ARTICLE

Modelling time to β-hCG remission in gestational trophoblastic disease: Comparative evaluation of Cox and parametric survival approaches

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ABSTRACT

Background: Traditional time-to-event analysis is usually compromised in the context of rare diseases like gestational trophoblastic disease (GTD), due to inherent constraints posed by limited sample sizes and non-constant hazards.

Objective: The study compared various survival models in estimating time to beta-human chorionic gonadotropin (β-hCG) remission among GTD patients and identifying consistent clinical predictors of β-hCG remission.

Methods: A retrospective cohort study of 258 post-molar evacuation patients was conducted using information from a Philippine specialty group database. Time-to-remission served as the primary outcome, with hazard ratio estimates derived across Cox proportional hazards, Firth's penalized Cox, Negative Exponential, Weibull, and Gompertz models. Model fit and diagnostics were also compared. Sensitivity analyses excluded the upper 5 to 10% of follow-up durations, while stratified Cox models used evacuation mode and histologic type as strata.

Results: Gravidity was a consistent predictor of shorter remission time while complete mole histology and high baseline β-hCG levels were associated with delayed remission. The Gompertz model produced clinically relevant GTD remission probabilities, yet the traditional Cox model yielded the highest C-index and robustness under sensitivity analyses.

Conclusion: Advanced survival methods can yield stable insights in small GTD datasets. The findings identified consistent key predictors of remission which can be accounted for in risk stratification. Parametric models like Gompertz may augment current management through individualized risk estimates with corresponding actions. The findings support the complementary value of looking at alternative modeling strategies and suggest the role of disease registries in improving validation and translation of such statistical models.

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Email Address: arsy3@outlook.up.edu.ph
Date received: 25 August 2025
Dates revised: 27 October 2025, 11 November 2025
Date accepted: 18 December 2025
DOI: https://doi.org/10.54645/202518SupQEM-88

KEYWORDS

gestational trophoblastic disease, proportional hazards models, calibration, rare diseases, patient-centered care

INTRODUCTION

Gestational trophoblastic disease (GTD) refers to a spectrum of gynecologic disorders arising from trophoblastic tissue, including hydatidiform moles (Capito et al. 2020). Although globally rare, GTD remains relatively common in Asia, with the Philippines reporting 13 to 14 cases per 1,000 pregnancies (Cagayan 2014). Majority of cases resolve following molar evacuation, but a subset of patients experience delayed remission or malignant progression to gestational trophoblastic neoplasia (GTN) (Ngan et al. 2021).

Serial measurements of β-hCG after evacuation serve as both diagnostic and prognostic biomarkers in GTD (Horowitz et al. 2021). β-hCG levels are expected to decline over time, and three consecutive values below the accepted threshold of 5 mIU/mL suggests remission (PSSTD 2011). In contrast, persistently high or rising hormone levels may signal complications such as GTN, persistent disease or chemoresistance. These cases require timely recognition and more intensive management (Tidy and Seckl 2021). Prompt identification of at-risk patients for delayed remission or progression is particularly important in low-resource settings where treatment delays can worsen outcomes (Soriano-Estrella 2023).

Most prognostic studies relied on logistic regression or semi-parametric Cox proportional hazards (PH) models to estimate GTN risk or time to β-hCG normalization (Brown et al. 2017; Sy and Cagayan 2023). These approaches rely on maximum likelihood estimation (MLE) to estimate hazard ratios (HR), and assume large sample asymptotics.In rare diseases like GTD, small cohorts and sparse event patterns violate these assumptions, leading to unstable coefficients, wide or even infinite interval estimares, and separation issues. Such constraints motivate the use of alternative models that better handle small samples or non-constant hazards.

Firth's correction, which applies a penalized likelihood (Heinze and Schemper 2001), offers one solution by reducing small-sample bias and producing more stable estimates (Puhr et al. 2017). Fully parametric survival models provide another option by specifying the baseline hazard. The Negative Exponential model assumes a constant hazard, whereas the Weibull model accommodates monotonic increases or decreases using its shape parameter, providing more flexibility. Similarly, the Gompertz model incorporates an exponentially varying hazard to represent remission dynamics in GTD. An example is the early steep hazard decline in the early phase followed by gradual stabilization (Hamdeni and Gasmi 2020). This pattern aligns with the observed trajectory of β-hCG regression and early patient response to molar evacuation (Schoeberl 2007).More complex hazard structures, like Royston-Parmar splines also exist, but also often require larger samples to obtain precise estimates (Ng et al. 2018).

This study compared five survival modeling approaches, specifically Cox PH, Firth's penalized Cox, Negative Exponential, Weibull, and Gompertz models, to identify consistent predictors of time-to-β-hCG remission among post-evacuation GTD patients. The analytic plan highlights the complementary value of alternative survival modeling strategies in informing equitable, data-driven care, and future GTD registry development in resource-limited settings.

MATERIALS AND METHODS

Study Design and Dataset

This retrospective cohort study utilized a single-center patient database from the Philippine Society for the Study of Trophoblastic Diseases, Inc. (PSSTD), specifically information from a tertiary hospital in Metro Manila between 2000 and 2010. Despite its timeframe, the dataset contained comprehensive longitudinal GTD data in the country. Given the rarity and consistent clinical management protocols for the disease over the past two decades, the cohort continues to yield valid insights into remission dynamics.

This dataset includes information from patients diagnosed with GTD who underwent uterine evacuation followed by serial β-hCG monitoring. This cohort, drawn from the earlier phase of registry accumulation, comprises a clinically heterogeneous group of patients with diverse histologic diagnoses, including complete (CHM) and partial (PHM) hydatidiform moles. Only patients fitting the eligibility criteria with complete baseline information were included.

While formal sample size and power calculations for time-to-event models were performed, these generally assume large event counts. Such computations, based on standard parameters like HR = 2.0, 10% censoring, a 25% attrition buffer, and considering ten events per predictor, indicate that approximately 500 patients would be required to achieve sufficient statistical power for a Cox PH model (Martens and Logan 2021). However, given the rarity of GTD, all eligible cases (n = 258) from the registry were included.

Definition of Variables

The study analyzed routinely collected clinical and demographic variables in GTD management. Maternal age was categorized according to established prognostic thresholds while reproductive history was summarized by gravidity and parity. Disease- and treatment-related variables included histologic type, mode of molar evacuation, receipt of chemoprophylaxis, and follow-up duration.

The primary outcome was time to spontaneous remission, defined as the interval from the date of uterine evacuation to the first of three consecutive normal β-hCG values (<5 mIU/mL). The date of evacuation served as the time origin for all analyses. Time-to-event data were recorded in days from molar evacuation and analyzed across all survival models. Patients who achieved remission were coded as events; those without remission or with GTN at last follow-up were right-censored, and those who developed GTN were censored at the time of diagnosis and classified as non-remission.

Baseline β-hCG levels were stratified according to International Federation of Gynecology and Obstetrics (FIGO) categories (Ngan et al. 2021). This maintained interpretability and avoided collinearity with longitudinal hormone trends evaluated in separate studies.

Statistical Analysis

Five survival models were compared using identical covariates: maternal age, gravidity, mode of evacuation, histologic subtype (complete (CHM) versus partial (PHM) mole), chemoprophylaxis administration, and baseline β-hCG classification. Estimated effects were expressed using hazard ratios (HRs) with 95% confidence intervals.

A set of univariable and multivariable traditional Cox PH models served as the primary analytic framework due to its interpretability and minimal distributional assumptions. This model specified the hazard of remission at time t for a patient with covariate vector X as shown below:

$$h(t|X) = h_0(t) \cdot e^{(\beta X)}$$

where $h_0(t)$ represents the baseline hazard function and β as the vector of log hazard coefficients. This model allows for proportional hazards without specifying the shape of the

baseline hazard. It has frequently been used in GTD modelling because of its ability to handle data when event times vary while controlling baseline covariates in the model. However, Cox PH assumes large samples so that the likelihood estimates are more well behaved.

