A Network Meta Analysis of Treatments for Advanced/Metastatic Pancreatic Cancer

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Abstract

A modified Multilevel Network Meta-Regression (ML-NMR) was performed on data from eight studies comparing Gemcitabine (GEM) with six combination therapies and one standalone therapy. The comparative efficacy of the combination therapies was assessed in terms of the median overall survival (OS) and restricted mean survival time (RMST) estimates. GEM in combination with nab-paclitaxel (NAB) or capecitabine (CAP) provides improved median OS and RMST estimates for the treatment of advanced/metastatic pancreatic cancer compared to GEM monotherapy.

Acknowledgements

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For my late grandfather, Norman Fredrick Taylor (July 1943 - April 2015).

"But they that wait upon the Lord shall renew their strength; they shall mount up with wings as eagles; they shall run, and not be weary; and they shall walk, and not faint." Isaiah 40:31

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CHAPTER
ONE

INTRODUCTION

1.1 Pancreatic Cancer

Pancreatic cancer is the 10^{th} most common cancer in the UK, accounting for 3% of all new cancer cases [Cancer Research UK, 2024]. Pancreatic cancer has a particularly poor prognosis, with 9,558 deaths from 10,452 cases between 2016 and 2018. Only 3% of patients survive for more than five years [National Institute for Health and Care Excellence, 2018]. Part of the reason for the poor prognosis is that pancreatic cancer is hard to detect at early stages, meaning most people who present with symptoms already have advanced-stage pancreatic cancer by the time they present. Often, patients only notice symptoms when the tumour has spread to surrounding tissues, or metastises to other organs [Kelsen et al., 1997]. The liver is the most common site of pancreatic cancer metastases [Deeb et al., 2015]. Common symptoms of pancreatic cancer include indigestion, stomach or back pain, loss of appeteite and jauncdice [Pancreatic Cancer UK, 2022]. These symtoms are common in other illnesses, which contributes to patients overlooking the fact their symptoms are consistent with pancreatic cancer.

Risk factors of pancreatic cancer include smoking, diabetes, obesity, and high-fat diets. Smoking is the dominant risk factor, with around 20% of cases being caused by cigarette smoking. In addition, cancers from smokers contain more genetic mutations when compared to cancers from non-smokers [Blackford et al., 2009].

1.2 Treatment Landscape

Gemcitabine (GEM) ($C_9H_{11}F_2N_3O_4$) is a standard first-line treatment for pancreatic cancer administered intrveneously [National Institute for Health and Care Excellence, 2018]. GEM is also used to treat other types of cancer, including breast cancer, bladder cancer and non-small-cell lung cancer [Wong et al., 2009]. GEM can be administered alone or in combination with another medication.

This dissertation considered six treatments that were given in combination with GEM: capecitabine (CAP) ($C_{15}H_{22}FN_3O_6$), axitinib (AXI) ($C_{22}H_{18}N_4OS$), pemetrexed (PEM) ($C_{20}H_{21}N_5O_6$), sorafenib (SOR) ($C_{21}H_{16}CIF_3N_4O_3$), nab-paclitaxel (NAB)[1] and irinotecan (IRI) ($C_{33}H_{38}N_4O_6$). In addition, one standalone treatment, FOLFIRINOX, was included. FOLFIRINOX is a combination of oxaliplatin ($C_8H_{14}N_2O_4Pt$), irinotecan ($C_{33}H_{38}N_4O_6$), leucovorin ($C_{20}H_{23}N_7O_7$), and fluorouracil ($C_4H_3FN_2O_2$), which is currently the recommended first-line treatment for metastatic pancreatic cancer in the UK.

A Network Meta Analysis (NMA) conducted by [Gresham et al., 2014], which included FOLFIRINOX, GEM-NAB, and GEM-CAP, found all three treatments to be associated with statisitically significant improvements in Overall Survival (OS) relative to GEM and several other treatments. Their NMA was a Bayesian NMA for calculating survival outcomes. The primary result outcomes of their NMA were the HR, and survival gain, as defined as in Equation 1.1.

[1] As nab-paclitaxel is a mixture of paclitaxel ($C_{47}H_{51}NO_{14}$) with albumin protein, it does not have a standard chemical formula

$$\frac{\frac{\text{GEM Median OS}}{HR} - \text{GEM Median OS}}{\frac{\text{GEM Median PFS}}{HR} - \text{GEM Median PFS}} \tag{1.1}$$

The National Insitute for Health and Care Excellence (NICE) last updated their guidance on the digangosis and management of pancreatic cancer in 2018 [National Institute for Health and Care Excellence, 2018]. The guidance for treatment is split for patients with locally advanced cancer and metastatic cancer.

1.2.1 Locally Advanced Pancreatic Cancer

Systemic combination chemotherapy is offered to patients who are well enough to tolerate. For those who are not well enough to tolerate combination therapy, GEM is offered. CAP should be considered as the radiosensitiser[2].

