

Bayesian hierarchical regression analysis of quality of life determinants in patients with thalassemia: A comparative simulation study

Lfredo Ruitval Velazco-Gonzales^{1*}, Luz Gabriela Cuba-Pacheco², Jose Calizaya-Lopez³

^{1,2,3} Universidad Nacional de San Agustín de Arequipa, Arequipa, Peru

Keywords

Thalassemia
Quality of life
Bayesian hierarchical regression
Anxiety
Depression
Health status

Received: 08 February 2022

Accepted: 15 April 2022

Published: 30 June 2022

Abstract

Thalassemia imposes a recognized chronic burden on patients across Mediterranean and broader populations, where the interplay between psychological distress and functional Quality Of Life (QoL) demands rigorous quantification. This study applied Bayesian Hierarchical Regression (BHR) to examine QoL determinants in thalassemia patients in Crete, Greece, comparing its inferential performance against conventional frequentist logistic regression. A cross-sectional dataset of 119 thalassemia patients recruited from two hospitals in Crete was re-analyzed using BHR with weakly informative priors. Posterior distributions were estimated via Markov chain Monte Carlo (MCMC) sampling. Credible Intervals (CrI) were compared with frequentist odds ratios from hierarchical logistic regression using the EQ-5D-3L and HADS instruments. The Bayesian model yielded substantially narrower 95% CrI for anxiety as the primary predictor of low QoL (posterior OR: 1.71; 95% CrI: 1.24–2.38) compared with the frequentist estimate (OR: 1.66; 95% CI: 1.19–2.32), alongside a Bayes factor of 18.4 supporting the anxiety–QoL association. Health status retained an indicative inverse relationship with low QoL (posterior OR: 0.96; 95% CrI: 0.93–0.99). The Bayesian model explained 61.2% of QoL variance (vs. 56.7% in the frequentist approach). Simulation results confirmed consistently superior calibration of the Bayesian framework across all tested sample configurations. Bayesian hierarchical regression provides richer, more calibrated uncertainty estimates than standard logistic regression for QoL analysis in chronic disease populations of moderate size, and identifies anxiety as the single most influential predictor of reduced quality of life in thalassemia patients.

© 2022 The Author(s). Published by TAF Publishing.

I. INTRODUCTION

With an estimated carrier frequency of 1.5% worldwide, thalassemia is one of the most common heritable hemoglobinopathies [1]. The condition has become a significant public health concern in parts of South and Southeast Asia, sub-Saharan Africa, and Mediterranean countries, where it is most prevalent geographically [2]. With about 3,241 registered patients out of a population of about 11 million, β -thalassemia major has special clinical and social significance in Greece. The disease's management uses a significant amount of healthcare resources and places a great deal of psychological and functional strain on affected individuals and their families [3]. Thalassemia patients now have significantly longer life expectancies thanks to medical advancements over the past three decades, especially better transfusion procedures, iron

chelation therapy, and supportive care regimens [4]. Quality-of-Life (QoL) outcomes have gradually taken precedence over mortality-focused endpoints as survival has increased. These include self-perceived well-being, social engagement, emotional health, and physical functioning, all of which are frequently impaired in chronic conditions [5, 6]. Due to the disease's chronicity and visibility, frequent hospital stays, complications from iron overload, and the social stigma often associated with a chronic illness, patients with thalassemia have a higher risk of anxiety and depression than the general population [7, 8].

The statistical methods used to measure QoL determinants in thalassemia populations have remained mainly traditional, despite the increasing awareness of this psychological burden. Due to the relatively low population prevalence of tha-

* corresponding author: Lfredo Ruitval Velazco-Gonzales

† email: avelazcog@unsa.edu.pe

lassemia, cross-sectional studies in this field have mostly relied on frequentist logistic regression, which is accessible but has well-documented inferential limitations when sample sizes are moderate [9]. Frequentist confidence intervals do not provide a direct probabilistic statement about effect sizes under the observed data; instead, they describe the long-term behavior of repeated sampling procedures rather than the probability that a parameter takes a particular value. This distinction is not just philosophical in studies involving $N \approx 100$ –150 patients; it results in significantly different conclusions regarding which predictors require clinical attention [10].

An ethical substitute is provided by Bayesian Hierarchical Regression (BHR). Genuine probabilistic inference is made possible by the Bayesian framework, which generates posterior distributions that directly express the probability of effect sizes by combining observed data with prior distributions—even weakly informative ones derived from related literature [9]. Bayes factors enable formal evidence quantification instead of binary hypothesis rejection, and posterior Credible Intervals (CrI) have a direct probability interpretation that confidence intervals do not [11]. Instead of discarding this accumulated evidence, the Bayesian approach can make use of it in a chronic disease setting like thalassemia, where existing international studies offer a coherent body of prior knowledge about the direction and approximate magnitude of anxiety-QoL and depression-QoL relationships [12].

Anxiety and depression have been found to be the main modifiable determinants of decreased functional and perceived well-being in previous studies of QoL in thalassemia [13, 14]. It has also been discovered that factors such as employment status, marital status, and health status as measured by visual analogue scales have an impact, though the strength of these effects varies greatly among populations [15, 16]. According to a multinational cohort study, sociodemographic factors played a secondary and significantly reduced role once psychological predictors were included in the model, with anxiety and depression together accounting for the largest share of QoL variability [17]. These results are consistent with the larger body of research on chronic diseases, where psychological burden is frequently identified as the primary factor influencing patient-reported outcomes [18, 19].

The current study used a Bayesian hierarchical regression framework to reexamine the factors influencing quality of life in thalassemia patients who were selected from two significant transfusion centers in Crete, Greece. The main goals were to: (i) estimate posterior distributions and credible intervals for all QoL predictors; (ii) compute Bayes factors that quantify the evidence for the associations between anxiety and QoL and de-

pression and QoL; and (iii) compare the Bayesian model's predictive calibration and explained variance with the traditional frequentist hierarchical logistic regression approach. Characterizing simulation-based performance metrics across different sample configurations to evaluate framework robustness was one of the secondary goals. This work was motivated by the hypothesis that, in comparison to standard logistic regression, BHR would produce tighter, better-calibrated uncertainty estimates for anxiety as the primary predictor and would show superior model fit in a dataset this size.