To address small-sample bias and potential separation, Firth's penalized Cox model incorporated a penalty term to stabilize estimates, as shown below:

$$\ell_{Firth}(\beta) = \ell_p(\beta) + \frac{1}{2}\log|I(\beta)|$$

where $\ell_p(\beta)$ refers to the standard partial likelihood from the Cox model, and I(β) is the expected Fisher information matrix for $\ell_p(\beta)$. The penalty term acts like a shrinkage factor, thus pulling extreme estimates toward more stable values. This correction has demonstrated effectiveness in small samples, rare events, and complete or quasi-separation issues (Heinze and Schemper 2001).

Three fully parametric models were also fitted to explore alternative hazard structures. The first of these alternative parametric models is the Negative Exponential model, fitted as the standard constant-hazard parametric model (Negative Exponential) such that the risk of remission is the same at every subsequent visit. It involves a rate parameter (λ) with hazard and survival functions, as shown below:

$$h(t) = \lambda$$
$$S(t) = \exp(-\lambda t)$$

To accommodate non-constant hazards, parametric Weibull and Gompertz models were fitted under the Accelerated-failure-time (AFT) parameterization. The Weibull model explicitly models the shape (p) to allow monotonic changes of how risk changes over time such that $p>1$ suggests an increasing hazard and $p<1$ a decreasing one. It is expressed as shown below:

$$h(t) = \lambda p t^{p-1}$$

In this study, it was assumed that the likelihood of remission increases with each subsequent follow-up visit; as β-hCG levels drop and disease burden reduces, patients are more likely to achieve remission the longer they are monitored (Galingan and Cagayan 2021). Lastly, the parametric Gompertz model was estimated to permit exponentially changing hazards, capturing the nonlinear remission trajectory typical of β-hCG decline in GTD, specifically shown below:

$$h(t) = \lambda e^{\gamma t}$$

$$H(t) = \frac{\lambda}{\gamma}(e^{\gamma t} - 1)$$

$$S(t) = exp\left(-\frac{\lambda}{\gamma}(e^{\gamma t} - 1)\right)$$

with $\lambda>0$ (scale) and γ (shape) parameters. Here, $\gamma>0$ implies an increasing hazard (accelerating remission rate), $\gamma=0$ reduces to the Negative Exponential model, and $\gamma<0$ implies a decreasing hazard. Thus, the likelihood of remission changes over time rather than remaining constant. In this model, the scale parameter represents the baseline hazard rate, while another parameter describes the shape of the hazard curve. Local studies suggest that although the likelihood of remission generally increases as β-hCG decline, some patients achieve remission shortly after evacuation, whereas others experience a slower rate of remission over time (Mendoza et al. 2017; Collett 2014). Given this pattern, the model was fitted using a positive γ to represent an accelerating hazard.

The five mentioned models were compared to capture different aspects of GTD remission. The Cox PH model served as the reference, with Firth's penalized model addressing small sample bias. Among the parametric models, the Negative Exponential model with a constant hazard acted as a simple benchmark, while the Weibull allowed hazards to rise or fall monotonically over time; and the Gompertz model reflected remission patterns that accelerate as β-hCG declines. More flexible spline or Bayesian parametric models were initially considered but these require larger sample sizes. Taken together these five models provided a balance between interpretability, practicality, and capacity to capture time-varying hazards in GTD remission.

Beyond HRs, median remission times, and survival probabilities were computed across GTD patient profiles or subgroups (e.g., histology), with group differences assessed using the log-rank test. Model diagnostics and evaluation were performed to ensure validity of assumptions and comparability across approaches. Schoenfeld residuals examined PH assumptions in Cox models, while log-log survival plots checked for appropriateness of parametric specifications. Collinearity among predictors was checked using the variance inflation factor (VIF) in the unpenalized Cox model.

Model fit was evaluated using Akaike information criterion (AIC) and log-likelihood ratio (LR); whereas discrimination was assessed with Harrell's concordance statistic (C-index), which quantifies the agreement between observed and predicted remission times. The C-index represents the proportion of concordant patient pairs over all comparable pairs, ranging from 0.5 (random prediction) to 1.0 (perfect discrimination).

For the Firth's model, conventional PH diagnostics such as Schoenfeld residuals as well as AIC or LR statistics were not applicable due to the modified penalized likelihood. Instead, adequacy was assessed using coefficient stability and the C-index.

Parametric models (Weibull, Negative Exponential, Gompertz) were compared using AIC, log-likelihood, and C-index values. LR was not computed for the Gompertz model since its likelihood formulation is not nested within standard models. Given that this study focused on comparative discrimination rather than overall goodness-of-fit, all models were evaluated primarily through the C-index and were fitted on the same dataset with identical covariates.

Visual overlays of model-based survival curves and predicted remission trajectories (with 95% confidence intervals) were generated to assess alignment with empirical Kaplan–Meier estimates. Additional diagnostics like Cox-Snell residual and deviance/quartile plots from the Gompertz model, evaluated model adequacy. Log–log survival plots and Cox–Snell residuals were inspected to assess proportionality and adequacy of hazard shape.

Sensitivity analyses were performed by excluding the top 5% and 10% of cases with the longest follow-up durations to assess the influence of potential outliers or extreme values. Stratified Cox models were also constructed by histologic type and mode of evacuation to account for possible PH violations. Changes in the magnitude and direction of adjusted HRs were examined to evaluate the robustness of parameter estimates under varying assumptions and sample subsets. Stability of HRs and C-index values across these models was interpreted as evidence of model consistency.

All analyses were performed in R version 4.5.0 (R Core Team 2025) using the following packages: coxphf (Heinze et al. 2023), eha (Broström 2022), flexsurv (Jackson 2016), ggplot2 (Wickham 2016), survminer (Kassambara et al. 2024), and survival (Therneau and Grambsch 2000).

Ethical Considerations

The said dataset was completely de-identified with time-sensitive data omitted to safeguard anonymity. Ethical approval was secured under UPMREB 2024-0368-01 prior to any data processing or analysis. All procedures conformed to the principles outlined in the Declaration of Helsinki.

RESULTS

Table 1 summarizes the clinical characteristics of the 258 patients included in the study and compares whether there are significant differences between the groups in terms of the covariates. The median age of the women in the study was 29 (18–57) years old, and most patients (83.33%) presented with CHM. Median baseline β-hCG levels showed wide variability at 28,801 mIU/mL (0.22–5,732,000), consistent with the biologic heterogeneity of GTD. Chemoprophylaxis was administered to 78.29% of patients, predominantly those at perceived higher risk for persistent disease.

Table 1: Baseline Characteristics of Patients in the Study Cohort

Characteristics	*Non-Remission* (*n* = 53)	*Remission* (*n* = 205)
Maternal Age[a]	29.26 ± 8.50	31.21 ± 9.07
<40 years	45 (84.91%)	163 (79.51%)
≥40 years	8 (15.09%)	42 (20.49%)
Gravidity[*]	2 (1, 3)	3 (1, 5)
G1	18 (33.96%)	60 (29.27%)
G2 – G3	22 (41.51%)	64 (31.22%)
G4 and above	13 (24.53%)	81 (39.51%)
Parity	1 (0, 2)	1 (0, 3)
Nulliparous	19 (35.85%)	65 (31.71%)
Parous	34 (64.15%)	140 (68.29%)
Baseline β-hCG (mIU/mL)[b]	71,300 (10,000, 285,000)	16,220 (1,808, 350,000)
<10,000 (Low)	12 (22.64%)	72 (35.12%)
10,000 - 100,000 (Moderate)	16 (30.19%)	50 (24.39%)
>100,000 (High)	25 (47.17%)	83 (40.49%)
Histological Type		
Partial mole (PHM)	6 (11.32%)	37 (18.05%)
Complete mole (CHM)	47 (88.68%)	168 (81.95%)
Mode of Molar Evacuation[**]		
Suction curettage	49 (92.45%)	147 (71.71%)
Surgical evacuation	4 (7.55%)	58 (28.29%)
Chemoprophylaxis[**]		
Not given	22 (41.51%)	34 (16.59%)
Given	31 (58.49%)	171 (83.41%)
Follow-up in weeks[b **]	9 (6, 14)	33 (21, 51)

[a]Mean ± SD, [b]Median (P25, P75)

[*] $p<0.05$, [**] $p<0.01$

The median time to reach normalization of β-hCG levels among patients in remission was 11 (1–63) weeks, but a longer follow-up is still done to determine if these levels will continue to decrease after evacuation. It was also found that 205 out of 258 patients (79.46%; 95% CI: 74.01–84.22%) with GTD included in the analysis, achieved spontaneous β-hCG regression, reflecting a favorable outcome distribution consistent with published GTD cohorts. However, a substantial subset experienced delayed regression, warranting further evaluation of baseline predictors.

