Inflammatory Biomarkers in Relation to Conventional JADAS27: An Exploratory Cross-Sectional Analysis of Juvenile Idiopathic Arthritis

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Abstract. A cross-sectional pediatric dataset was used to examine whether routinely available inflammatory measures accompany variation in conventional JADAS27 among patients with juvenile idiopathic arthritis (JIA). Relations were assessed for C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and haptoglobin (HPTG). Of 269 observations, 266 provided complete information for the multivariable analysis. Poor distributional and residual behavior on the original outcome scale led to modeling of log(JADAS27 + 1). HPTG was selected at the first step and produced $R^2 = 0.2659$; admission of ESR raised R^2 by 0.0363 to 0.3022. Since normalized ESR is one element used to calculate conventional JADAS27, the ESR coefficient partly reflects predictor-outcome overlap and cannot establish stand-alone predictive value. HPTG contributed more to the fitted model, although this dataset cannot determine whether it marks general acute-phase activity or a separate process. The analysis is intended for hypothesis generation. Resampling and prospective replication in an independent cohort are needed before the equation is considered for clinical use.

Keywords: juvenile idiopathic arthritis, disease activity score, acute-phase markers, haptoglobin, ESR

1 Introduction

Juvenile idiopathic arthritis (JIA) comprises inflammatory joint disorders that start before 16 years of age, continue for at least six weeks, and lack a more appropriate alternative diagnosis [1]. Persistent activity can restrict movement, interfere with growth, damage joints, and occur alongside uveitis. Since activity may change during follow-up, current management emphasizes repeated assessment against explicit treatment targets instead of relying only on an overall clinical impression [1-3].

Four inputs make up JADAS27: an active-joint count based on 27 joints, the clinician global rating, the child or parent global rating, and a normalized ESR value. Clinical JADAS removes the laboratory input, while activity cutoffs and alternative JADAS formats have been evaluated in prior work [4-6]. Only the conventional score was available for this analysis. Thus, a regression containing measured ESR on the right-hand

© The Author(s) 2026
L. L. Kuan et al. (eds.), *Proceedings of the 2026 3rd International Symposium on Agricultural Engineering and Biology (ISAEB 2026)*, Advances in Biological Sciences Research 56,
https://doi.org/10.2991/978-94-6239-847-4_15

side and conventional JADAS27 on the left-hand side reuses related information. The ESR slope is best understood as a feature of the score definition, not as demonstration of an independent laboratory predictor.

ESR and CRP are commonly used indicators of inflammatory activity, although infection, anemia, treatment exposure, and sampling conditions may alter their values independently of JIA [1,2]. Haptoglobin (HPTG) is another liver-derived acute-phase protein and is therefore a plausible candidate marker of inflammatory burden [7]. The present dataset, however, contains no pathway-level measurements. The study objective was limited to estimating the statistical relationships between JADAS27 and the available laboratory variables; questions of causation and mediation could not be addressed.

2 Materials and Methods

2.1 Dataset and Measures

The analysis used 269 pediatric records obtained for a secondary cross-sectional evaluation. Each record included laboratory measurements and conventional JADAS27. Missing CRP in three records reduced the complete multivariable sample to 266. Unusual biomarker observations were retained unless influence diagnostics indicated otherwise; all Cook's D values remained under 1. The dependent measure was conventional JADAS27, which combines normalized ESR with active-joint count and the two global assessments. Recorded gender, age, CalcAlpha2, HPTG, CRP, and ESR comprised the candidate set. The source file did not contain separate JADAS27 components or several relevant clinical variables. It was therefore impossible to derive a clinical JADAS27 score that excluded ESR.

2.2 Analytical Strategy

All variables were first summarized for distributional shape and missingness. Pearson coefficients were used to describe unadjusted linear relationships with JADAS27. Regression on the original outcome showed positive skew, non-normal errors, and increasing residual spread. The analysis therefore used the natural-log transformation log(JADAS27 + 1). Model checking included residual-versus-predicted plots, a normal quantile plot, leverage, studentized residuals, and Cook's distance. Because ESR is part of conventional JADAS27, estimates involving ESR were designated as descriptive results affected by score overlap rather than independent biomarker effects.

