Relationship between Hemoglobin Levels and EQ-5D-5L Utility Index in Patients with Cold Agglutinin Disease

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BACKGROUND

- Cold agglutinin disease (CAD) is a rare form of autoimmune hemolytic anemia.[1]
- CAD is characterized by the activation of the classical complement pathway, leading to hemolysis and symptoms such as severe anemia, fatigue, weakness, dizziness, and circulatory problems such as acrocyanosis and the Raynaud's phenomenon, significantly impacting the patient's quality of life (QoL).[1,2]
- EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L) is a standardized generic self-reported instrument used to calculate utility index scores, a measure of health status across five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[3]
- The relationship between hemoglobin (Hb) levels and health-related QoL, as assessed by the EQ-5D-5L utility index, remains poorly understood in patients with CAD.

OBJECTIVES

- To investigate the relationship between Hb levels and the EQ-5D-5L utility index scores (utility) in patients with CAD using data from the phase 3 trials of sutimlimab—CARDINAL and CADENZA.

METHODS

Study design

- This analysis utilized pooled data from the CARDINAL (NCT03347396) and CADENZA (NCT03347422) trials.
  - CARDINAL was an open-label, single-arm, phase 3 trial evaluating the efficacy and safety of sutimlimab in patients with CAD with a recent history of blood transfusion.[4]
  - CADENZA was a randomized, double-blind, placebo-controlled, phase 3 trial evaluating the efficacy and safety of sutimlimab in patients with CAD without a recent history of blood transfusion.[5]
- The Hb levels and EQ-5D-5L utility index scores were to be collected from baseline up to Week 171 (end of study).
  - Data were collected every 2 weeks from week 1 to week 26 (Part A) and then every 2 weeks for 2 years after week 25 (Part B, open-label extension phase).

Statistical analysis

- The utility index scores were derived from the EQ-5D-5L using US tariffs.[6]
- Six linear mixed-effect models were investigated using data from CARDINAL and CADENZA trials with baseline and post-baseline utility as dependent variable, and other selected covariates as fixed effects: utility = intercept + slope × Hb + covariates (including random intercept and/or random slope).
- Covariates such as study (CARDINAL/CADENZA), treatment, study parts (4 parts), and their interactions with treatment were also explored.
- The best-fitting model was determined by the lower Akaike Information Criterion and Bayesian Information Criterion.
- Marginal and conditional coefficient of determination (R^2) were estimated to characterize the variance explained by the model and specific effects.

RESULTS

- A total of 704 observations with baseline and post-baseline Hb levels and utility data from 66 patients were analyzed from CARDINAL (N = 24) and CADENZA (N = 42).
- The mean (SD) Hb (g/dL) level at baseline was 8.531 (1.617) in CARDINAL and 9.235 (1.033) in CADENZA, and post-baseline was 11.549 (2.097) in CARDINAL and 11.269 (1.863) in CADENZA.
- The mean (SD) EQ-5D-5L index score at baseline was 0.727 (0.249) in CARDINAL and 0.769 (0.221) in CADENZA, and post-baseline was 0.837 (0.186) in CARDINAL and 0.828 (0.219) in CADENZA.
- The baseline and demographic characteristics of patients have been provided in **Table 1**.

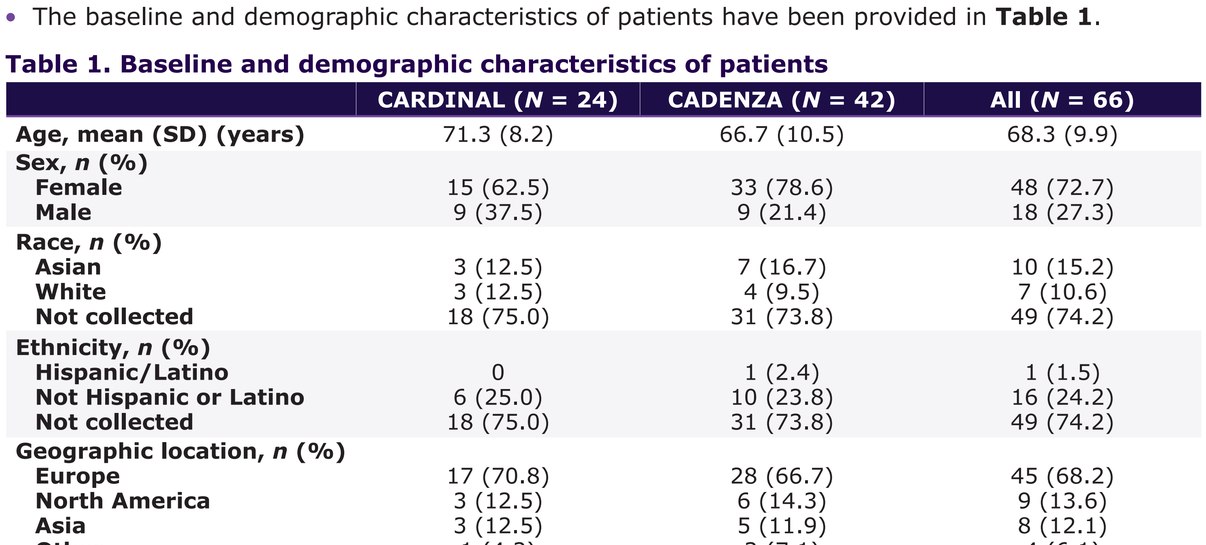
Table 1. Baseline and demographic characteristics of patients