Survival analysis using the traditional Cox PH model was performed first (Table 2), with only gravidity found to be a statistically significant crude predictor of remission. The multivariable model showed modest discrimination in determining outcomes (C-index: 0.59, SE: 0.02) demonstrating good model fit (LR: 17, Wald: 17.21, p: 0.02) despite the modest sample size of the dataset.

Table 2: Summary of Proportional Hazards and Parametric Survival Models

Predictors	*Crude Cox PH (95% CI)*	*Adjusted Cox PH (95% CI)*	*Firth's PMLE (95% CI)*	*Weibull AFT (95% CI)*	*Negative Exponential AFT (95% CI)*	*Gompertz AFT (95% CI)*
Maternal Age						
<40 years	1.00	1.00	1.00	1.00	1.00	1.00
≥40 years	1.03 (0.73–1.45)	0.78 (0.49–1.24)	0.78 (0.49–1.25)	0.89 (0.71–1.12)	0.85 (0.55–1.33)	0.82 (0.52–1.31)
Gravidity	1.07 (1.01–1.13)[*]	1.11 (1.03–1.21)[**]	1.12 (1.03–1.21)[*]	1.06 (1.02–1.10)[*]	1.06 (0.98–1.14)	1.10 (1.02–1.19)[*]
Mode of Evacuation						
Suction curettage	1.00	1.00	1.00	1.00	1.00	1.00
Surgical evacuation	1.13 (0.84–1.54)	0.91 (0.55–1.51)	0.92 (0.56–1.52)	1.03 (0.81–1.32)	1.07 (0.68–1.69)	1.12 (0.69–1.80)

Predictors	*Crude Cox PH (95% CI)*	*Adjusted Cox PH (95% CI)*	*Firth's PMLE (95% CI)*	*Weibull AFT (95% CI)*	*Negative Exponential AFT (95% CI)*	*Gompertz AFT (95% CI)*
Histological Type						
PHM	1.00	1.00	1.00	1.00	1.00	1.00
CHM	0.72 (0.50–1.02)	0.67 (0.47–0.96)*	0.67 (0.46–0.96)*	0.80 (0.67–0.96)*	0.77 (0.54–1.10)	0.67 (0.47–0.96)*
Chemoprophylaxis						
Not given	1.00	1.00	1.00	1.00	1.00	1.00
Given	1.30 (0.90–1.88)	1.36 (0.91–2.02)	1.35 (0.90–2.01)	1.09 (0.90–1.34)	1.28 (0.86–1.89)	1.16 (0.78–1.74)
Baseline β-hCG						
Low	1.00	1.00	1.00	1.00	1.00	1.00
Moderate	0.83 (0.58–1.20)	0.91 (0.63–1.33)	0.92 (0.63–1.34)	1.02 (0.85–1.23)	0.96 (0.66–1.39)	1.05 (0.72–1.54)
High	0.75 (0.55–1.03)	0.71 (0.52–0.99)*	0.72 (0.52–0.99)*	0.85 (0.73–0.99)*	0.81 (0.59–1.12)	0.78 (0.56–1.07)

*$p<0.05$, **$p<0.01$

Controlling for other baseline covariates, for each additional pregnancy, the hazard of remission is increased by 11% (HR: 1.11, 95% CI: 1.03–1.21) thus implying that those with higher gravidity exhibited faster times to remission. It was also shown that patients with complete moles appeared to have a 33% (HR: 0.67, 95% CI: 0.47–0.96) lower adjusted hazard of remission at any given time point compared to those with partial moles. Similarly, it can be noted controlling for the other covariates, a higher level of pre-treatment β-hCG (>100,000 IU/L) has a 29% (HR: 0.71, 95% CI: 0.51–0.98) lower instantaneous risk of remission compared to patients with low baseline β-hCG (<10,000 IU/L). There was no statistically significant difference in the hazard of the outcome between moderate and low pre-evacuation β-hCG, and other covariates such as maternal age, manner of molar evacuation, and chemoprophylaxis administration did not exhibit notable associations with the outcome.

A Kaplan-Meier plot of the time to remission across histology subtype (Figure 1) demonstrates that patients with PHM tend to have shorter times to achieve remission than those with CHM. Median time to remission was 10 weeks (95% CI: 9–13) for PHM and 13 weeks (95% CI: 12–14) for CHM (log-rank p = 0.06).

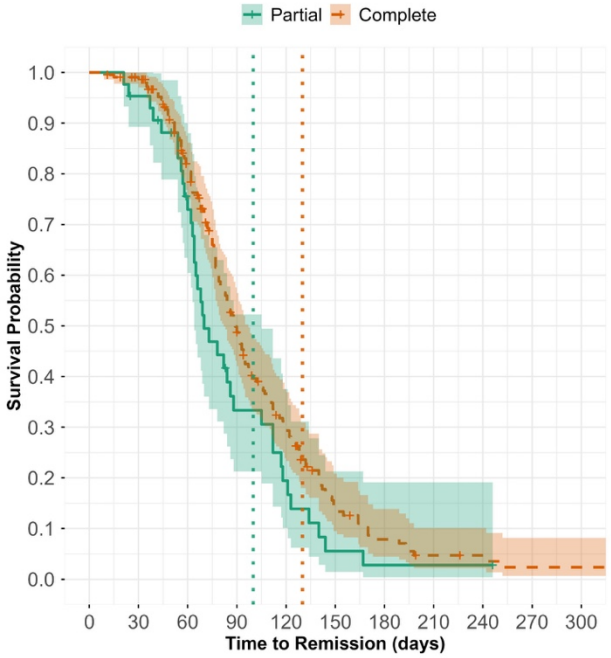


Figure 1: Kaplan–Meier Plot Comparing Remission Times by Histology.

The limited number of observations that comes with studying a rare disease like GTD supports the need for an alternative approach like Firth's penalized Cox regression to mitigate the effects of small-sample bias and possible convergence issues. Table 2 presents the multivariable Firth's model which produced robust results (penalized LR: 17.23, Wald: 17.38, p: 0.02). The latter model appeared to almost have identical point estimates to the traditional Cox model, and a slight reduction in the width of the confidence interval estimates in certain covariates like chemoprophylaxis and histologic subtype. The association of gravidity, histology, and baseline levels of β-hCG as notable predictors of time to remission remained robust after Firth's adjustment.

In addition, standard methods for testing model assumptions cannot be straightforwardly applied within Firth's penalized framework thus, fit evaluation and diagnostics are carried out on the traditional Cox model. The global test statistic of 6.98 (df: 7, p: 0.43) suggest the PH assumption was satisfied at the model level though some covariates like maternal age and mode of evacuation had p-values implying deviation from the assumption. However, inspection of the Schoenfeld residual plots insinuates only a mild violation of the assumption, with only subtle deviations in the smoothed curves though staying within the confidence bands (Supp Fig A). The residuals appear scattered randomly without strong or systematic deviations notable. Further, Supp Tab A also showed that the final model covariates did not demonstrate major multicollinearity issues (GVIF < 2.0) reinforcing the inclusion of these measured predictors in the model.