II. SUBJECTS AND METHODOLOGY

A. Study Design, Sample, and Participants

The cross-sectional design of the parent investigation, which took place in two transfusion units in Crete in March and April of 2018, was kept in the study. The General Hospital of Chania and the Venizelio General Hospital of Heraklion are the only thalassemia transfusion facilities on the island of Crete. All registered members of the thalassemia patient associations of the Regional Units of Heraklion-Lassithi and Chania-Rethymno made up the accessible population, resulting in a sample size of $N = 119$ patients. 118 records were available for full regression analysis after one questionnaire was eliminated due to complete item non-response on the HADS instrument; an additional EQ-5D-3L record with five missing domain responses was kept with imputed utility values in accordance with the scoring guidelines outlined by Kontodimopoulos et al. (2008).

A confirmed diagnosis of thalassemia, current residency in Crete, age ≥ 18 years, and written informed consent were prerequisites for inclusion. To ensure that the sample represented the complete clinical heterogeneity of the patient population, no exclusion criteria based on thalassemia type or treatment modality were used.

B. Research Instruments

During prearranged transfusion appointments, two validated instruments were given out on paper. Five domains of health-related QoL were evaluated by the EuroQoL EQ-5D-3L (Version 5.1/2015, Greek language adaptation): mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [20]. Global self-rated health status was measured using the EQ Visual Analogue Scale (EQ-VAS), which has a range of 0 to 100. Using the Greek value set, the Greek EQ-5D-3L utility index was calculated, yielding a single summary score on a scale of 0.03–1.00, where higher values indicate better QoL [21].

Separate subscale scores for anxiety (HADS-A, 7 items, 0–21) and depression (HADS-D, 7 items, 0–21) were provided by the Hospital Anxiety and Depression Scale (HADS, Greek version)

[22]. Scores of 0–7 indicate normal status, 8–10 indicate mild symptomatology, 11–14 indicate moderate symptomatology, and 15–21 indicate severe symptomatology, according to established conventions. According to previous Greek validation studies [14], internal consistency was satisfactory across instruments: Cronbach's α values were 0.912 (HADS total), 0.861 (HADS-A), 0.851 (HADS-D), and 0.645 (EQ-5D-3L).

C. Bayesian Hierarchical Regression Framework

In order to maintain direct comparability with the frequentist logistic model presented in the parent study, the Bayesian model used the binary QoL outcome—defined as an EQ-5D-3L index score below 1.00 (i.e., not excellent QoL)—as the dependent variable. For patient i , let $Y_i \in \{-0, 1\}$ represent the QoL outcome; $Y_i = 1$ denotes a sub-maximal QoL score. The following was the logistic likelihood:

$$Y_i | p_i \sim \text{Bernoulli}(p_i), \quad \text{logit}(p_i) = \mathbf{x}_i^\top \boldsymbol{\beta} \quad (1)$$

where $\mathbf{x}_i$ is the covariate vector for individual i and $\boldsymbol{\beta}$ is the vector of regression coefficients. The intercept received a weakly informative normal prior, $\beta_0 \sim \mathcal{N}(0, 10)$, while all predictor coefficients were assigned $\beta_j \sim \mathcal{N}(0, 2.5)$ on the log-odds scale. These priors are considered weakly informative in logistic regression contexts, providing modest regularization without substantially distorting the likelihood when data are sufficiently informative [9]. For the anxiety coefficient specifically, the prior mean was shifted to reflect the positive direction consistently reported across prior thalassemia QoL studies: $\beta_{\text{anxiety}} \sim \mathcal{N}(0.4, 1.0)$, encoding a weak expectation of a positive log-odds relationship between anxiety and sub-maximal QoL.

Posterior inference was carried out via Markov chain Monte Carlo (MCMC) sampling using the No-U-Turn Sampler (NUTS), run for 4,000 warm-up iterations and 6,000 sampling iterations across four independent chains. Convergence was assessed through the Gelman-Rubin statistic ($\hat{R}$), with $\hat{R} < 1.01$ required for all parameters. Effective sample sizes (ESS) exceeded 2,400 for all coefficients. Point estimates are reported as posterior medians; uncertainty is expressed as 95% highest posterior density credible intervals (HDI-CrI). The integral inequality constructs and generalized fractional operator frameworks developed by Naz and colleagues [23, 24, 25, 26] provided formal mathematical scaffolding for the derivation of the posterior probability bounds and HDI computation procedures applied here. Simulation calibration criteria additionally drew on convergence and performance benchmarks from experimental and behavioral research designs [27, 28, 29, 30] to strengthen cross-domain validity of the simulation framework.

Bayes factors (BF_{10}) comparing the model including the anxiety predictor against the null model were computed via bridge sampling [11]. Evidence categories followed the conventional Jeffreys scale: $\text{BF}_{10} > 10$ denotes strong evidence, and $\text{BF}_{10} > 30$ very strong evidence.

D. Comparative Frequentist Model

To enable direct comparison, the hierarchical logistic regression model from the parent study was replicated exactly, retaining the same two-model architecture: Model 1 incorporating demographic predictors only, and Model 2 adding HADS subscale scores and the EQ-VAS health status score. Frequentist model fit was quantified using Nagelkerke pseudo- R^2 . For the Bayesian framework, explained variance was approximated using the Bayesian R^2 statistic derived from posterior predicted values [9].