1.2.2 Metastatic Pancreatic Cancer

In first line treatment, if a patient has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 and is well enough, they are offered FOLFIRINOX. If the patient is not well enough to tolerate FOLFIRINOX, then GEM combination therapy is offered. Further, if the patient is not well enough to tolerate GEM combination therapy, then GEM monotherapy is offered.

In second-line treatment, oxaliplatin-based chemotherapy is offered to patients who did not recieve first-line oxaliplatin. GEM combination therapy is offered in the second-line treatment case for patients who progressed after first-line FOLFIRINOX.

1.3 Project Aim

To assess the comparative efficacy of treatments for advanced/metastatic pancreatic cancer using Multilevel Network Meta-Regression (ML-NMR). As the focus of this project was not on a thoroguh literature review, but rather on the methodology, inclusion criteria for studies were not particularly strict, but studies had to be a phase II or phase III trial, and contain published Kaplan-Meier (KM) curves with numbers at risk. In addition, studies had to report the proportion of male patients on each treatment arm. Only the OS endpoint was considered.

The secondary aim was to corroborate the findings of current guidance. NICE TA476 [National Institute for Health and described some uncertainty in the comparison between GEM-NAB and GEM-CAP, so the NMA also aimed to provide some clarification on the comparative efficacy of GEM-NAB and GEM-CAP. The other piece of literature that the NMA aimed to verify was an NMA conducted in 2014 [Gresham et al., 2014], which used different outcome measures.

1.4 Dissertation Structure

Chapter 2 outlines some concepts in survival analysis that are important to this dissertation. The survival and hazard functions are introduced along with some key metrics. In particular, the median survival time and restricted mean survival time (RMST) are introduced. Finally, there is some discussion on parametric survival models, which the later chapters rely on.

Chapter 3 discusses the theory of NMAs. First, the idea of a network of evidence is outlined using graph theory. The standard NMA model is then discussed, looking at the relative effect of treatments in a network of evidence. The notion of different types of effects NMAs are introduced, and some discussion on types of variables considered in NMAs is presented. This is then expanded on to derive the ML-NMR model for general likelihoods, which is in turn expanded on to describe the ML-NMR model for survival outcomes. There is some discussion of the numerical integration techniques used when implementing the survival ML-NMR model. Following this, the outcome measures are introduced in the ML-NMR context, building on the initial definitions in Chapter 2. Finally, the model selection criteria and metrics are introduced.

[2] A radiosensitiser is a treatment that makes cancer cells more susceptible to radiotherapy

Chapter 4 presents the clinical trials that were included in the NMA. A summary table presents the treatments, number of patients, and summary covariate information in each trial. There is some discussion on the similarity of the studies based on the data in the table. The discussion of similarity is aided by two forest plots presenting the variation of the median OS in each study. The KM curves for each study are also presented. Finally, the extrapolation plots of the parametric models fit to each treatment arm of each study are presented.

Chapter 5 presents the NMA itself. First, the network of evidence is presented along with some discussion. The model fitting and selection is then presented, with discussion on which model provided the best fit and was therefore selected. A table presenting the information criterion scores for each model is used to compare each model. The results are then presented. These include survival and hazard plots, along with forest plots of median OS and RMST.

Chapter 6 discusses the results of Chapter 5 and the interpretation thereof. The aims presented in Section 1.3 are adressed before some more general discussion and comments on potential future work.

Appendix A contains some definitions that are referred to, but not directly required, in the outline of the analysis. Appendix B presents some additional results from the NMA that were not required for drawing any conclusions, but may be of value to the interested reader. Finally, Appendix C outlines the development of the `PCNMA` R package that was developed for conducting this NMA. While not relevant to understanding any of the results, this appendix may be interesting to the more programming-minded reader.

CHAPTER

TWO

SURVIVAL ANALYSIS BAKGROUND

2.1 Survival Functions

Given a homogeneous population of individuals, the time of death for each individual is drawn from a continuous random variable $T > 0$ with probability density function $f(t)$ and distribution function $F(t) = \int_0^t f(\tau)d\tau$. Survival analysis is concerned with estimating the distribution T from Time-To-Event (TTE) data. There are two functions central to survival analysis, the *survival function* and *hazard function*.