Parametric survival models were utilized to enhance understanding of GTD remission dynamics beyond standard effect measures (Table 2). The Weibull and Gompertz models had comparable results with the Cox PH and Firth's models, and identified gravidity, histopathology, and baseline β-hCG levels associated with remission timing.

The Weibull model had a shape parameter of 2.03 (95% CI: 1.85–2.23) implying an increasing likelihood of remission over time while the Gompertz model demonstrated a non-linear pattern of remission with a very low rate parameter (rate HR: 0.01) thus, a low hazard of remission during early observations followed by slight but gradual accelerating hazard over time (shape HR: 1.01). Both these models aligned with expected decline of β-hCG levels after molar evacuation. As expected, the Negative Exponential model had different results since it assumes constant risk over time, which is not the case for GTD.

The appropriateness of the Weibull model was confirmed via inspecting the log-log plot (Supp Fig B), and the predicted

remission curve (Figure 2) showed a classic concave decay typical of the Gompertz assumption. However, the confidence interval that widens over time suggests increasing uncertainty in the predictions, especially beyond five months. Nevertheless, the Gompertz model implies that most remissions occur within 180 days after evacuation and is aligned with clinical practice guidelines and biomarker behavior in GTD literature.

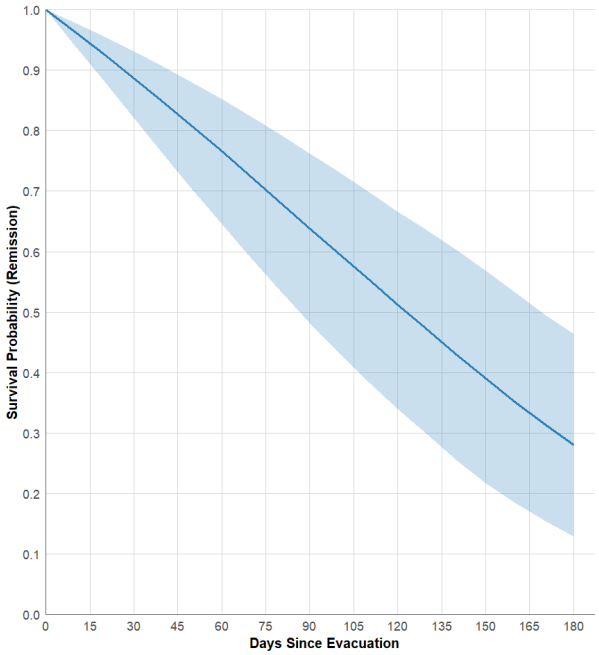


Figure 2: Gompertz-based Predicted Time to Remission Consistent with β-hCG Regression Patterns.

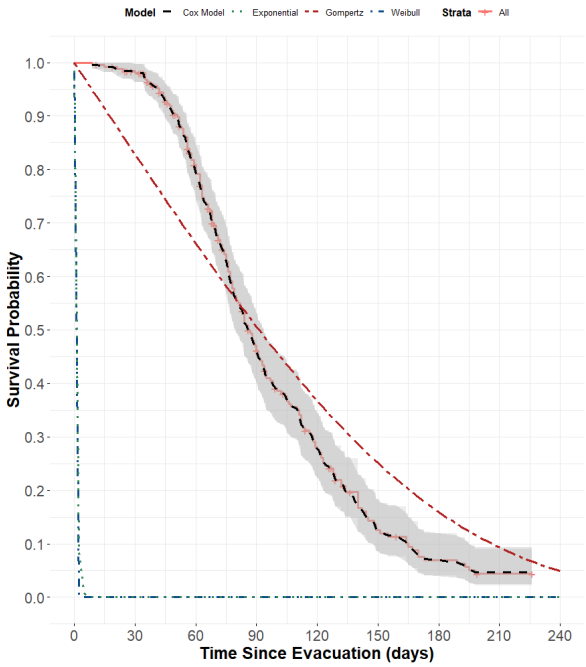
Using the Gompertz model, survival probabilities for remission were estimated across two clinically relevant profiles (Table 3). Profile 1 represents older patients (≥40 years) undergoing surgical evacuation with at least two pregnancies, given chemoprophylaxis and with high pre-evacuation β-hCG levels. The median time to remission occurred at approximately 123 days, and by 90 days, 64% of patients remained under surveillance. On the other hand, younger patients (<40 years) with similar baseline characteristics and management (Profile 2), had shorter remission trajectory (median ~ 116 days) with only a small fraction of patients followed up by five months. These estimated probabilities aid clinicians in tailoring patient monitoring after evacuation.

Table 3: Gompertz-Based Remission Probabilities with 95% CI between GTD Patient Profiles

Days since Evacuation	Older, High-Risk	Younger, Low-Risk
30 days	88.68% (81.96–92.99%)	87.75% (83.99–90.93%)
60 days	76.54% (64.45–84.86%)	74.76% (67.98–80.75%)
90 days	63.90% (48.55–75.95%)	61.43% (52.64–69.75%)
120 days	51.21% (34.10–65.81%)	48.28% (38.42–57.92%)
150 days	39.04% (22–55%)	35.94% (26.12–46%)

The Gompertz Accelerated-failure-time (AFT) model showed notable deviations in the long tail of survival distribution when overlaid with the Kaplan-Meier curve (Supp Fig C). Although AFT models provide time ratios, these were not reported since they are not directly comparable to HRs from PH frameworks. Instead, interpretation focused on the generated survival probabilities and model discrimination. Cox-Snell residuals (Supp Fig E) and deviance/quantile plots (Supp Fig F) demonstrated adequate fit during the first 100 days post-evacuation but showed progressive departure from model assumptions thereafter; consequently, model fit is most reliable and clinically interpretable during early to mid-term follow-up; and consistent with typical β-hCG monitoring timelines.

Figure 3 illustrates how the survival curves from different models diverge over time, comparing the Kaplan-Meier curve (shaded gray area), Cox PH (dashed), the Weibull (dot dash), Negative Exponential (dotted), and the Gompertz PH (long dash dot) curves. Firth's penalized model was excluded since it does not estimate a baseline hazard. The curves were truncated at 240 days to emphasize the clinically relevant follow-up period for GTD, while the complete plot is shown in Supp Fig D. The parametric models were originally fitted under an AFT framework and subsequently converted to the hazard scale for visual comparison with the Cox PH model.



†Accelerated-failure-time (AFT) models converted to hazard scales

Figure 3: Kaplan–Meier Plot Comparing Survival Curves across Models†

It can be noted that traditional Cox PH model closely fits to the Kaplan-Meier curve until day 150 then diverges. The Weibull and Gompertz models also track well but their curves vary in slope and shape. The monotonic hazard pattern for the Weibull model suggests deceleration in time to remission, while the non-constant hazard curves of the Gompertz model closely resemble the traditional Cox matching with the KM but beyond five months, tends to slightly overestimate survival. The Negative Exponential model poorly fits, generating an implausible survival curve of too early remissions that are not consistent with GTD prognosis.

Gravidity (adjusted HRs: 1.06–1.11, p<0.05) was consistently found to be associated with shorter remission, reaching statistical significance in four out of five models and highlighting its prognostic relevance in GTD. Similarly, histologic subtype has shown a stable, protective associations for partial mole (adj HRs: 0.67–0.80, p<0.05) as compared to complete moles on most of the models. The findings suggest that patients with partial moles reach biochemical remission more rapidly than those with complete moles. However, this trend should not be conflated with a lower risk of developing persistence or malignant transformation among those with the partial mole subtype.

Conversely, pre-evacuation β-hCG levels >100,000 mIU/mL were found to have a statistically significant association with delayed remission in three models (Cox, Firth, and Weibull) compared with patients whose baseline levels were <10,000 mIU/mL (adj HRs: 0.71–0.85, p<0.05). Contrastingly, non-statistically significant associations were noted for maternal age, mode of evacuation, and prophylactic chemotherapy. Although the direction of HRs across models remained consistent, the wide interval estimates and limited statistical precision indicate limited prognostic value of these covariates within this cohort.