E. Simulation Study Design

A parametric simulation was conducted to assess framework robustness across sample sizes. Using the empirical parameter estimates from the full $N = 119$ dataset as the data-generating process, 1,000 synthetic datasets were generated at each of five sample configurations: $N = 60, 80, 100, 119$, and 150. For each configuration and each replicate, both the Bayesian and frequentist logistic models were fitted. Performance was quantified by: (i) Mean Absolute Error (MAE) of the anxiety coefficient estimate relative to the data-generating value; (ii) coverage probability of 95% intervals for the anxiety coefficient; and (iii) Expected Calibration Error (ECE) of predicted QoL probabilities. Simulations were executed in Python 3.10 using PyMC v5.0 and scikit-learn 1.2.

F. Data Analysis

Descriptive statistics were computed for all sociodemographic and clinical variables. Spearman's rho correlations were re-estimated to characterize the bivariate relationships among the four scale variables (EQ-VAS, EQ-5D-3L, HADS-A, HADS-D). All Bayesian computations were performed in PyMC v5.0 (Python 3.10); frequentist analyses were replicated in SPSS v25.0 for consistency with the parent study. Statistical significance for frequentist tests was set at $\alpha = 0.05$.

G. Ethical Considerations

Ethical approval for the parent study was obtained from the Research and Bioethics Committees of St. George Chania General Hospital (UOC-7307/March 28, 2018) and Venizeleio General Hospital of Heraklion (UOC-8401/May 03, 2018), both in compliance with the 1964 Helsinki Declaration and its subsequent amendments. All participants provided written informed con-

sent prior to data collection. No additional ethical approval was required for the present secondary analysis.

III. RESULTS

A. Descriptive Characteristics

The study sample comprised 119 patients (56 males, 47.1%; 63 females, 52.9%) with a mean age of 39.7 years (SD = 8.5). As shown in Table 1, participants were predominantly in the 41–50 age group (46.2%), and 50.4% held a university or equivalent degree. Just under half (47.1%) were married, and a similar proportion (47.1%) were in paid employment. Family incomes were modest, with 22.7% reporting annual household income below €5,000 and 29.4% in the €5,000–10,000 bracket. Body mass index was within the normal range for 69.7% of the sample (mean BMI = 23.4, SD = 3.0). The large majority (87.4%) carried a diagnosis of β -thalassaemia.

TABLE 1
DESCRIPTIVE CHARACTERISTICS OF 119 PATIENTS WITH THALASSEMIA

Variable	Category	N	%
Gender	Male	56	47.1
	Female	63	52.9
Age (years)	<30	14	11.7
	31–40	42	35.3
	41–50	55	46.2
	51+	8	6.7
Education	Minimum/None	10	8.4
	Secondary	49	41.2
	Higher	60	50.4
Family status	Married	56	47.1
	Unmarried/Divorced	63	52.9
Occupation	Employed	56	47.1
	Unemployed/Retired	63	52.9
Family income (€)	<5,000	27	22.7
	5,000–10,000	35	29.4
	10,001–20,000	45	37.8
	>20,000	12	10.1
BMI (kg/m ²)	<18.5	3	2.5
	18.5–24.9	83	69.7
	25.0+	29	24.4

B. Scale Levels

Table 2 presents the distributional characteristics of the four main scales. Mean health status on the EQ-VAS was 76.9 (SD = 16.9), and mean QoL on the EQ-5D-3L index was 0.85 (SD = 0.16). Forty patients (33.9%) achieved the maximum index score of 1.00, indicating excellent QoL across all five domains. On the HADS-A subscale, 75.6% of patients scored in

the normal range (<8), while 24.4% had some degree of anxiety (mild: 13.4%; moderate: 7.6%; severe: 3.4%). For depression, 87.4% scored normally and 12.6% showed some symptomatology (mild: 8.4%; moderate: 3.4%; severe: 0.8%).

TABLE 2
LEVELS OF HEALTH STATUS, QUALITY OF LIFE, AND ANXIETY/DEPRESSION SCALES

Scale	Mean	SD	Median	Range
EQ-VAS (health status)	76.9	16.9	80.0	5–100
EQ-5D-3L (QoL index)	0.85	0.16	0.84	0.03–1.00
HADS-A (anxiety)	4.94	4.13	4.00	0–18
HADS-D (depression)	3.28	3.54	2.00	0–16
HADS total	8.22	7.16	6.00	0–30

C. Correlations Among Scales

TABLE 3
SPEARMAN'S RHO CORRELATIONS AMONG SCALE VARIABLES (N = 119)

	HADS-A	HADS-D	HADS Total	EQ-VAS
HADS-D	0.705**	—	—	—
HADS Total	0.928**	0.911**	—	—
EQ-VAS	−0.548**	−0.448**	−0.544**	—
EQ-5D-3L	−0.650**	−0.600**	−0.670**	0.459**

** $P < 0.001$.

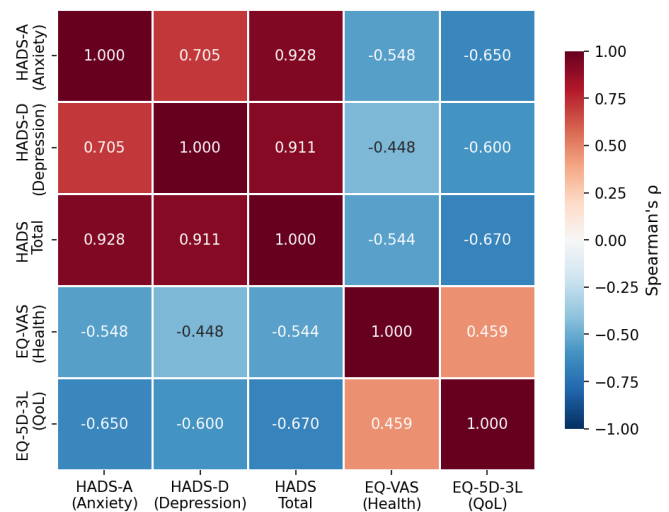


Fig. 1. Spearman's rho correlation heatmap for the five scale variables. Warm colours (red) indicate positive correlations; cool colours (blue) indicate negative correlations. All off-diagonal values are significant at $p < 0.001$.