Definition 2.1.1: Survival Function

The **Survival Function** $S(t)$, gives the probability of an individual surviving longer than time t.

$$S(t) = P(T \geq t) = 1 - F(t) = \int_t^\infty f(\tau)d\tau$$

Definition 2.1.2: Hazard Function

The **Hazard Function** gives the risk of death at time t, given that the individual has survived up to time t.

$$h(t) = -\frac{d}{dt}\log S(t)$$

2.2 The Kaplan-Meier Estimator and Digitisin Survival Curves

2.2.1 The Kaplam-Meier Estimator

The KM estimator is a non-parametric method for estimating the survival function from event and censoring times. TTE data contains, at a bare minimum, a subject identifier, an event time, and a censoring indicator. The Censoring indicator is given in Equation 2.1. The time column of data gives the time that either the event (i.e, death due to the disease being investigated, in overall survival), or censoring (i.e a chemotherapy patient dies after being hit by a bus not their cancer) occurs.

$$c_i = \begin{cases} 1 \text{ If inividual i has an event} \\ 0 \text{ If individual i is censored} \end{cases} \tag{2.1}$$

Let d_i and n_i be the number of events and total individuals at risk at the i^{th} timepoint, t_i. Define the discrete hazard rate h_i as the probability that individual experiences an event at time t_i. The survival rate is then defined as in Equation 2.2, and the likelihood function for the hazard function up to time t_i is given by Equation 2.3.

$$S(t) = \prod_{i:t_i \leq t} (1 - h_i) \tag{2.2}$$

$$\mathcal{L}(h_{j\leq i}|d_{j:j\leq i}, n_{j:j\leq i}) = \prod_{j=1}^{i} h_j^{d_j}(1-h_j)^{n_j-d_j}\binom{n_j}{d_j} \tag{2.3}$$

The KM estimator can be derived by Maximum Likelihood Estimation (MLE) of the discrete hazard function. By obtaining an maximum likelihood estimate of h_i, $\hat{h}_i$, and substituting it into Equation 2.2, the resulting estimate of the survival function, $\hat{S(t)}$, is the KM estimator.

Taking logs of Equation 2.3 gives Equation 2.4.

$$log(\mathcal{L}) = \sum_{j=1}^{i}\left(d_j \log(h_j) + (n_j - d_j)\log(1-h_j) + \log\binom{n_j}{d_j}\right) \tag{2.4}$$

By taking the derivative of Equation 2.4 with respect to h_i, and setting the resulting fraction equal to zero, $\hat{h}_i$ is obtained as in Equation 2.7.

$$\frac{\partial \log(\mathcal{L})}{\partial h_i} = \frac{\partial}{\partial h_i}\left(\sum_{j=1}^{i}\left(d_j \log(h_j) + (n_j - d_j)\log(1-h_j) + \log\binom{n_j}{d_j}\right)\right) \tag{2.5}$$

$$= \frac{d_i}{\hat{h_i}} - \frac{n_i - d_i}{1-\hat{h_i}} \tag{2.6}$$

$$\frac{\partial \log(\partial)}{\partial h_i} = 0 \Rightarrow \hat{h_i} = \frac{d_i}{n_i} \tag{2.7}$$

Definition 2.2.1: Kaplain-Meier Estimator

The **Kaplan-Meier Estimator**, $\hat{S(t)}$, estimates the survival probability that an individual survives longer than time t, and is given by Equation 2.8.

$$\hat{S(t)} = \prod_{i:t_i\leq t}\left(1 - \frac{d_i}{n_i}\right) \tag{2.8}$$

2.3 Reconstructing Survival Data from Published Curves

The ML-NMR method requires aggregate survival data to be in the form of the TTE data previously described. Often, the actual patient level event and censoring times/indicators are not published, and therefore must be reconstructed from the published KM curves, which are usually readily available. Indeed, one of the study selection criteria outlined in Section 1.3 was that studies must publish KM curves with numbers at risk. This was motivated by the method for reconstructing patient-level data from KM curves, the Guyot algorithm [Guyot et al., 2012] requiring numbers at risk.

2.4 Regression Models for Survival

The survival time of patients may be dependent on several explanatory variables such as age, sex, the presence of a genetic mutation, etc. We wish to incorperate these variables into our survival functions. There are two forms of models for survival data. Accelerated Failure Time (AFT) models, and Proportional-Hazards (PH models).

2.4.1 Accelerated Failure Time Models

Let x be a vector of explanatory variables for each individual in a trial. The survival function can be extended to include this,

$$S(t, x) = S_0(t\Psi(x)).$$

Here, $S_0(t) = S(t, x = 0)$, i.e the survival function at baseline. We define the density and hazard functions accordingly,

$$f(t,x) = f_0(t\Psi(x))\Psi(x)$$
$$h(t,x) = h_0(t\Psi(x))\Psi(x).$$

This is equivalent to defining a random variable T such that

$$T = T_0/\Psi(x).$$

Here, T_0 has survivor function S_0. It is required that $\Psi(x) \geq 0$ and $\Psi(0) = 1$, leading to the natural choice

$$\Psi(x) = \exp(-\beta' x).$$

We can then write

$$\begin{aligned} T &= T_0/\Psi(x) \\ \implies E(T) &= E(T_0)/E(e^{-\beta' x}) \\ &= E(T_0)/e^{-\beta' x} \\ &= E(T_0)e^{\beta' x} \end{aligned}$$

In practice, we assume a distribution for T, and estimate parameters using maximum likelihood estimation.