Table 4 showed that concordance (C-index) ranged from 0.42–0.59 across models, indicating poor to modest fit only. Although demonstrating only modest discrimination (C: 0.59), the standard Cox model yielded the best predictive performance, outperforming the penalized and parametric models. Nevertheless, the Gompertz model, despite its lower concordance, offered additional interpretive value by generating individualized remission probability estimates over time, which the semi-parametric Cox model does not directly compute.

Table 4: Model Performance Comparisons

Model	*AIC*	*Log-Likelihood*	*C-index*
Traditional Cox	1,851	-918	0.59
Firth's Cox	-	-	0.58
Weibull	2,215	-1,099	0.58
Negative Exponential	2,356	-1,170	0.59
Gompertz	2,303	-	0.42

The use of parametric models offered additional insights into biochemical remission dynamics. Among these, the Gompertz model uniquely captured the accelerating likelihood remission among GTD patients over time, reflecting a biologically plausible trajectory of decline in β-hCG levels. It also offered additional interpretive value by generating individualized remission probability estimates over time, which the Cox-based models do not directly compute.

The traditional Cox PH model was used for sensitivity and stratified procedures due to having the best fit (Table 5). The sensitivity models showed minimal changes in both magnitude and direction of the HRs, supporting the robustness of the main model. Notably, chemoprophylaxis became a significant predictor in one model suggesting that its association with remission time may be more sensitive to extreme observations.

Among the stratified Cox outputs, the mode-stratified model yielded the highest concordance and preserved the statistical significance of key predictors. Other stratified models produced similar effect estimates but did not improve discriminatory performance. Gravidity remained a consistent predictor across all models, while the histologic subtype had a diminished association when stratified by baseline β-hCG – attributed to differential effects on the pre-evacuation β-hCG levels. Across all sensitivity and stratified analyses, the concordance metrics remained stable, reinforcing the robustness of the traditional Cox model under varying assumptions (Supp Tab B).

Table 5: Sensitivity and Stratified Analysis for Time to GTD Remission

Model Description	n (Events)	HR[a]	HR[b]	HR[c]	C-index
Base Cox PH Model	258 (205)	1.12 (1.03–1.22)*	1.34 (0.90–2.00)	0.70 (0.50–0.96)*	0.59
Sensitivity: 5% removed	244 (194)	1.12 (1.03–1.22)*	1.49 (1.00–2.23)	0.75 (0.52–1.09)	0.59
Sensitivity: 10% removed	231 (182)	1.10 (1.01–1.20)*	1.53 (1.01–2.31)*	0.68 (0.46–0.99)*	0.59
Stratified by mode	258 (205)	1.12 (1.03–1.22)*	1.34 (0.90–2.00)	0.67 (0.46–0.96)*	0.59
Stratified by histology	258 (205)	1.12 (1.03–1.22)*	1.37 (0.92–2.05)	— (stratified)	0.58
Stratified by β-hCG	258 (205)	1.11 (1.03–1.21)*	1.35 (0.90–2.01)	0.70 (0.48–1.00)	0.57
Stratified by gravidity	258 (205)	— (stratified)	1.34 (0.90–2.00)	0.66 (0.46–0.95)*	0.57

a) Multivariable HR for gravidity

b) Multivariable HR for chemoprophylaxis

c) Multivariable HR for histology: CHM

*p<0.05, **p<0.01

These results serve as a springboard for examining how these survival models affect prognostic interpretation and clinical utility of such methods in GTD.

DISCUSSION

The current study utilized traditional, penalized, and parametric survival models to determine consistent predictors of the time to remission among GTD patients. Across approaches, the Cox PH model remained stable and interpretable, highlighting the importance of baseline β-hCG, histologic type, and gravidity. Higher gravidity was associated with faster remission, whereas elevated β-hCG levels and CHM were associated with slower recovery. These patterns mirror existing clinical observations and reinforce their methodological and practical relevance.

Prognostic Role of Measured Covariates

While not widely emphasized in GTD literature, the consistent association between increased gravidity and shorter remission times provides a meaningful insight. Parity and antecedent pregnancy have been linked to post-molar GTN risk, yet gravidity may exert a more subtle, conditioning role. Repeated pregnancies could "prime" the uterine microenvironment, enhancing immune recognition and clearance of aberrant trophoblastic cells (Robertson et al. 2018; Xu et al. 2021). Animal studies also show pregnancy-induced remodeling of the myometrium, which may indirectly facilitate resolution of

trophoblastic proliferation (Shynlova et al. 2004; Shynlova et al. 2009).

Histologic type also demonstrated clear prognostic value. CHM is known to carry a higher likelihood of malignant progression and likewise associated with a longer remission time (Seckl et al. 2010). Its proliferative nature contrasts with PHM, which contains some fetal tissue and generally demonstrates less aggressive biology (Lurain 2010; Goldstein and Berkowitz 2012). The improvement in model fit after stratifying by histology suggests that its effect may not be entirely independent. This may be partially mediated by baseline disease burden, molecular differences, or stricter follow-up practices among CHM cases (Feltmate et al. 2006).

Although the log-rank test narrowly missed statistical significance between histologic types, the three-week median delay in remission among CHM patients holds practical importance. Even brief delays in β-hCG normalization can influence follow-up schedules, patient reassurance, and resource allocation.

The faster biochemical remission in PHM compared to CHM should not be mistaken for a lower likelihood of persistence or malignant transformation. Rather, it reflects differences in trophoblastic proliferation and tumor burden (Soper 2021). Hence, supporting the long-standing practice of extended monitoring regardless of mole subtype (Swift et al. 2025).

High baseline β-hCG (>100,000 IU/L) consistently predicted delayed remission. This reinforces evidence that elevated values reflect a greater volume of proliferative tissue and more active trophoblastic burden thus, requiring longer follow-up duration or more intensive regimens (Seckl et al. 2013). The absence of meaningful differences between moderate group (10,000–100,000 mIU/mL) and the low β-hCG categories underscores the established high-risk threshold in GTD (El-Helw et al. 2009). Additionally, this supports existing guidelines that treat markedly high β-hCG levels as a marker for persistent disease and chemoresistance (Ngan et al. 2021).

Even as these predictors reached statistical significance, their effects were not large. For instance, a 10 % increase in remission hazard with every additional pregnancy may shorten time-to-β-hCG normalization by only one to two weeks. This remains clinically informative, but not enough to change GTD management.

Penalized and Parametric Survival Models

Small-sample bias, sparse covariate patterns, and separation issues commonly complicate rare disease research. Firth's penalized regression was employed to address these concerns, but the resulting estimates were nearly identical to those from the traditional Cox PH model. This suggests covariate stability and the absence of substantial separation or monotone likelihood issues in this dataset (Heinze and Schemper 2001). Furthermore, the slight reduction in standard errors from the penalized model indicates that the conventional Cox PH model may have mildly overstated uncertainty for some predictors. These observations reaffirm penalization as a useful safeguard in rare disease modelling, despite the dataset appearing stable, because it tempers coefficient inflation rather than changing results (Rahman and Sultana 2017).

Parametric survival models were likewise explored, since GTD remission rarely follows a linear or predictable timeline (Royston and Parmar 2002). Among such models, the Negative Exponential model performed least favorably, constrained by its assumption of a constant hazard over time. Weibull and Gompertz models, which accommodate time-varying hazards, provided better representation of the underlying patterns. The Gompertz model with its exponentially increasing hazard rate, made it more suitable for modeling scenarios where the risk of event accelerates over time (Collett 2014). Specifically, the non-constant hazard rate characterized by a steep early decline followed by a plateau (Schoeberl 2007). The model performed best within the first 100 days, a period during which most patients achieve remission (Joyce et al. 2022). Its predictive performance declined thereafter, reflective of real-world variation and the complexity of late biochemical normalization.