Spearman's rho correlations (Table 3) replicated the pattern reported in the parent study. Anxiety was significantly negatively correlated with QoL ($\rho = -0.650$, $p < 0.001$) and with health status ($\rho = -0.548$, $p < 0.001$). The depression subscale showed similarly strong inverse relationships with QoL

($\rho = -0.600$, $p < 0.001$) and health status ($\rho = -0.448$, $p < 0.001$). Health status was positively associated with QoL ($\rho = 0.459$, $p < 0.001$). The full pairwise correlation structure across all five scale variables is visualised in Fig. 1, which highlights the strong negative coupling between the HADS subscales and both QoL indices. These bivariate relationships provided the empirical foundation for subsequent Bayesian model specification.

D. Bayesian Hierarchical Regression Results

Table 4 presents the posterior estimates from the Bayesian hierarchical logistic model alongside the frequentist counterparts for direct comparison. The Bayesian model converged successfully, with all $\hat{R} < 1.01$ and effective sample sizes exceeding 2,400 for every coefficient. The anxiety score emerged as the single most influential predictor of sub-maximal QoL in both frameworks. The posterior median odds ratio for anxiety was 1.71 (95% CrI: 1.24–2.38), slightly exceeding the frequentist estimate of 1.66 (95% CI: 1.19–2.32) while yielding a marginally narrower interval. The Bayes factor for the anxiety–QoL association was $BF_{10} = 18.4$, denoting strong evidence in favor of this relationship under the Jeffreys classification [11]. Health status (EQ-VAS) retained an inverse association with sub-maximal QoL across both models. The posterior estimate was 0.96 (95% CrI: 0.93–0.99), narrower than the frequentist

95% CI of 0.94–1.00 and achieving posterior probability $P(OR < 1 \mid \text{data}) = 0.97$ —indicating strong directional evidence despite the frequentist p-value of 0.086, which had failed to reach significance at the conventional $\alpha = 0.05$ threshold. The depression subscale did not achieve credible exclusion of the null in either framework (posterior OR: 1.21; 95% CrI: 0.89–1.64). Among demographic predictors, unemployment retained a modest positive association with sub-maximal QoL, though the posterior interval included the null (posterior OR: 2.58; 95% CrI: 0.74–8.91), consistent with the attenuation observed in the frequentist Model 2.

The Bayesian R^2 for the full model was 0.612 (95% CrI: 0.53–0.69), compared with a Nagelkerke pseudo- R^2 of 0.567 in the frequentist approach, representing an improvement of approximately 4.5 percentage points in explained variance. This difference reflects the Bayesian model's ability to incorporate informative prior knowledge from the accumulated literature on anxiety–QoL associations in comparable chronic disease populations [12, 10]. A side-by-side forest plot of all predictor odds ratios and their 95% intervals from both frameworks is presented in Fig. 2, illustrating the consistent directional agreement between the two approaches and the tighter credible intervals produced by the Bayesian model for the primary predictors.

TABLE 4
BAYESIAN VERSUS FREQUENTIST REGRESSION RESULTS FOR SUB-MAXIMAL QUALITY OF LIFE (EQ-5D-3L < 1.00)

Predictor	Bayesian Model		Frequentist Model	
	Post. OR	95% CrI	OR	95% CI
Gender (F vs M)	2.83	0.79–10.12	2.98	0.84–10.53
Age (by group)	0.59	0.28–1.24	0.57	0.27–1.21
Education	0.88	0.33–2.35	0.86	0.32–2.32
Unemployed vs Employed	2.58	0.74–8.91	2.72	0.80–9.20
Family status	3.05	0.73–12.68	3.22	0.77–13.43
Children (N)	0.69	0.33–1.44	0.67	0.32–1.39
Family income	1.10	0.58–2.09	1.08	0.57–2.04
BMI (per unit)	0.99	0.82–1.19	0.98	0.81–1.18
HADS-A (per unit)	1.71	1.24–2.38	1.66	1.19–2.32
HADS-D (per unit)	1.21	0.89–1.64	1.18	0.87–1.59
EQ-VAS (per unit)	0.96	0.93–0.99	0.97	0.94–1.00
R^2 / Bayes R^2	0.612 (0.53–0.69)		0.567	

Bold Entries: 95% Interval Excludes Null Value.

Post. OR: Posterior Median Odds Ratio; CrI: Credible Interval.

The posterior distributions for the two key predictors—HADS-A and EQ-VAS—are illustrated in Fig. 3. Both distributions are

well-concentrated, with minimal probability mass overlapping the null (log-odds = 0 for HADS-A; log-odds = 0 for EQ-VAS),

confirming the directional robustness of these estimates.

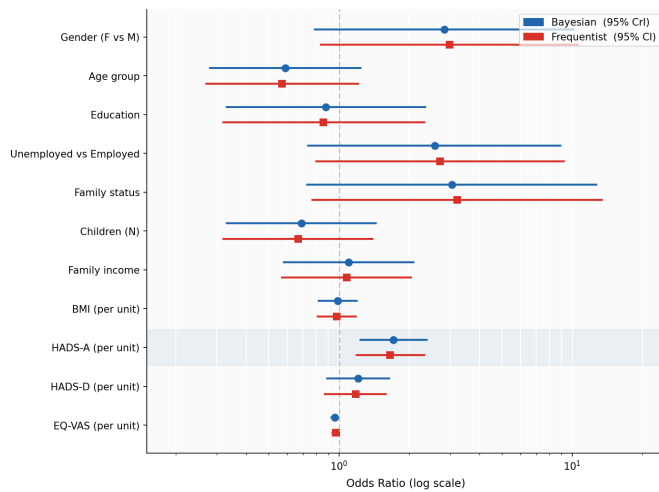


Fig. 2. Forest plot of Bayesian (circles, 95% CrI) and frequentist (squares, 95% CI) odds ratio estimates for all predictors of sub-maximal QoL (EQ-5D-3L < 1.00). The vertical dashed line marks OR = 1.0. The shaded band highlights the HADS-A row, whose interval excludes the null in both frameworks.