Candidate variables were screened with a forward stepwise procedure and an entry threshold of $p < 0.05$. Since selecting and estimating a model in the same dataset can make coefficients and fit appear more favorable than they would be in new data, the resulting equation was treated as sample-specific and exploratory. Potential effect modification by recorded gender was examined separately through ESR-by-gender and HPTG-by-gender terms. Confounding was screened by comparing each biomarker coefficient before and after gender adjustment; a relative change close to 10% was

considered potentially meaningful. SAS was used for all analyses, and all tests were two-sided.

3 Results

3.1 Sample Characteristics and Bivariate Results

The outcome was asymmetric: JADAS27 averaged 9.47, had a median of 7.20, and extended from 0.30 to 56.50. Broad or skewed values were also evident for the three acute-phase measures. Pearson analysis gave r = 0.471 for HPTG and r = 0.474 for ESR. The corresponding values were 0.332 for CalcAlpha2 and 0.398 for CRP. For age, the coefficient was -0.018 and the test result was p = 0.6603 (Table 1).

Table 1. Laboratory distributions, age, outcome values, and their bivariate correlations.

Measure	r	Median [minimum, maximum]	Mean ± SD	n
HPTG	0.471*	119.00 [0.44, 799.10]	142.80 ± 106.78	269
ESR	0.474*	14.00 [1.00, 157.00]	22.28 ± 24.59	269
CalcAlpha2	0.332*	0.87 [0.44, 2.05]	0.89 ± 0.21	269
CRP	0.398*	0.07 [0.00, 11.39]	0.46 ± 1.24	266
Age (years)	-0.018	8.82 [1.34, 19.40]	8.69 ± 4.63	269
JADAS27	—	7.20 [0.30, 56.50]	9.47 ± 8.30	269

**For ESR, CRP, HPTG, and CalcAlpha2, $p < 0.0001$. For age, $p = 0.6603$. Three CRP values were missing.*

3.2 Transformation and Predictor Selection

The untransformed fit showed larger residual dispersion at higher fitted values together with clear deviation in the normal-quantile display. Applying log(JADAS27 + 1) produced more acceptable residual symmetry and spread. None of the 266 observations had Cook's D of 1 or greater. At the first selection step, HPTG generated $R^2 = 0.2659$. Adding ESR supplied another 0.0363, so the reduced model reached $R^2 = 0.3022$. Age, CRP, and CalcAlpha2 remained outside the model at the prespecified entry level. Because ESR participates in the outcome formula, its apparent addition should not be treated as fully independent predictive content. The diagnostic evaluation of the fitted regression model is presented in Figure 1.

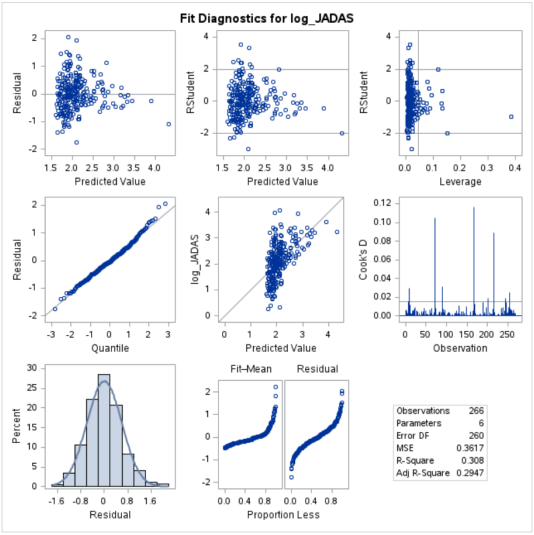


Fig. 1. Diagnostics for the model with log-transformed JADAS27. The panels summarize residual patterns, quantile behavior, leverage, observed-versus-fitted agreement, Cook's distance, and the residual distribution.