Despite the biological plausibility of the Gompertz model and its favorable early performance, the Cox PH model demonstrated a slightly superior overall fit. This may be due to the traditional model not assuming a specific baseline hazard function and can adapt to varying patterns without misspecification penalties (Cortese et al. 2010). Parametric models, while efficient in small samples and valuable for extrapolation, can produce misleading results when the assumed hazard shape diverges from the underlying pattern.

From a methodological perspective, the Cox PH model outperformed its stratified and parametric counterparts. This corroborates existing literature showing that extensions to the Cox model improve precision without considerable gains in interpretability (Maharela et al. 2024). Nevertheless, exploring alternative survival models remains important. Such practice allows testing the stability of predictors under different assumptions and ensures that model behavior aligns with clinical reasoning and data structure.

Clinical and Public Health Implications

The study highlights the enduring value of traditional models in understanding GTD remission dynamics (Lurain 2010). In the absence of advanced tools, careful history taking and serial β-hCG monitoring remains essential for detecting GTN and initiating timely interventions. The consistent predictive value of gravidity underscores that reproductive history still offers meaningful prognostic insight despite increasing reliance on biomarkers and risk scores.

While underused in existing literature, the Gompertz model offers practical isnight. It produced biologically plausible curves that closely resemble the observed remission patterns (Habibi et al. 2018). Simulated survival probabilities can guide follow-up intensity. Older women, CHM cases, or those with high pre-evacuation β-hCG may benefit from closer monitoring every one to two weeks, whereas low-risk patients can extend monitoring intervals safely. These probability-based insights point toward more individualized surveillance, especially in low-resource settings.

Moreover, local time-to-remission estimates can contribute towards refining national practice guidelines, particularly where patient adherence varies (Capito et al. 2020). The models exhibited moderate discrimination, which does not imply model inadequacy. GTD is biologically diverse, datasets are modest in size and with limited predictive variables. In such contexts, the observed performance-indices reflect the analytic constraints in rare disease modelling (Carrasco-Zanini et al. 2024).

Moreover, while there is no hard-and-fast threshold for acceptable C-index, values near 0.5 indicate modest discrimination (Brentnall and Cuzick 2016). The consistency of C-index values across sensitivity and stratified analyses demonstrate stability rather than model deficiency.

Strengths, Limitations, and Future Directions

A major strength of the study lies in its use of traditional, penalized, and parametric survival models to explore remission patterns in a rare disease dataset. By incorporating Firth's

correction and sensitivity analyses, the study responded to the common challenges of small samples and sparse events. Beyond methodological depth, the inclusion of parametric AFT models, particularly the Gompertz model, added interpretative depth by providing probabilistic estimates of remission. Trimmed and stratified Cox models contextualized predictors such as histologic type and evacuation method. The decade-long dataset offers a glimpse into remission trends before widespread changes in referral patterns.

Still, several limitations warrant acknowledgement. The retrospective, single-center design limits generalizability. Some subgroup analyses remained underpowered despite a moderate cohort size. External validity of the survival models remains uncertain given the non-constant hazards observed beyond early follow-up. Missing prognostic variables like WHO risk score, disease stage, or timing between diagnosis and evacuation restricted exploration of interaction effects. Likewise, the modest discrimination may reflect unmeasured patient-level and health system factors. Selection bias from follow-up attrition or an overrepresentation of high-risk cases may also have influenced estimates, although sensitivity analyses supported the stability of the key associations.

Future research can incorporate longitudinal β-hCG measurements through joint or flexible modeling frameworks that better capture how biomarkers change over time. These strategies can also better handle small or censored datasets, which are common in rare diseases. Newer tools like spline-based methods or machine learning–assisted survival models, may enhance discrimination and calibration.

Collaboration across institutions, particularly within Southeast Asia, would expand data diversity and strengthen external validation. Larger, pooled datasets could support the use of dynamic survival modeling for more heterogeneous GTD populations. As data resources grow, refined analytic strategies may guide individualized follow-up and sharper prognostic estimates. The consistent effects of gravidity, histologic type, and elevated baseline β-hCG reaffirm their clinical value while reminding that GTD remission is best understood through a combination of clinical judgment and evolving methodological perspectives.

CONCLUSION

The study sought to identify consistent predictors of time-to-remission among post-evacuation GTD patients by comparing various modeling strategies, including traditional and Firth's penalized Cox PH, and parametric AFT models. The analysis demonstrated how appropriately chosen survival models can yield clinically meaningful insights even from modest-sized datasets. Across models, higher gravidity was consistently linked to faster remission, while high baseline β-hCG levels and CHM histology were associated with delayed remission. These patterns mirror existing literature and reinforce their prognostic value in clinical practice.

Among the tested models, the traditional Cox PH model showed the best overall performance. From the parametric options, the Gompertz model offered an acceptable fit and practical value by enabling individualized remission probability estimates, despite weaker calibration at later follow-up periods. Together, these findings support GTD specialists in tailoring interventions and optimizing follow-up strategies based on patient risk profiles.

The results highlight the need for more systematic and routine collection of clinical and biomarker data to make personalized care more achievable, especially in resource-limited settings where GTD remains a significant burden. Moreover, the findings strengthen the call for a national GTD registry, an initiative that not only improves standardized data capture but also advances outcomes research in this rare and often overlooked reproductive disease.

ACKNOWLEDGMENTS

The authors sincerely thank Dr. Maria Febi de Ramos, Dr. Melissa de Quiros, and all trophoblastic disease specialists under PSSTD for allowing us to make use of their data for secondary analysis.

CONFLICT OF INTEREST

All authors have stated explicitly that there are no conflicts of interest in connection with this article.

CONTRIBUTIONS OF INDIVIDUAL AUTHORS

Conceptualization: ARS; Data curation: ARS, MSC; Formal analysis: ARS; Funding acquisition: ARS, MSC; Investigation: ARS, MSC; Methodology: ARS, ASA, MCL; Project administration: MSC; Resources: MSC; Software: ARS; Supervision: MSC, CLV, ASA, MCL, FBG; Validation: MSC, CLV, ASA, MCL, FBG; Visualization: ARS; Writing – original draft: ARS; Writing – review & editing: all authors.

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APPENDIX A: SUPPLEMENTARY TABLES

Table A: Model Checks on the Cox PH Model

Covariates	*Schoenfeld residuals*	*p-value*	*Adjusted GVIF*
Maternal Age	4.138	0.04*	1.370
Gravidity	0.564	0.45	1.431
Mode of Molar Evacuation	4.164	0.04	1.640
Histological Type	0.835	0.36	1.017
Chemoprophylaxis	0.380	0.54	1.082
Baseline β-hCG	1.598	0.45	1.037
Global	6.980	0.43	-

Table B: Fit Statistics across Sensitivity and Stratified Models

Model	*n*	*Events*	*C-index*	*Notable Predictors*
Sensitivity analysis (5% removed)	244	194	0.586	Gravidity, chemotherapy
Sensitivity analysis (10% removed)	231	182	0.586	Gravidity, chemotherapy, histology
Stratified by mode of evacuation	258	205	0.593	Gravidity, chemotherapy, β-hCG
Stratified by baseline β-hCG	258	205	0.572	Gravidity, histology
Stratified by gravidity categories	258	205	0.583	Gravidity, histology