2.4.2 Proportional Hazards Models

Let h_0 represent the hazard function for an individual at baseline. In addition, let $\mathbf{x}$ be a vector of explanatory variables. The proportional hazards model, also known as the Cox model [Cox, 1972] is then given by

$$h(t,x) = \exp(\beta' x)\ h_0(t) \tag{2.9}$$

Consider the following defintion.

Definition 2.4.1: Semi Parametric Model

A statistical model is a parameterised family of distributions $\{P_\theta : \theta \in \Theta\}$. For a parametric model, $\Theta \subseteq \mathbb{R}^k$ for $k \in \mathbb{N}$. Similarly, for a non-parametric model, $\Theta \subseteq V$, where V is some (possibly infinite) dimensional space V. A **Semi-parametric** model is a statistical model with both parametric and non-parametrc components. For a semi-parametric model we have $\Theta \subseteq \mathbb{R}^k \times V$.

The Cox model is semi-parametric then β is of finite dimension and $h_0(t)$ is infinite-dimensional and does not need to be specified.

2.5 Key Survival Metrics

2.5.1 The Hazard Ratio

The Hazard Ratio (HR) follows from Equation 2.9. Consider two treatments, $i = 1, 2$, then $h_1(t,x) = \exp(\beta' x)\ h_0(t)$ and $h_2(t,x) = \exp(\beta' x)\ h_0(t)$. The HR is obtained as in Equation 2.10.

$$HR = \frac{h_1}{h_2} = \exp(\beta' x) \tag{2.10}$$

In practice, the HR is a useful endpoint in performing network meta-analyses on survival outcomes. However, in order to conduct a HR-based Network Meta Analysis (NMA), the proportional hazards assumption (PHA), must be satisfied. The PHA is the assumtpion that the HR remains constant

throughout the observation period of a trial. It can be tested by visual-inspection of a log-cumulative hazards plot.

Definition 2.5.1: Cumulative Hazard Function

The **Cumulative Hazard Function**, $H(t)$ is given by

$$H(t) = \int_0^x h(t)dt = -\log(S(t))$$

By extention, the log-cumulative hazard function is given by $\log(-\log(S(t)))$. When plotting this for both arms of a clinical trial, if the curves remain roughly parallel, the PHA is likely satisfied, but if they curves cross, it indicates violation of the PHA.

2.5.2 Restriced Mean Survival Time

The RMST is alternative measure to the (log) HR in NMAs. RMST is the mean survival time up to a pre-specified time. This measure can be thought of visually as the area under the survival curve. Definition 2.5.2 presents the formal definition.

Definition 2.5.2: RMST

For a survival function $S(t)$, the **RMST** for some pre-specified time $x > 0$,

$$RMST = \int_0^x S(t)dt$$

2.5.3 Median Survival

Median survival is simply the earliest timepoint at which 50% of patients have died.

2.6 Parametric Models for Survival Analysis

This section discusses the parametric models commonly used in Survival Analysis. In particular, the seven parametric models recommended by the National Institute for Health and Care Excellence (NICE) in Technical Support Document (TSD) 14 [Latimer, 2011]. All parametric model fitting for this project was performed in `R` using the `flexsurv` package [Jackson, 2016]. The first section outlines how the `flexsurv` package works.

2.6.1 Model Setup

The general model of a `flexsurv` survival model takes the form

$$f(t|\mu(\mathbf{z}), \alpha(\mathbf{z})). \tag{2.11}$$

Equation 2.11 gives the probability density for death at time $t \geq 0$. The *mean* or *location* of the distribution is given by $\mu = \alpha_0$. The remaining parameters, $\alpha^{\mathbf{1}} = (\alpha_{\mathbf{1}}, \ldots, \alpha_{\mathbf{R}})$ are called *ancillary* parameters.

Chapter 2 discussed AFT and PH models. Under the `flexsurv` framework, if the hazard function, $h(t) = \frac{f(t)}{S(t)}$, can be factorised as

$$h(t|\alpha, \mu(\mathbf{z})) = \mu(\mathbf{z})\mathbf{h_0}(\mathbf{t}|\alpha).$$

Then we have a PH model. On the other hand, an AFT model would be written as

$$S(t|\mu(\mathbf{z}), \alpha) = \mathbf{S_0}(\mu(\mathbf{z})\mathbf{t}/\alpha).$$

All parameters may depend on $\mathbf{z}$, a vector of covariates. This is done through the link-transformed linear models

$$\begin{aligned} g_0(\mu(\mathbf{z})) &= \gamma_0 + \beta_{\mathbf{0}}^{\mathbf{T}}\mathbf{z} \\ g_r(\alpha_r(\mathbf{z})) &= \gamma_r + \beta_{\gamma}^{\mathbf{T}}\mathbf{z} \end{aligned} \tag{2.12}$$

g is usally chosen to be $log()$ if the parameter is positive, or the identity function if the parameter is unrestricted.