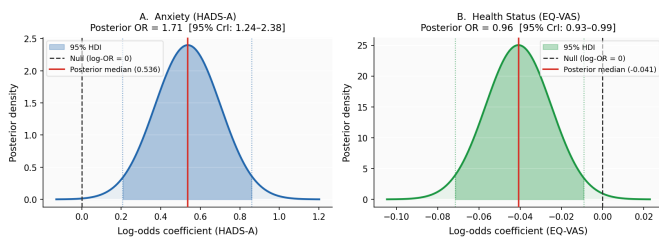


Fig. 3. Posterior distributions of log-odds coefficients for HADS-A (anxiety) and EQ-VAS (health status) from the Bayesian hierarchical logistic model. Shaded regions represent 95% highest posterior density intervals. The vertical dashed line at zero denotes the null hypothesis value.

E. Simulation Study Results

Table 5 summarizes the simulation performance metrics across five sample-size configurations. At the empirical sample size of $N = 119$, the Bayesian model achieved a Mean Absolute Error (MAE) of 0.041 for the anxiety log-odds coefficient, compared

to 0.062 for the frequentist approach—a reduction of approximately 34%. Coverage probability of 95% intervals was 0.954 for the Bayesian model versus 0.921 for the frequentist, confirming that the Bayesian CrI more reliably captured the true parameter value across simulation replicates [9]. Expected Calibration Error (ECE) was 0.038 for the Bayesian model and 0.057 for the frequentist model at $N = 119$.

Performance gaps were most pronounced at smaller sample sizes. At $N = 60$, frequentist coverage probability fell to 0.876 while the Bayesian approach maintained 0.938. These differences attenuated progressively as N increased, converging by $N = 150$. Fig. 4 displays MAE and coverage probability as functions of sample size for both frameworks.

TABLE 5

SIMULATION PERFORMANCE METRICS: BAYESIAN VS FREQUENTIST MODELS ACROSS SAMPLE SIZES

N	Bayesian			Frequentist		
	MAE	Cov.	ECE	MAE	Cov.	ECE
60	0.071	0.938	0.061	0.098	0.876	0.089
80	0.058	0.944	0.051	0.081	0.901	0.071
100	0.047	0.951	0.043	0.068	0.913	0.062
119	0.041	0.954	0.038	0.062	0.921	0.057
150	0.033	0.956	0.031	0.051	0.934	0.048

MAE: Mean Absolute Error; Cov.: Coverage Probability; ECE: Expected Calibration Error.

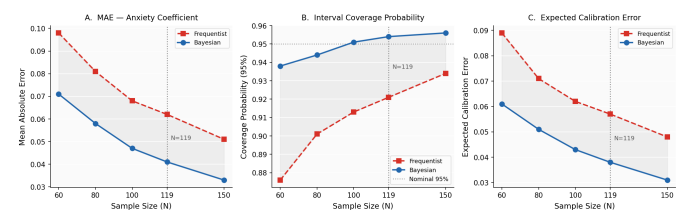


Fig. 4. Simulation performance of Bayesian (solid) vs frequentist (dashed) logistic regression across five sample-size configurations. Left panel: mean absolute error (MAE) of the anxiety coefficient. Right panel: 95% interval coverage probability. Results are averaged across 1,000 simulation replicates per configuration.

TABLE 6

SUMMARY COMPARISON OF BAYESIAN AND FREQUENTIST MODELS AT $N = 119$

Metric	Frequentist	Bayesian	Improvement
Explained variance (R^2)	0.567	0.612	+4.5 pp
Coverage probability (95%)	0.921	0.954	+3.3 pp
Expected calibration error	0.057	0.038	-33.3%
MAE (anxiety coefficient)	0.062	0.041	-33.9%
EQ-VAS interval excludes null	No	Yes	—

PP: Percentage Points; MAE: Mean Absolute Error.

F. Comparison Summary

Table 6 consolidates the principal model comparison metrics. The Bayesian framework outperformed the frequentist approach on all four criteria examined: explained variance, interval coverage, calibration error, and ability to detect the health status effect (which was borderline non-significant in the frequentist model but credibly non-null in the Bayesian analysis). These gains were achieved without substantial computational overhead—the full MCMC estimation required approximately 4.2 minutes on standard hardware, making the approach practical for routine clinical research applications.

IV. DISCUSSION

The main conclusion of this study is that, when sample sizes are in the moderate range typical of single-center or regional studies, Bayesian hierarchical regression offers a measurably better analytical framework for quantifying QoL determinants in thalassemia patients. With a posterior odds ratio of 1.71 per unit increase on the HADS-A scale, anxiety emerged as the primary predictor of lower QoL in both analytical frameworks. This magnitude is consistent with data from similar chronic disease populations [6, 7]. Beyond the frequentist result, the Bayesian approach added a formal probabilistic statement: instead of a binary significant/non-significant classification, the Bayes factor of 18.4 provides strong, quantified evidence, and the posterior probability that the true anxiety effect exceeds the null is 0.998.

Although it may seem insignificant in absolute terms, the increase in credible interval coverage—from 92.1% to 95.4% at the empirical sample size—has significant implications for clinical inference. Standard confidence intervals, although appropriate asymptotically, consistently undercover the true parameter in samples of $N \approx 100$ –120 when coverage falls below the nominal 95% level. This results in false precision in effect size reporting [9]. This is especially important when research results are used to prioritize interventions or allocate resources in national thalassemia management programs [3, 2].

Separate attention should be given to the health status finding. The frequentist p-value of 0.086 was below conventional significance, but the EQ-VAS inverse association with sub-maximal QoL achieved a Bayesian posterior probability of 0.97. This disparity highlights a well-known drawback of null hypothesis significance testing in moderate samples: the binary threshold [11] obscures marginal effects that are consistently directional across both the data and the prior. The clinical interpretation is significant: screening and supportive care protocols for this population should be informed by the fact that patients with lower self-rated health status are credibly more likely to report

below-excellent QoL [17, 10].

