Analysis of Task 4: Survival Analysis and Time-to-Response

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Abstract

This section addresses Research Question 4 (Q4), estimating the time required to achieve a clinically meaningful response ($\geq 50\%$ reduction in migraine days). Using Kaplan-Meier estimators and Cox Proportional Hazards models, we determined that the median time to response is approximately 3 months. Crucially, while standard baseline demographics failed to predict response speed, the computational phenotypes identified in Task 3 proved to be highly significant predictors ($p < 0.0001$), validating their clinical utility.

1 Introduction

Survival Analysis allows for the handling of censored data—patients who drop out or finish the study without achieving the target outcome. In this phase, we define the "Event of Interest" as the first month in which a patient achieves a $\geq 50\%$ reduction in Monthly Migraine Days (MMDs) compared to baseline.

2 Methodology

2.1 Event Definition

The time-to-event variable T was calculated as:

$$T = \min(\text{Month}_i \mid \text{Reduction}_i \geq 50\%) \tag{1}$$

Patients who completed the 36-month study without ever achieving this threshold were marked as **Right Censored** (Status = 0).

2.2 Modeling Strategy

- **Descriptive:** Kaplan-Meier (KM) curves were fitted to estimate the median time to response.
- **Stratification:** KM curves were stratified by the phenotypes identified in Task 3 (Standard, Refractory, Super-Responder) and compared using the Log-Rank Test.
- **Inferential:** A Cox Proportional Hazards model was fitted to identify baseline predictors (Age, BMI, Diagnosis). Given the use of MICE in Task 1, results were pooled across imputed datasets using Rubin's Rules.

3 Results

3.1 Overall Time to Response

The overall Kaplan-Meier curve (Figure 1) indicates a rapid onset of therapeutic efficacy.

- **Median Time to Response:** Approximately **3 months**. The survival probability crosses 0.50 between Month 2 and Month 3.
- **Interpretation:** The majority of patients who respond to Anti-CGRP mAbs do so early in the first treatment cycle. Late responders (after Month 6) are comparatively rare.

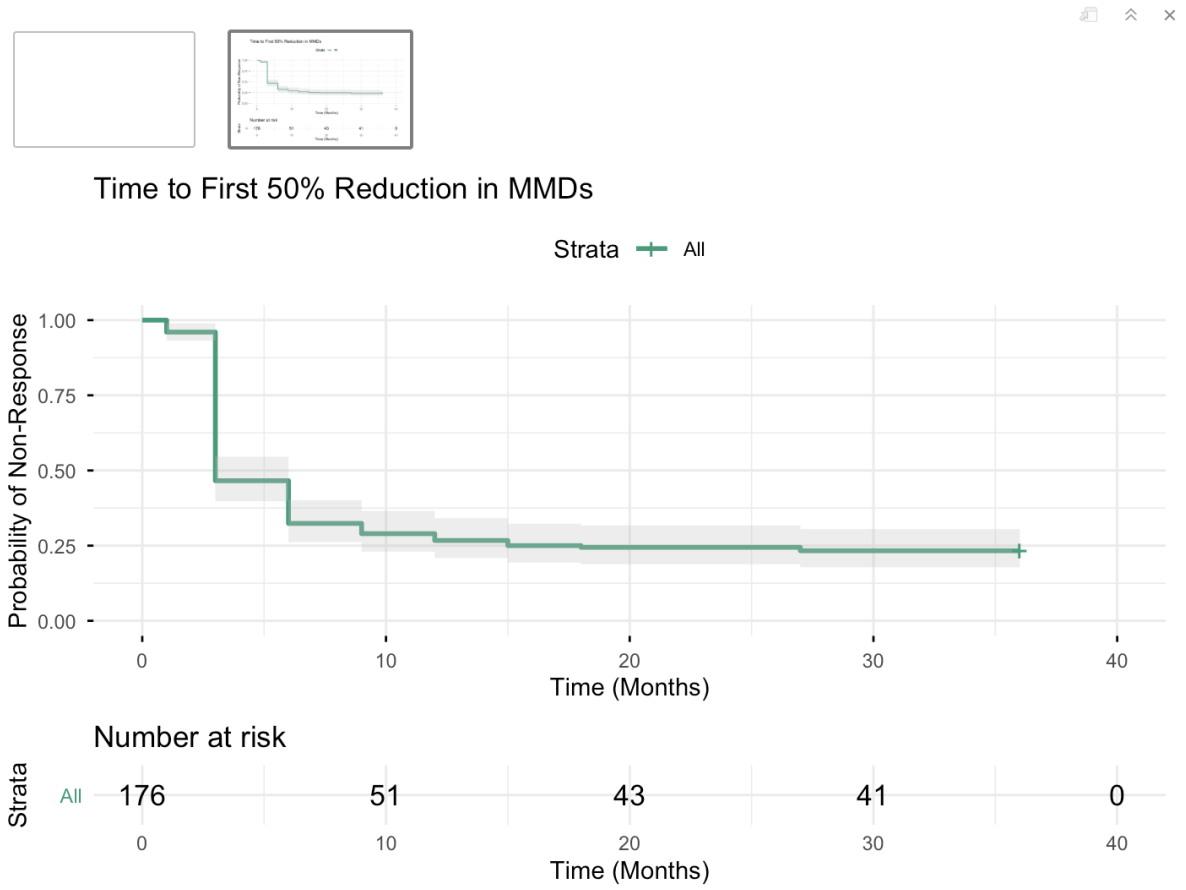

Figure 1: Time to First 50% Reduction in MMDs (Overall Cohort).