2.6.2 Fitting Models

Let t_i, $i \in \{1, \ldots, n\}$, be a sample of times from n individuals. Define c_i such that

$$c_i = \begin{cases} 1 & \text{if } t_i \text{ is an observed death time} \\ 0 & \text{if } t_i \text{ is censored} \end{cases}.$$

Introduce s_i, which are delayed-entry times. This means for an individual i who is delayed-entry, the survival time is only observed conditionally on individual i having survived up to time s_i. $s_i = 0$ when there is no delayed-entry.

2.6.2.1 Right Censoring

In the case of right-censoring and nothing else, the likelihood for the parameters $\theta = \{\gamma, \beta\}$ required in Equation 2.12 is given by

$$l(\theta|\mathbf{t}, \mathbf{c}, \mathbf{s}) = \frac{\prod_{\mathbf{i:c_i=1}} \mathbf{f_i}(\mathbf{t_i}) \prod_{\mathbf{i:c_i=0}} \mathbf{S_i}(\mathbf{t_i})}{\prod_{\mathbf{i}} \mathbf{S_i}(\mathbf{s_i})} \tag{2.13}$$

2.6.2.2 Interval Censoring

In the case of interval-censoring, where the survival time is censored on $(t_i^{\min}, t_i^{\max})$, the likelihood for $\theta = \{\gamma, \beta\}$ is

$$l(\theta|t^{\min}, t^{\max}, c, s) = \frac{\prod_{i:c_i=1} f_i(t_i) \prod_{i:c_i=0} \left(S_i(t_i^{\min}) - S_i(t_i^{\max})\right)}{\prod_i S_i(s_i)} \tag{2.14}$$

Maximum Likelihood Estimation is performed in `R` using the analytic derivatives of Equation 2.13 and/or Equation 2.14.

CHAPTER

THREE

NETWORK META ANALYSIS THEORY

3.1 Building a Network of Evidence

Consider a set of N two-arm randomised-controlled trials (RCTs). In each trial $i \in 1, \ldots, N$, the patients are randomised to recieve a treatment A_i, or a placebo P_i. This can be represented as N graphs with two nodes, A_i and P_i, connected by an edge representing the trial comparing A_i and P_i. It is useful at this stage to recall the formal definition of an (undirected) graph.

Definition 3.1.1: Graph

A **Graph** is an ordered triple $G = (V, E, \varphi)$. Where V is a set of nodes, E is a set of edges, and $\varphi : E \to \{\{x, y\} | x, y \in V$ such that $x \neq y\}$ is an **incidence function** mapping every edge to a pair of verticesa.

We can construct N graphs under the formal definition. Namely, for trial T_i, we have $G_i = (V_i, E_i, \varphi_i)$ where $V_i = \{A_i, P_i\}$, $E_i = \{T_i\}$ and $\varphi_i : E_i \to \{\{x, y\} | x, y \in V_i$ such that $x \neq y\}$. For construction of the grpahs, we can drop the subscript on P_i, and take the placebo as a reference treatment. This is done under the assumption that the effect of placebo is constant across all trials. This is a strong assumption, and implications of this are discussed later. Under this assumption however, each V_i now contains a common element, P.

Let

$$V_{trts} = \bigcup_{i=1}^{N} V_i$$
$$E_{trials} = \bigcup_{i=1}^{N} E_i.$$

The incidence function becomes

$$\varphi : E_{trials} \to \{\{x, y\} | x, y \in V_{trts} \text{ such that } x = P\}.$$

Then the ordered triple $G = (V_{trts}, E_{trials}, \varphi)$ is the network of evidence given by these two arm trials that forms the basis of a network meta analysis. This process expands to trials that compare more than two treatments by weighting the edges by the number of trials making that particular comparison.

3.2 Standard NMA Model

Let d_{ab} denote the relative effect of treatment b versus treatment a. Suppose we have summary outcomes y_{jk} of treatment k in study j. This summary outcome may be, for example, HRs, or RMST values. The standard NMA model is written as in Equation 3.1-Equation 3.2. In Equation 3.1, π_{Agg} is a suitable likelihood for the aggregate data, and θ_{jk} represents the expected summary outcome of treatment k in study j. The link function g serves to transform θ_{jk} onto the linear predictor scale. In