APPENDIX B: SUPPLEMENTARY FIGURES

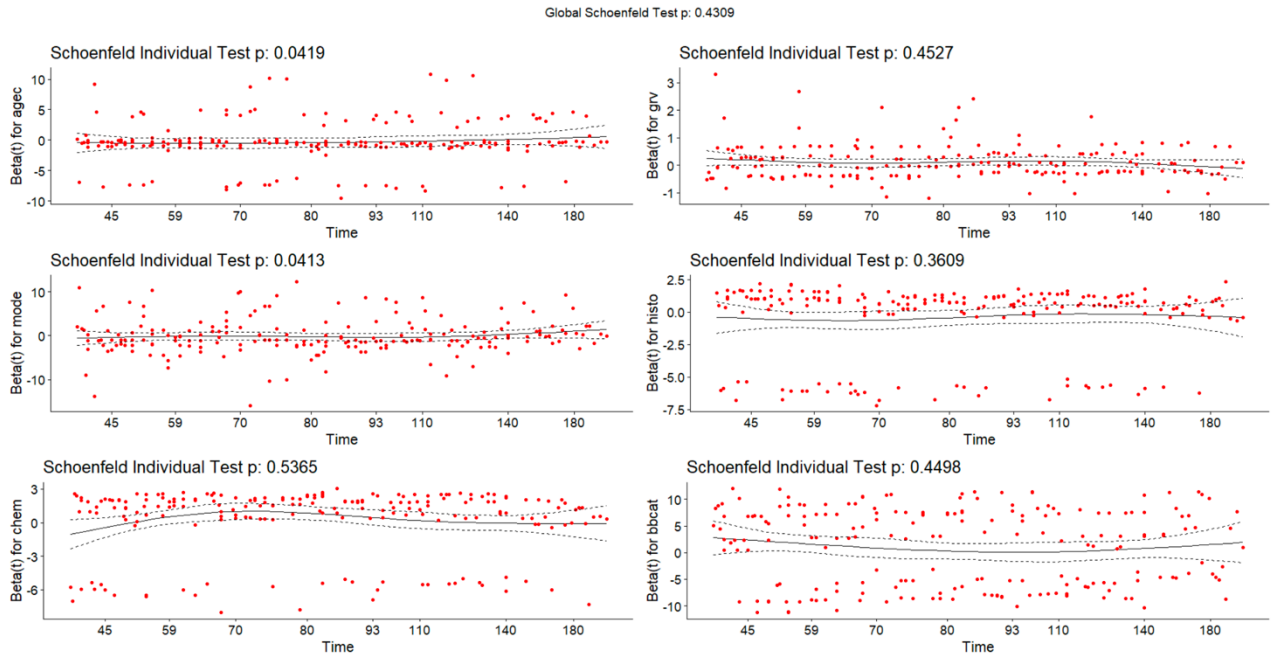

Figure A: Schoenfeld Residuals from the Cox PH Model satisfying assumptions

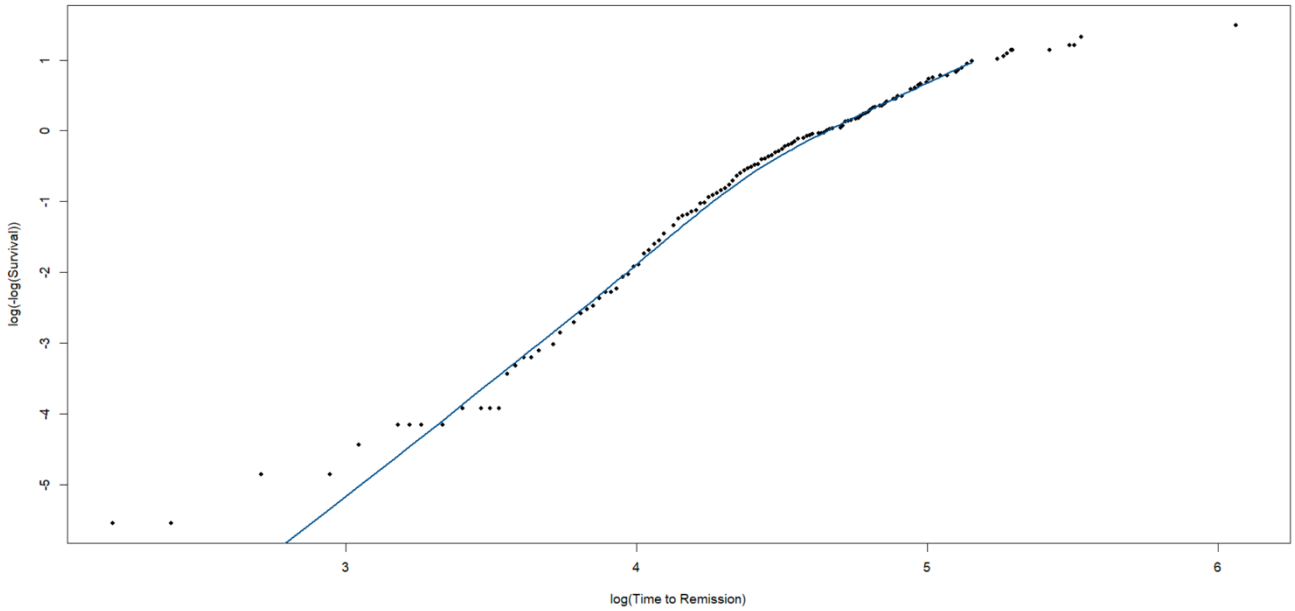

Figure B: Log-Log Plot of Survival Functions assessing PH Assumptions

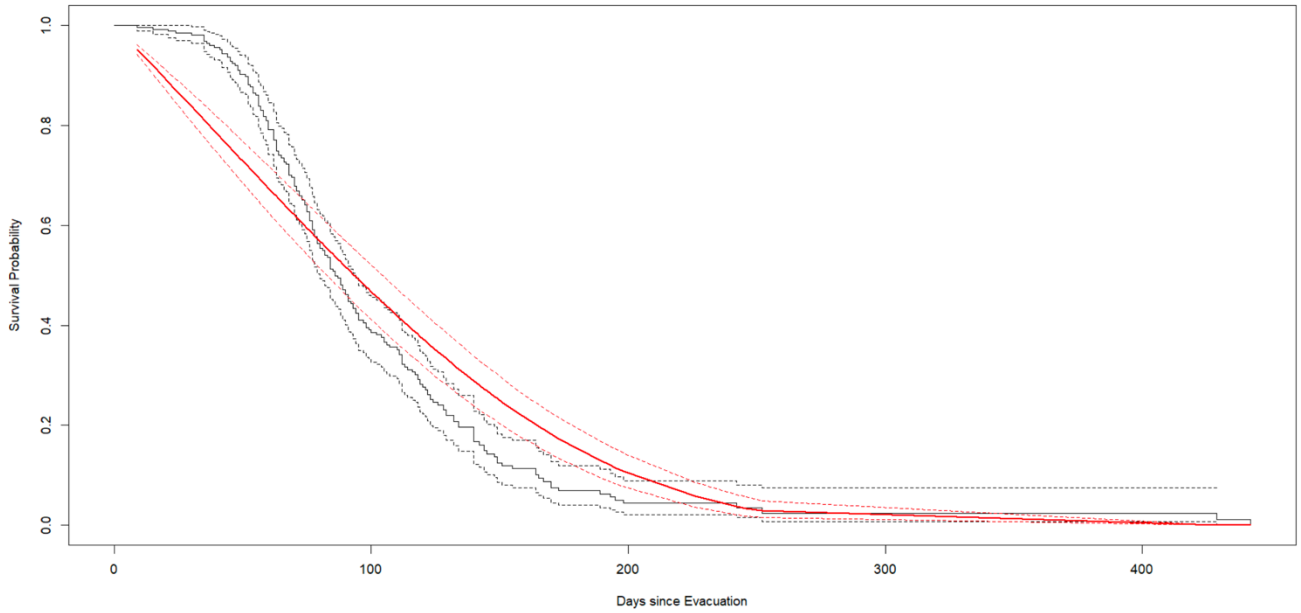

Figure C: Overlayed Gompertz and Kaplan-Meier Plots Demonstrating Model Fit