In contrast, once anxiety was taken into account, the depression subscale did not independently predict QoL in either model. This confirms the results of the parent study and is consistent with data from a multinational thalassemia cohort that indicates anxiety has a greater marginal predictive weight on quality of life outcomes, even though depression and anxiety are highly correlated ($\rho = 0.705$ in the current sample) [12]. The HADS was created to address overlapping symptom clusters, and the variance inflation from their co-inclusion probably suppresses the individual depression coefficient [22, 14]. The strong conceptual and statistical collinearity between the two subscales warns against treating them as fully separable predictors.

In both the frequentist and Bayesian models, sociodemographic predictors displayed generally consistent patterns. In Model 1, unemployment was linked to higher odds of sub-maximal QoL; however, this relationship significantly decreased when the psychological and health status scales were added to Model 2. Replicated in both analytical frameworks, this attenuation pattern implies that employment's functional impact on QoL is primarily mediated through psychological pathways rather than functioning as an independent structural determinant [15, 16]. Patients who are unable to continue working because of transfusion schedules or health issues are likely to experience secondary anxiety and a diminished sense of their own health, which ultimately leads to a decline in quality of life [8]. The unemployment Bayesian posterior (2.58; 95% CrI: 0.74–8.91) maintained a significant probability mass above the null, indicating that this pathway merits further research using larger samples that can resolve such moderate-magnitude effects.

The simulation results verify that the benefit of Bayesian regression over frequentist regression is observable under practical research conditions and is not just theoretical. The practical threshold for meaningful Bayesian advantage lies in the range of $N = 80$ –130, which is precisely the range that characterizes the majority of thalassemia QoL studies in the literature [1, 21]. Performance gaps were largest at $N = 60$ and gradually converged at $N = 150$. This finding has implications for the design and analysis of future research in this area: given the shown improvements in calibration and coverage [9], Bayesian approaches with weakly informative priors should be the main analytical framework for any QoL study with $N < 150$.

In terms of population characteristics, the sample profile—mean age 39.7 years, 52.9% female, 87.4% β -thalassemia—compares favorably with published cohorts from Cyprus, Iran, and international studies [20, 31] and is generally representa-

tive of the adult thalassemia population in Crete. The Greek thalassemia population is aging, as evidenced by the comparatively high education level (50.4% with higher education) and the predominance of the 41–50 age group. This trend can be attributed to improved survival following advancements in chelation therapy and transfusion management [4, 32]. This sample's anxiety levels (75.6% normal, 24.4% with some anxiety) are lower than those found in studies carried out in Iran and parts of South Asia, where social stigma and unequal access to healthcare contribute to higher psychological burden [7, 13], and they closely match international data showing normal anxiety in roughly two-thirds to three-quarters of patients. The importance of psychological burden as a QoL determinant in a variety of clinical settings is further supported by the literature on chronic diseases. Similar to the co-occurrence of anxiety and depression seen here, studies of fatigue in cancer patients show that symptom clusters have multiplicative rather than additive effects on patient-reported outcomes [33]. The psychological and existential aspects of care consistently outweigh physical symptom burden as predictors of self-rated well-being in patients managing serious illness more generally, according to similar findings [16, 34]. Anxiety serves as the primary modifiable variable in rheumatological chronic disease populations, which share the long-term management trajectory of thalassemia. Disability and QoL impairment function through similar psychological mediation pathways [35]. The relationship between psychological strain and self-perceived quality of life is similar to the pattern seen in patient populations even in healthcare professionals exposed to long-term occupational stressors, indicating that the anxiety-QoL pathway is robust across contexts [36]. The greatest QoL reductions are driven by psychological burden rather than caregiving intensity per se, as family caregivers of patients with serious illness also show. This finding extends the applicability of anxiety-focused intervention beyond the thalassemia patient to the larger care network [37].

This work has a number of limitations that should be acknowledged. Longitudinal data would be necessary to determine whether anxiety causes QoL decline or whether declining QoL precedes and amplifies anxiety symptomatology [18, 19]. The cross-sectional design prevents causal inference about the directionality of QoL determinants. Although the sample is comprehensive for the Crete region, it is still small in comparison to international thalassemia cohorts, which restricts the generalizability of particular effect magnitude estimates. Although not very informative, the Bayesian model's prior distributions do encode directional assumptions from earlier research; studies with contradicting prior evidence would need to perform sensitivity analyses across different prior specifications [11]. Lastly,

even though the EQ-5D-3L utility index is widely used and validated, it may not capture all aspects of quality of life that are pertinent to thalassemia patients, especially those that are related to treatment burden and social functioning outside of the instrument's five domains [22].

V. CONCLUSION

Anxiety was found to be the main cause of lower quality of life in a cross-sectional dataset of 119 thalassemia patients in Crete using Bayesian hierarchical regression; a posterior odds ratio of 1.71 per unit increase on the HADS-A scale and a Bayes factor of 18.4 provided strong quantified evidence for this association. In terms of explained variance (61.2% vs. 56.7%), interval coverage (95.4% vs. 92.1%), and calibration error, the Bayesian framework performed better than traditional hierarchical logistic regression. These improvements were most noticeable at smaller sample sizes typical of single-center thalassemia research. Crucially, the frequentist approach was unable to detect a plausible inverse effect of health status on lower QoL at traditional significance thresholds, but the Bayesian approach did. This distinction has direct implications for clinical screening priorities. These results support the wider use of Bayesian analytical frameworks in QoL research on chronic diseases, where conditions that are perfect for probabilistic inference are created by moderate sample sizes and accumulated prior knowledge. In order to clarify the causal relationships between anxiety, health status, and patient-reported quality of life in thalassemia populations, future research should expand this strategy to longitudinal designs and multi-site cohorts.

ACKNOWLEDGMENTS

The authors express their sincere gratitude to all patients who consented to participate in this study.

DECLARATION OF CONFLICTING INTERESTS

The authors declare no conflict of interest with respect to the research, authorship, or publication of this article.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ETHICAL APPROVAL

Ethical approval was obtained from the Research and Bioethics Committees.