	CARDINAL (N = 24)	CADENZA (N = 42)	All (N = 66)
Age, mean (SD) (years)	71.3 (8.2)	66.7 (10.5)	68.3 (9.9)
Sex, *n* (%)			
Female	15 (62.5)	33 (78.6)	48 (72.7)
Male	9 (37.5)	9 (21.4)	18 (27.3)
Race, *n* (%)			
Asian	3 (12.5)	7 (16.7)	10 (15.2)
White	3 (12.5)	4 (9.5)	7 (10.6)
Not collected	18 (75.0)	31 (73.8)	49 (74.2)
Ethnicity, *n* (%)			
Hispanic/Latino	0	1 (2.4)	1 (1.5)
Not Hispanic or Latino	6 (25.0)	10 (23.8)	16 (24.2)
Not collected	18 (75.0)	31 (73.8)	49 (74.2)
Geographic location, *n* (%)			
Europe	17 (70.8)	28 (66.7)	45 (68.2)
North America	3 (12.5)	6 (14.3)	9 (13.6)
Asia	3 (12.5)	5 (11.9)	8 (12.1)
Other	1 (4.2)	3 (7.1)	4 (6.1)
BMI, mean (SD) (kg/m²)	24.3 (4.2)	24.4 (3.3)	24.4 (3.6)

Note: Percentages were based on the number of patients in each treatment arm and the total of full analysis set. No patients were reported from the following groups: Black or African-American, American-Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and Others. Europe included Austria, France, Germany, Italy, the Netherlands, Norway, Spain, and the United Kingdom. North America included Canada and the United States. Asia included Japan. Others included Australia and Israel.
BMI, body mass index; SD, standard deviation.

- A ceiling effect was observed, with 175 (24.9%) observations having utility equal to the maximal value (i.e., 1.0) across the range of Hb levels. This indicated a substantial proportion of observations with "full health" at baseline or post-baseline, for which the level of QoL could not be differentiated across Hb levels. This might have added some noise in determining the relationship (**Figure 1**).

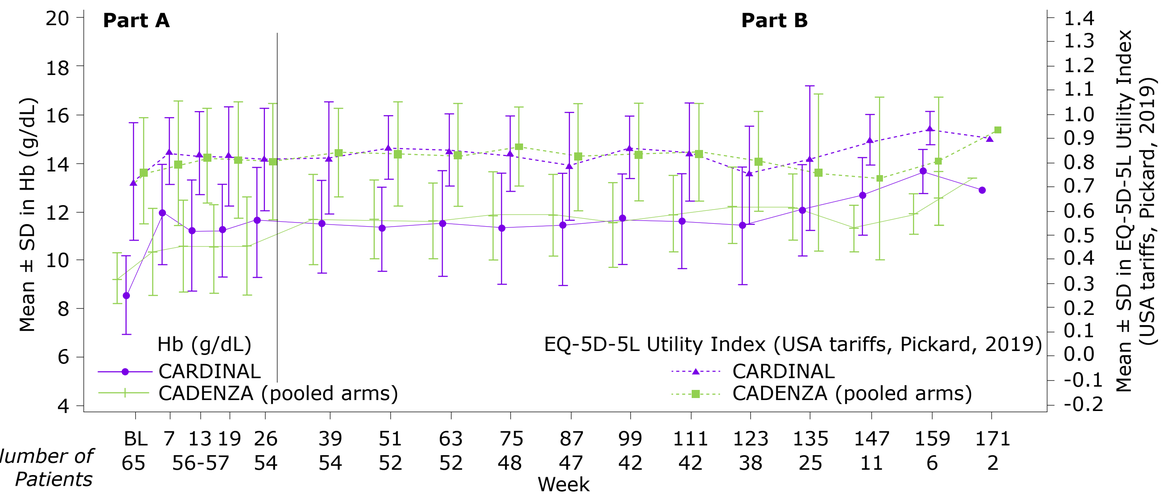
Figure 1. Relationship between Hb levels and EQ-5D-5L utility index scores



EQ-5D-5L, EuroQoL-5 Dimensions-5 Levels; Hb, hemoglobin; N, number of patients; USA, United States of America.