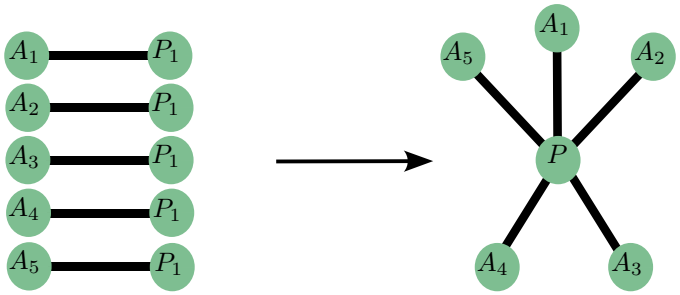

Figure 3.1: Visualisation of combining trials into a network of evidence

Equation 3.2, μ_j and δ_{jk} are study-specific intercepts and study-specific relative effect of treatment k versus the reference treatment.

$$y_{jk} \sim \pi_{Agg}(\theta_{jk}) \tag{3.1}$$
$$g(\theta_{jk}) = \mu_j + \delta_{jk} \tag{3.2}$$

There are two types of NMAs: fixed effect (FE) and relative effects (RE) NMAs. In an FE NMA, $\delta_{jk} = d_{1k} = d_k$, with $d_1 = 0$. In an RE NMA, $\delta_{jk} \sim N(d_k, \tau^2)$ for the heterogeneity variance τ^2, with $\delta_j 1 = d_1 = 0$.

The standard NMA model assumes that any effect modifiers, i.e covariates that alter the relative effect on a given scale of an active treatment versus control, are balanced across populations. While this can often be a valid assumption, methods such as Matching-Adjusted-Indirect-Comparisons (MAICs), Simulated Treatment Comparisons (STCs), and mlnmragg have saught to relax this assumption by using IPD from at least one of the studies in a population.

3.3 Multilevel Network Meta-Regression

The derivation in this chapter is based on the work of [Phillippo et al., 2024]. Under an NMA framewrok, there are J RCTs investigating a subset $K_j \subset K$ $(j = 1, \ldots, J)$ treatments. In this project, $|K_j| = 2 \; \forall \; j$. Depending on data avialbility, we may have individual-patient-data (IPD) for some studies, and only aggregate data for the remaining. This would be an ideal scenario, however it is not always the case.

Definition 3.3.1: General IPD Meta-Regression Model

Let y_{ijk} be the IPD outcome for individual $i = 1, \ldots, N_{kj}$ in study j recieving treatment $k \in K_j$ given the likelihood distribution $\pi_{Ind}(\theta_{ijk})$.

$$\begin{aligned} y_{ijk} &\sim \pi_{Ind}(\theta_{ijk}) \\ g(\theta_{ijk}) &= \mu_j + x_{ijk}^T(\beta_1 + \beta_{2,k}) + \gamma_k \\ &= \eta_{jk}(x_{ijk}) \end{aligned}$$

Here, g links the likelihood parameter θ_{ijk} to $\eta_{jk}(x_i jk)$. The μ_j are study-specific intercepts, and β_1, $\beta_{2,k}$ are regression coefficients for prognostic and effect-modifying covariates respectively. Additionally, the γ_k are individual-level treatment effects. For the reference treatment, $\beta_{2,1} = \gamma_1 = 0$.

It is clear to see how the model in Definition 3.3 extends Equations 3.1-3.2. Let $\xi = \{\mu_j, \beta_1, \beta_{2,k}, \gamma_k | \forall \; j, k\}$ be the parameter space. Using ξ, we can denote the individual conditional likelihood function by $L^{\text{Con}}_{ijk|x}(\xi; y_{ijk}, x_{ijk})$. The form of $L^{\text{Con}}_{ijk|x}$ depends on π_{Ind}, g, and η_{jk}.

By integrating the individual conditional likelihood ovr the joint covariate distributoin f_{jk}, we obtain Equation 3.3, the individual marginal likelihood function.

$$L^{\text{Mar}}_{ijk}(\xi; y_{ijk}) = \int_{\mathfrak{X}} L^{\text{Con}}_{ijk|x}(\xi; y_{ijk}, x) f_{jk}(x) dx \tag{3.3}$$

It is clear from Equation 3.3 that L^{Mar}_{ijk} does not depend on x. Let i be an individual, on treatment k in study j with outcome y_{ijk}. If we don't know the covariate vector for i, x_{ijk}, but we do know f_{jk}, then we know that the likelihood contribution of i is given by Equation 3.3.