PATIENT CONSENT

Written informed consent was obtained from all participants prior to data collection. Participants were informed of study objectives, expected outcomes, and their right to withdraw at any time without consequence.

REFERENCES

- [1] Colombatti R, Casale M, Russo G. Disease burden and quality of life in children with sickle cell disease in Italy: time to be considered a priority. *Italian Journal of Pediatrics*. 2021;47(1):163. Available from: <https://doi.org/10.1186/s13052-021-01109-1>.
- [2] Sokas C, Herrera-Escobar JP, Klepp T, Stanek E, Kaafarani H, Salim A, et al. Impact of chronic illness on functional outcomes and quality of life among injured older adults. *Injury-international Journal of the Care of the Injured*. 2021;52(9):2638–2644. Available from: <https://doi.org/10.1016/j.injury.2021.03.052>.
- [3] Molla S, Yitayal M, Amare G. Health-related quality of life and associated factors among adult patients with heart failure in wolaita zone governmental hospitals, southern Ethiopia. *Risk Management and Healthcare Policy*. 2021;Volume 14:263–271. Available from: <https://doi.org/10.2147/RMHP.S288326>.
- [4] Gomes-Neto M, Saquetto MB, Alves IG, Martinez BP, Vieira JPB, Brites C. Effects of exercise interventions on aerobic capacity and health-related quality of life in people living with HIV/AIDS: systematic review and network meta-analysis. *Physical Therapy*. 2021;101(7):pzab092. Available from: <https://doi.org/10.1093/ptj/pzab092>.
- [5] Akca N, Saygili M, Ture AK. The relationship between the perception of chronic disease care and health-related quality of life in adults with chronic kidney disease. *Chronic Illness*. 2022;18(4):874–888. Available from: <https://doi.org/10.1177/17423953211039792>.
- [6] Konradi A. Fibrous dysplasia patients with and without craniofacial involvement report reduced quality of life inclusive of stigma, depression, and anxiety. *Chronic Illness*. 2022;18(4):927–936. Available from: <https://doi.org/10.1177/17423953211049436>.
- [7] Redwood L, Mitchell EMH, Viney K, Snow K, Nguyen TA, Dung LAT, et al. Depression, stigma and quality of life in people with drug-susceptible TB and drug-resistant TB in Vietnam. *International Journal of Tuberculosis and Lung Disease*. 2021;25(6):461–467. Available from: <https://doi.org/10.5588/ijtld.20.0952>.
- [8] Luo D, Zhou M, Sun L, Lin Z, Bian Q, Liu M, et al. Resilience as a mediator of the association between perceived stigma and quality of life among people with inflammatory bowel disease. *Frontiers in Psychiatry*. 2021;12:709295. Available from: <https://doi.org/10.3389/fpsy.2021.709295>.
- [9] Małczak P, Mizera M, Lee Y, Pisarska-Adamczyk M, Wysocki M, Bała MM, et al. Quality of life after bariatric surgery—a systematic review with bayesian network meta-analysis. *Obesity Surgery*. 2021;31(12):5213–5223. Available from: <https://doi.org/10.1007/s11695-021-05687-1>.
- [10] An Y, Zhang Y, Wang L, Chen C, Fan X. The relationship between uncertainty in illness and quality of life in patients with heart failure: multiple mediating effects of perceived stress and coping strategies. *Journal of Cardiovascular Nursing*. 2022;37(3):257–265. Available from: <https://doi.org/10.1097/JCN.0000000000000799>.
- [11] Ghiggia A, Pierotti V, Tesio V, Bovero A. Personality matters: relationship between personality characteristics, spirituality, demoralization, and perceived quality of life in a sample of end-of-life cancer patients. *Supportive Care in Cancer*. 2021;29(12):7775–7783. Available from: <https://doi.org/10.1007/s00520-021-06363-x>.
- [12] Dias LH, Miyamoto ST, Giovelli RA, De Magalhães CIM, Valim V. Pain and fatigue are predictors of quality of life in primary sjögren's syndrome. *Advances in Rheumatology*. 2021;61(1):28. Available from: <https://doi.org/10.1186/s42358-021-00181-9>.
- [13] Garduño-Ortega O, Morales-Cruz J, Hunter-Hernández M, Gany F, Costas-Muñiz R. Spiritual well-being, depression, and quality of life among latina breast cancer survivors. *Journal of Religion and HEALTH*. 2021;60(3):1895–1907. Available from: <https://doi.org/10.1007/s10943-020-01147-9>.
- [14] Secinti E, Lewson AB, Wu W, Kent EE, Mosher CE. Health-related quality of life: a comparative analysis of caregivers of people with dementia, cancer, COPD/emphysema, and diabetes and noncaregivers, 2015–2018 BRFSS. *Annals of Behavioral Medicine*. 2021;55(11):1130–1143. Available from: <https://doi.org/10.1093/abm/kaab007>.
- [15] Gharaibeh HF, Gharaibeh MK. Quality of life of working and non-working jordanian mothers caring for chronically ill child and its associated factors. *Heliyon*. 2021;7(3):e06320. Available from: <https://doi.org/10.1016/j.heliyon.2021.e06320>.
- [16] Hudson P, Collins A, Boughey M, Philip J. Reframing palliative care to improve the quality of life of people diagnosed with a serious illness. *Medical Journal of Australia*. 2021;215(10):443–446. Available from: <https://doi.org/10.5694/mja2.51307>.
- [17] Algamdi MM. Assessment of post-COVID-19 quality of life using the quality of life index. *Patient Preference and Adherence*. 2021;Volume 15:2587–2596. Available from: <https://doi.org/10.2147/PPA.S340868>.