- Similar evolution (no delay) was observed between Hb levels and utility (**Figure 2**).

Figure 2. Hb levels and EQ-5D-5L utility index scores from baseline up to the end of the study (Week 171)



BL, Baseline; EQ-5D-5L, EuroQoL-5 Dimensions-5 Levels; Hb, hemoglobin; N, number of patients; SD, standard deviation; USA, United States of America.

- A significant, albeit weak, positive correlation was observed between Hb levels and utility (Spearman correlation: 0.25; p <0.0001).
- The relationship between Hb and EQ-5D-5L appeared consistent across different studies, study parts, and treatment groups:
  - According to scatterplots (data not shown), there was no need to assess the treatment arm alone, as it showed no effect.
  - In the investigated models, study, study part, study-by-treatment interaction, and study-part-by-treatment interaction were not significant (all p-values >0.05). The best-fitting model, based on Akaike Information Criterion (AIC)/Bayesian Information Criterion (BIC) criteria (**Table 2**), did not include these factors.
- The best-fitting model was the one with a random intercept and a random slope with no covariate adjustment (conditional R^2 of 0.756).
- The coefficient estimate for Hb was 0.0263 (standard error: 0.0056, p <0.0001; **Table 3**), indicating that a 2 g/dL increase in Hb levels corresponded to a 0.0526 (95% confidence interval: 0.0302–0.0750) increase in utility.

Table 2. List of linear mixed-effect models tested, using baseline and post-baseline Hb levels and EQ-5D-5L utility index scores

Model	Random-effects		Fixed-effects tested			Interactions** tested		AIC/BIC
	Intercept	Slope	Hb levels (g/dL)	Study	Study part*	Study-by-treatment arm	Study-part-by treat-ment-arm	
1	Y	-	Y	-	-	-	-	–779/ –774.6
2	Y	-	Y	Y	-	-	-	–774.8/ –770.4
3	Y	-	Y	-	-	Y	-	–771/ –766.6
4	Y	-	Y	-	Y	-	-	–761.4/ –757.1
5	Y	-	Y	-	-	-	Y	–752.5/ –748.1
6	Y	Y	Y	-	-	-	-	–819.1/ –810.3

*Study parts are CARDINAL PART A and PART B; and CADENZA PART A and PART B.
**Interactions: recoded variables.
AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; Y, Yes.

Table 3. Estimates of linear mixed-effect models for Hb levels and EQ-5D-5L utility index scores in the final model

Response variable	Parameter	Unit	Estimate (95% CI)	p-value
EQ-5D-5L Utility Index scores (*US tariffs, Pickard, 2019*)	Intercept	-	0.5187 (0.3809–0.6566)	<0.0001
	Hb (g/dL)	1 g/dL	0.0263 (0.0151–0.0375)	<0.0001

Number of observations = 704
CI, confidence interval; EQ-5D-5L, EuroQoL-5 Dimensions-5 Levels utility index; Hb, hemoglobin.

LIMITATIONS

- Some patients demonstrated good Hb levels along with a low utility. This could be due to factors such as recent blood transfusions or the limited ability of the EQ-5D-5L to capture fatigue, a significant symptom of CAD.[7]
- Incorporating Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale as a covariate in the model may enhance the analysis, as demonstrated by Meregaglia et al., who mapped FACIT-Fatigue onto utility.[8]
- All analyses were post hoc and unadjusted for multiple testing; therefore, a prospective validation is warranted to confirm these findings.
- A few patients received placebo for 26 weeks. A lingering effect of the treatment, known as sutimlimab effect, was observed, which might have impacted the outcomes.

CONCLUSIONS

- Our findings suggest a direct relationship between Hb levels and utility in patients with CAD.
- Higher Hb levels were associated with increased utility, suggesting a positive impact of improved Hb levels on the QoL in this patient population.
- Hb levels alone explained 5.8% of EQ-5D-5L variability (marginal R^2 of 0.0580) across all time points.
- Further research is needed to fully elucidate the complex relationship between Hb levels and QoL in patients with CAD to enhance patient care and disease management strategies.

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COI disclosure: EG, JM, KA, and **LP** are employees of Sanofi and may hold stocks and/or stock options in Sanofi. **RP** was an employee of Sanofi at the time this research was conducted.

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