It is likeliy that a closed-form of Equation 3.3 does not exist. We can therefore take a set of N integration points, $\hat{x}$ from f_{jk}, giving Equation 3.4.

$$L^{\text{Mar}}_{ijk}(\xi; y_{ijk}) \approx \frac{1}{N} \sum_{\hat{x}} L^{\text{Con}}_{ijk|x}(\xi; y_{ijk}, x) \tag{3.4}$$

Consider a summary outcome $y_{\hat{jk}}$ aggregated over all individuals on treatment k in study j. Each individual i in on treatment k in study i contributes to the aggregate likelihood. Let y_{ijk} denote the observed value of this summary measure for individual i. The aggregate maginal likelihood function is then the product of these y_ijk up to a normalising constant, as in Equation 3.5.

$$L^{\text{Mar}}_{\hat{jk}} \propto \prod_{i=1}^{N_{jk}} L^{\text{Mar}}_{ijk}(\xi; y_{ijk}) \tag{3.5}$$

The full, general, ML-NMR model is then given by

Definition 3.3.2: General ML-NMR Model

Individual:

$$L^{\text{Con}}_{ijk|x}(\xi; y_{ijk}, x_{ijk}) = \pi_{\text{Ind}}(y_{ijk}|\theta_{ijk}) \tag{3.6}$$

$$g(\theta_{ijk}) = \eta_{jk}(x_{ijk}) = \mu_j + x^T_{ijk}(\beta_1 + \beta_{2,k}) + \gamma_k \tag{3.7}$$

Aggregate:

$$L^{\text{Mar}}_{ijk}(\xi; y_{ijk}) = \int_{\mathfrak{X}} L^{\text{Con}}_{ijk|x}(\xi; y_{ijk}, x) f_{jk}(x) dx \tag{3.8}$$

$$L^{\text{Mar}}_{\hat{jk}} \propto \prod_{i=1}^{N_{jk}} L^{\text{Mar}}_{ijk}(\xi; y_{ijk}) \tag{3.9}$$

Under a Bayesian framework, priors are place on μ_j, β_1, $\beta_{2,l}$, and γ_k.

3.4 Survival ML-NMR

Each study reports a pair $y_{ijk} = \{t_{ijk}, c_{ijk}\}$ consisting of outcome times t_{ijk} and censoring indicators c_{ijk}, either from IPD or reconstructed IPD. For IPD studies, the covariates x_{ijk} will naturaly be avialble, but for aggregate studies (those for which pseudo-IPD has been re-created), only the joint covariate distribution of covariates at baseline, denoted f_{jk}.
The censoring indicator for patient i in study j on treatment k is defined as in Equation 2.1. In practice, the censoring indicator can be the other way round- i.e 1 denotes censoring instead of an event, as in Equation 2.1. Therefore, when cleaning data for this dissertation, manual reversing of the censoring indicator was conducted to ensure all data used the same definition.

Let $S_{jk}(t|\mathbf{x})$ and $h_{jk}(t|x)$ be the survival and hazard functions conditional on the covariates x. Then the individual conditional likelihood contributions for each time t_{ijk} in the IPD studies are given by

$$L^{Con}_{ijk|x}(\zeta; t_{ijk}, c_{ijk}, x_{ijk}) = S_{jk}(t_{ijk}|x_{ijk}) h_{jk}(t_{ijk}|x_{ijk})^{c_{ijk}} \tag{3.10}$$

The forms of S and h depend on the specific survival models chosen. Starting from Equation 3.3, the marginal likelihood equations for each event/censoring time in the aggregate data studies can be derived. Substituting $y_{ijk} = \{t_{ijk}, c_{ijk}\}$

$$L_{ijk}^{\text{Mar}}(\xi; y_{ijk}) = \int_{\mathfrak{X}} L_{ijk|x}^{\text{Con}}(\xi; y_{ijk}, x) f_{jk}(x) dx \tag{3.11}$$

$$L_{ijk}^{\text{Mar}}(\xi; t_{ijk}, c_{ijk}) = \int_{\mathfrak{X}} L_{ijk|x}^{\text{Con}}(\xi; t_{ijk}, c_{ijk}, x) f_j k(x) dx \tag{3.12}$$

$$= \int_{\mathfrak{X}} S_{jk}(t_{ijk}|x_{ijk}) h_{jk}(t_{ijk}|x_{ijk})^{c_{ijk}} f_{jk}(x) dx \tag{3.13}$$

As with Equation 3.4, Equation 3.13 can be evalueated with quasi-Monte Carlo integration to obtain Equation 3.14.

$$L_{ijk}^{\text{Mar}}(\xi; t_{ijk}, c_{ijk}) = \frac{1}{N} \sum_{\hat{x}} S_{jk}(t_{ijk}|\hat{x}) h_{jk}(t_{ijk}|\hat{x})^{c_{ijk}} \tag{3.14}$$

Quasi-Monte-Carlo (QMC) is a method for efficient numerical integration. Equation 3.15 gives the form of a Mote-Carlo integration problem for a real integrable function f over the s-dimensional hypercube $I^s = [0,1]^s$. QMC differs from standard Monte-Carlo (MC) integration in the way the x_i are chosen for which f is evaluated at.

$$\int_{[0,1]^S} f(u) du \approx \frac{1}{N} \sum_{i=1}^{N} f(x_i) \tag{3.15}$$

Regular MC integration uses random numbers[1], whereas QMC uses a low-discrepencey sequence, which is a sequence such that for all N, the set $P = \{x_1, \ldots, x_N\}$ has low discrepency, as definted in Definition 3.4.