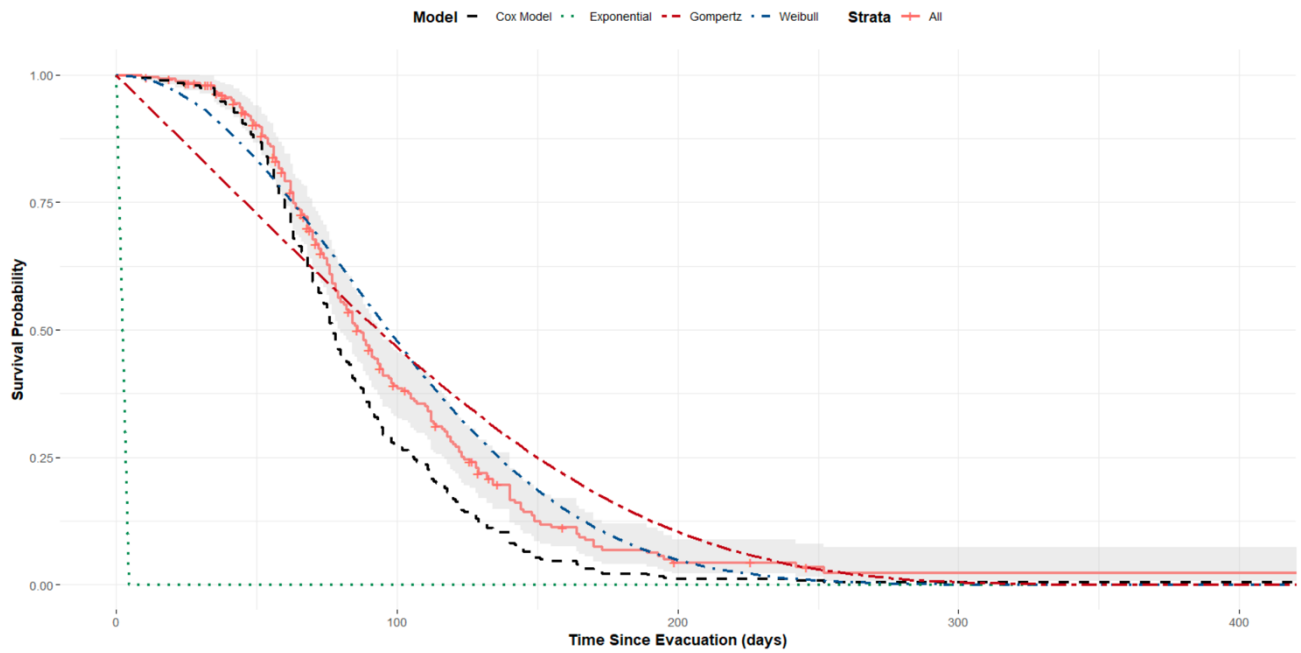

Figure D: Kaplan–Meier Curves for All Models (Full Time Window) comparing Long-term Agreement

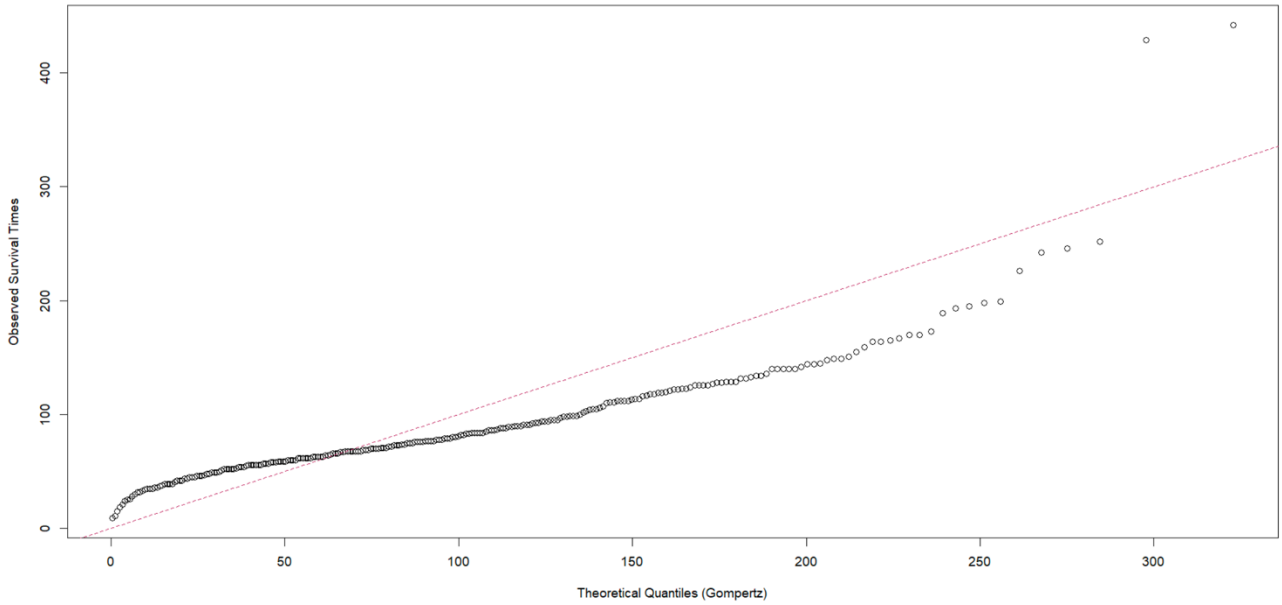

Figure E: Gompertz-Based Q-Q Plot comparing Observed and Fitted Agreement

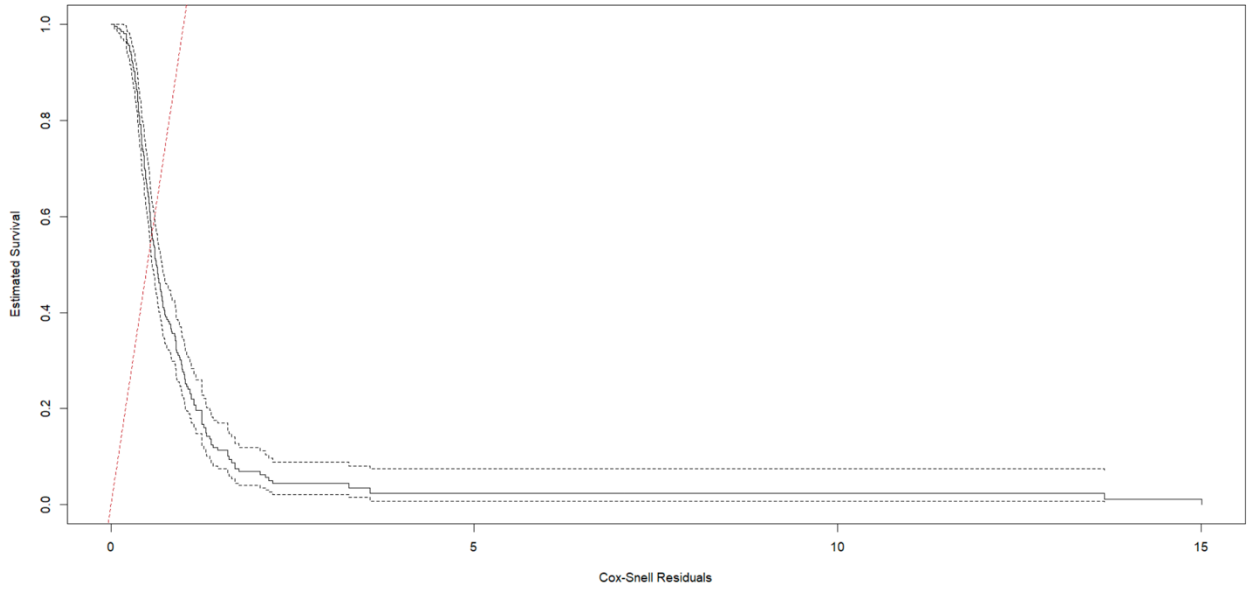

Figure F: Kaplan–Meier Curves of Cox-Snell residuals for the Gompertz Model evaluating Overall Model Adequacy