3.3 Regression Estimates and Gender Checks

The interaction tests yielded p = 0.1197 for ESR with gender and p = 0.1787 for HPTG with gender. After gender was introduced, the relative slope change was 0.013 for ESR and 0.014 for HPTG. These shifts were substantially smaller than the 0.10 screening benchmark; the final reduced specification therefore excluded gender.

Written with the HPTG term first, the selected equation was log(JADAS27 + 1) = 0.00215(HPTG) + 0.00769(ESR) + 1.61592 (Table 2). A difference of 100 HPTG units multiplies expected JADAS27 + 1 by exp(0.215), which is about 1.24. A 10-unit ESR difference gives exp(0.0769), approximately 1.08. Entering HPTG = 150 and ESR = 30 produces a JADAS27 estimate of 7.75. The figures apply only to this sample, and the ESR contribution remains inseparable from its role in constructing the outcome.

Table 2. Parameter estimates for the reduced log-scale regression.

Parameter	Meaning on JADAS27 + 1 scale	Approximate 95% interval	β (SE)
HPTG	100 units correspond to about 24%	0.00116 to 0.00314	0.00215 (0.00050)
ESR	10 units correspond to about 8%	0.00340 to 0.01198	0.00769 (0.00219)
Intercept	Reference on the transformed scale	1.49524 to 1.73660	1.61592 (0.06156)

Apparent R^2 was 0.3022 for 266 complete observations. Interval limits equal each coefficient plus or minus 1.96 standard errors.

4 Discussion

Under the prespecified selection rule, the reduced specification included two markers. HPTG supplied the larger share of in-sample explanation, and the subsequent ESR step added a smaller amount. Neither gender nor CRP met the criterion for retention. Because variable choice and coefficient estimation used the same observations, these statistics characterize the analyzed dataset and do not quantify accuracy for future patients.

The ESR result has an unavoidable structural limitation. Conventional JADAS27 is calculated partly from normalized ESR, whereas the regression used raw ESR as an explanatory variable. The analysis therefore relates a measurement to an outcome containing a transformed version of that same measurement. At least part of the 3.63% increase in R^2 and the ESR slope is a consequence of score construction. The HPTG association is not affected by that exact overlap, but it remains descriptive. Haptoglobin is recognized as an acute-phase protein [7], yet no mechanistic variables were measured here. The data cannot distinguish a general inflammatory signal from a separate biological role in JIA.

This equation is not ready to support treatment decisions. With an R^2 of 0.3022, most variation in the transformed outcome remained outside the model. Unavailable information on joint findings, pain, patient-reported impact, JIA category, current therapy, imaging activity, and measurement variability could account for part of the remainder. Disease activity in JIA is multidimensional, so a two-marker equation should be viewed as a starting point for further study rather than a clinical prediction rule.

4.1 Study Constraints and Next Steps

Several features limit the conclusions. A cross-sectional snapshot cannot determine temporal order and cannot support causal or mediational claims. The analysis lacked key clinical covariates, used complete records, and selected predictors in the same sample in which their coefficients were estimated. No bootstrap assessment, cross-validation, or independent cohort evaluation was available. In addition, ESR overlapped with the conventional JADAS27 outcome, and absent component-level data prevented construction of a clinical score without ESR. Future research should use an outcome independent of the biomarker being evaluated, quantify model optimism through resampling or penalized methods, and test reproducibility and temporal prediction in an external longitudinal cohort.

5 Conclusion

The exploratory analysis selected HPTG together with ESR and achieved an apparent R^2 of 0.3022 after transforming the outcome as log(JADAS27 + 1). ESR offers no independent interpretation in this setting because conventional JADAS27 already contains normalized ESR. HPTG could be functioning as an indicator of general acute-phase response, but a distinct mechanism cannot be tested with the available variables.

Further use requires an outcome free of candidate-marker overlap, internal assessment of optimism, and prospective confirmation.

Conflict of Interest

The author reports no competing interests.

Data Availability

Individual-level records cannot be shared under the data custodian's restrictions; aggregate results are provided in this manuscript.

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