were adjusted for age, sex, smoking, comorbidities, past TEs, and index season.
aHR, adjusted hazard ratio; CAD, cold agglutinin disease; CI, confidence interval; LDH, lactate dehydrogenase; TE, thromboembolic event

CONCLUSIONS

- **The clinical burden associated with CAD is significant and extends beyond anemia.**
- **Patients with CAD were twice as likely to die or experience TEs than those without CAD, these risks were particularly high in the early periods after diagnosis with mortality risk 16 times and TE risk 5 times higher in the first 100 days.**
- **Within the CAD cohort, abnormal markers of hemolysis (biluribin, LDH) were associated with increased mortality risk, while abnormal marker of anemia (Hb) was associated with increased mortality and TE risks.**
- **Early and chronic control of complement activation and the resulting hemolysis in CAD may therefore help manage the risk of mortality and TEs.**

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