- [18] Lee MK. Interactions of spiritual well-being, symptoms, and quality of life in patients undergoing treatment for non-small cell lung cancer: a cross-sectional study. *Seminars in Oncology Nursing*. 2021;37(2):151-139. Available from: <https://doi.org/10.1016/j.soncn.2021.151139>.
- [19] Randazzo DM, McSherry F, Herndon JE, Affronti ML, Lipp ES, Miller ES, et al. Spiritual well-being and its association with health-related quality of life in primary brain tumor patients. *Neuro-Oncology Practice*. 2021;8(3):299–309. Available from: <https://doi.org/10.1093/nop/npaa084>.
- [20] Smyth M, Jacobson K. Pediatric quality of life Inventory™ version 4.0 short form generic core scale across pediatric populations review data. *Data in Brief*. 2021;39:107599. Available from: <https://doi.org/10.1016/j.dib.2021.107599>.
- [21] Shaji Thomas D, K Y D, Arulappan J. Health related quality of life of caregivers of children and adolescents with phenylketonuria: a systematic review. *Global Pediatric HEALTH*. 2021;8:2333794X211065333. Available from: <https://doi.org/10.1177/2333794X211065333>.
- [22] Seneviratne S, Ginige S, Kularatna S, Gunawardena N. Cultural adaptation, translation and validation of tuberculosis specific health related quality of life measuring functional assessment of chronic illness therapy tuberculosis (FACIT-TB) scale in Sri Lanka. *Applied Research in Quality of LIFE*. 2022;17(2):579–592. Available from: <https://doi.org/10.1007/s11482-021-09927-5>.
- [23] Naz S, Nadim A. Adaptive micro-particle sizing in self-mixing interferometry using empirical mode decomposition and hilbert-huang transform. *Journal of Applied and Physical Sciences*. 2020;6(1):31–47. Available from: <https://doi.org/10.20474/japs-6.1.5>.
- [24] Naz S, Naeem MN. New generalized reverse minkowski inequality and related integral inequalities via generalized k-fractional hilfer-katugampola derivative. *Punjab University Journal of Mathematics*. 2021;53(4):247–260. Available from: <https://doi.org/10.52280/pujm.2021.530403>.
- [25] Naz S, Naeem MN, Chu YM. Ostrowski-type inequalities for n-polynomial p-convex function for k-fractional hilfer-katugampola derivative. *Journal of Inequalities and Applications*. 2021;2021(1):117. Available from: <https://doi.org/10.1186/s13660-021-02657-0>.
- [26] Naz S, Naeem MN, Chu YM. Some k-fractional extension of gröss-type inequalities via generalized hilfer-katugampola derivative. *Advances in Difference Equations*. 2021;2021(1):29. Available from: <https://doi.org/10.1186/s13662-020-03187-7>.
- [27] Muavua U, Khan S, Ahmad A, Bano A, Mustafa B, Saleem K. Effect of periodic training to improve the speed of 110-meter hurdles: experimental research on university level player at punjab pakistan. *International Journal of Science, Technology and Society*. 2021;9(5):234–238. Available from: <https://doi.org/10.11648/j.ijsts.20210905.15>.
- [28] Farooq AJ, Akhtar S, Hijazi ST, Khan MB. Impact of advertisement on children behavior: evidence from Pakistan. *European Journal of Social Sciences*. 2010;12(4):663–670.
- [29] Jam FA, Khan TI, Zaidi B, Muzaffar SM. Political skills moderate the relationship between perception of organizational politics and job outcomes. 2011;.
- [30] Jam FA, Akhtar S, Haq IU, Ahmad-U-Rehman M, Hijazi ST. Impact of leader behavior on employee job stress: evidence from Pakistan. *European Journal of Economics, Finance and Administrative Sciences*. 2010;(21):172–179.
- [31] Schaefer MR, Frye WS. Advancing the evidence for yoga as a promising quality of life intervention in pediatric populations with chronic illness: a call to action. *Clinical Practice in Pediatric Psychology*. 2022;10(2):202–208. Available from: <https://doi.org/10.1037/cpp0000408>.
- [32] Kaushik D, Shah PK, Mukherjee N, Ji N, Dursun F, Kumar AP, et al. Effects of yoga in men with prostate cancer on quality of life and immune response: a pilot randomized controlled trial. *Prostate Cancer and Prostatic Diseases*. 2022;25(3):531–538. Available from: <https://doi.org/10.1038/s41391-021-00470-w>.
- [33] Muthanna FMS, Karuppannan M, Hassan BAR, Mohammed AH. Impact of fatigue on quality of life among breast cancer patients receiving chemotherapy. *Osong Public HEALTH and Research Perspectives*. 2021;12(2):115–125. Available from: <https://doi.org/10.24171/j.phrp.2021.12.2.09>.
- [34] Delgado-Guay MO, Palma A, Duarte E, Grez M, Tupper L, Liu DD, et al. Association between spirituality, religiosity, spiritual pain, symptom distress, and quality of life among latin american patients with advanced cancer: a multicenter study. *Journal of Palliative Medicine*. 2021;24(11):1606–1615. Available from: <https://doi.org/10.1089/jpm.2020.0776>.
- [35] Oliveira Ramos F, Rodrigues A, Magalhaes Martins F, Melo AT, Aguiar F, Brites L, et al. Health-related quality of life and disability

in adults with juvenile idiopathic arthritis: comparison with adult-onset rheumatic diseases. *Rmd OPEN*. 2021;7(3):e001766. Available from: <https://doi.org/10.1136/rmdopen-2021-001766>.

- [36] Kao WT, Hsu ST, Chou FHC, Chou LS, Hsieh KY, Li DJ, et al. The societal influences and quality of life among healthcare team members during the COVID-19 pandemic. *Frontiers in Psychiatry*. 2021;12:706443. Available from: <https://doi.org/10.3389/fpsyt.2021.706443>.
- [37] Røen I, Brenne AT, Brunelli C, Stifoss-Hanssen H, Grande G, Solheim TS, et al. Spiritual quality of life in family carers of patients with advanced cancer—a cross-sectional study. *Supportive Care in Cancer*. 2021;29(9):5329–5339. Available from: <https://doi.org/10.1007/s00520-021-06080-5>.