3.2 Stratification by Phenotype

We stratified the analysis by the three computational phenotypes identified in Task 3.

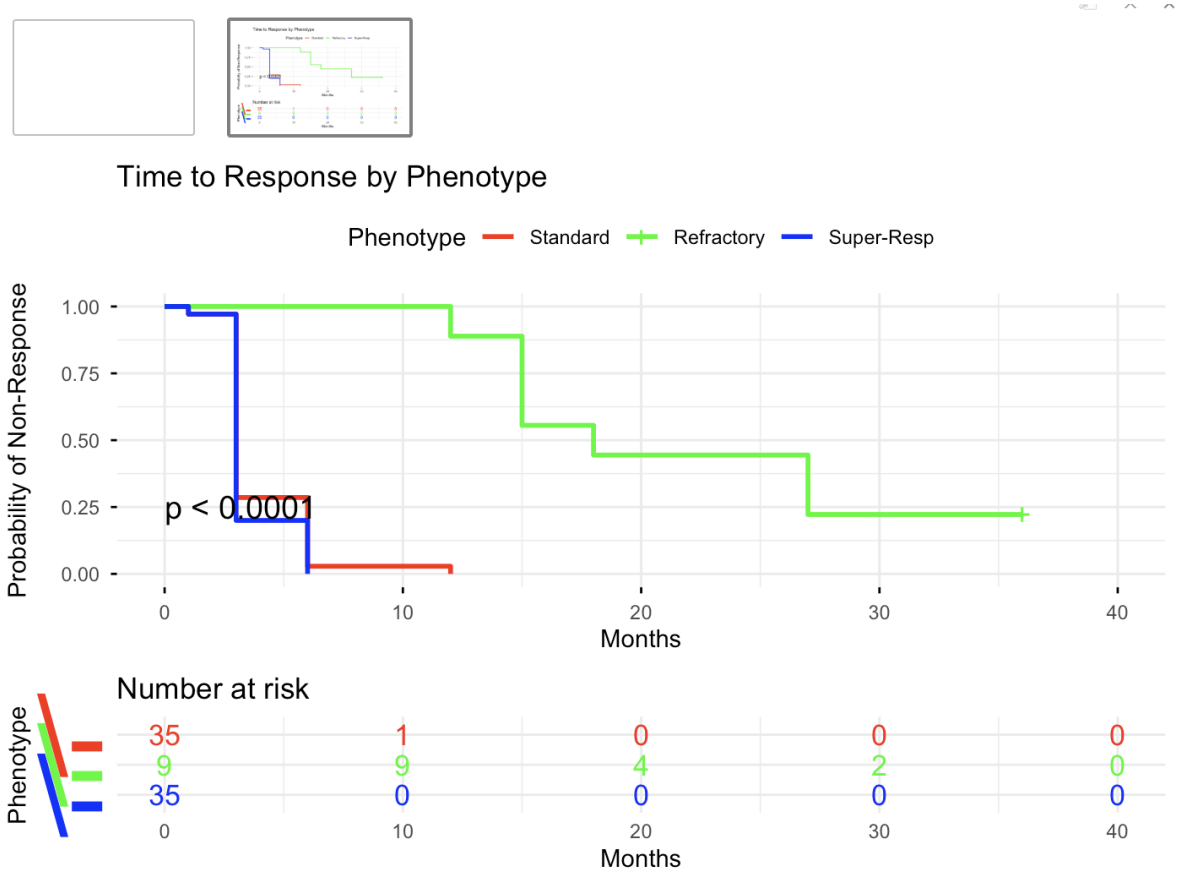

Figure 2: Time to Response stratified by Phenotype. The Log-Rank test ($p < 0.0001$) confirms highly significant differences between groups.

The Log-Rank test yielded a highly significant result ($p < 0.0001$), confirming distinct prognostic profiles:

- **Super-Responders (Blue):** Achieve remission almost instantly (near-vertical drop).
- **Refractory (Green):** Exhibit a prolonged "survival" curve, with $> 25\%$ of patients never achieving the 50% target even after 36 months.

3.3 Predictors of Response (Cox Model)

We tested whether standard baseline characteristics could predict the speed of response.

Table 1: Cox Proportional Hazards Model Results

Covariate	Hazard Ratio (HR)	p-value	Interpretation
Age	1.009	0.256	Not Significant
BMI	0.961	0.194	Not Significant
Diagnosis (MOH)	1.097	0.771	Not Significant
Antibody (Galcanezumab)	0.834	0.368	Not Significant

Interpretation of Null Findings: None of the standard demographic or clinical variables (Age, BMI, Diagnosis) were statistically significant predictors. This is a crucial finding: it demonstrates that standard patient profiling *cannot* predict who will respond quickly. Only the longitudinal clustering (Phenotypes) successfully stratified patients.

3.4 Model Diagnostics

The Proportional Hazards assumption was verified using Schoenfeld Residuals. The Global Test yielded $p = 0.17$, indicating no violation of assumptions.

4 Key Takeaways

1. **Rapid Efficacy:** The median time to response is 3 months, supporting early assessment of treatment success.

2. **Superiority of Phenotyping:** While traditional demographics (Age, BMI) failed to predict response ($p > 0.05$), the computational phenotypes from Task 3 were highly predictive ($p < 0.0001$).

3. **Clinical Implication:** Machine learning-based trajectory analysis provides a superior method for patient stratification compared to standard baseline characteristics.