Definition 3.4.1: Low-Discrepency Sequence

Consider the set $P = \{x_1, \ldots, x_N\}$. The **discrepency** of P, $D_N(P)$ is defined as in Equation 3.16.

$$D_N(P) = \sup_{B \in J} \left| \frac{A(B;P)}{N} - \lambda_s(B) \right| \tag{3.16}$$

Here, $A(B;P)$ is the number of points in P that fall into B. λ_s is the s-dimension Lebasgue measure, and J is the set of s-dimensional intervals as in Equation 3.17, where $0 \leq a_i < b_i \leq 1$.

$$\prod_{i=1}^{s} [a_i, b_i) = \{x \in \mathbb{R}^s | a_i \leq x_i < b_i\} \tag{3.17}$$

In particular, `multinma` uses a Sobol sequence [Sobol', 1967] to sample $\hat{x_{jk}}$ from the covariate distribution f_{jk} [Phillippo et al., 2020]. For each covariate in the analysis, the Sobol sequence generates points in $I^s = [0,1]^s$ with a dimension for each covariate. The Smirnov transform (Definition 3.4) is then used to transform the points generated by the Sobol sequence to the required distribution.

Definition 3.4.2: Smirnov Transformation

Let $X \in \mathbb{R}$ be any random variable. Then the random variable $F_X^{-1}(U)$ has the same distribution as X. Here, F_X^{-1} is the generalised inverse of the cumulative distribution function F_X of X, as defined in Equation 3.18 for all $p \in [0,1]$. Further, $U \sim Uniform[0,1]$.

$$F^{-1}(p) = \inf\{x \in \mathbb{R} | F(x) \geq p\} \tag{3.18}$$

3.5 Population-average estimates

Recall d_{ab} is the relative effect of treatment b versus treatment a. Let $d_{ab(P)}$ be the population-average relative effect of b versus a in population P. $d_{ab(P)}$ can be calculated as in Equation 3.20.

[1] Strictly speaking, these are pseudo-random numbers when considering the implementation of this method.

$$d_{ab(P)} = \int_{\mathfrak{X}} (\eta_{(P)b}(x) - \eta_{(P)a}(x)) f_{(P)}(x) dx \tag{3.19}$$

$$= \gamma_b - \gamma_a + \bar{x}_{(P)}^T (\beta_{2,b} - \beta_{2,a}) \tag{3.20}$$

For this dissertation, The estimates considered for results were the RMST and median OS. The survival and hazard functions were also analysed but were not primary outcomes for the NMA.

3.5.1 Survival function

Let $\bar{S}_{(P)k}(t)$ be the population-average marginal survival probability of treatmentt k in population P at time t. $\bar{S}_{(P)k}(t)$ is obtained by integrating $S_{(P)k}(t|x)$ over $f_{(P)}(x)$, as in Equation 3.21.

$$\bar{S}_{(P)k}(t) = \int_{\mathfrak{X}} S_{(P)k}(t|x) f_{(P)}(x) dx \tag{3.21}$$

3.5.2 Hazard function

The population-average marginal hazard function and cumulative hazard function are given by Equation 3.22, and Equation 3.23, respectively.

$$\bar{h}_{(P)k}(t) = \frac{\int_{\mathfrak{X}} S_{(P)k}(t|x) h_{(P)k}(t|x) f_{(P)k}(x)}{\bar{S}_{(P)k}(t)} \tag{3.22}$$

$$\bar{H}(P)k(t) = -\log(\bar{S}_{(P)k}(t)) \tag{3.23}$$

3.5.3 RMST

Let x be some time horizon. The population-average marginal RMST follows from Definition 2.5.2.

$$RMST_{(P)k}(x) = \int_0^x \bar{S}_{(P)k}(t) dt. \tag{3.24}$$

3.5.4 Median OS

In general, the α% quantile is obtained by solving

$$\bar{S}_{(P)k}(t) = 1 - \alpha. \tag{3.25}$$

Since the median OS is a special case of this with $\alpha = \frac{1}{2}$, the population-average marginal median OS, m is estimated by Equation 3.26.

$$\bar{S}_{(P)k}(m) = \frac{1}{2} \tag{3.26}$$

3.6 Model Selection and Convergence

Model selection was based primarily on the Leave-One-Out Information Criterion (LOOIC) score (Defintion A.1). The LOOIC was calculated using the `LOO` R package [Vehtari et al., 2024]. The model with the lowest LOOIC score was selected as the best fitting model. The Deviation Information Criterion (DIC) score (Definition A.1) was used a secondary selection criterion. Again, models with lower DIC indicated better fit.

CHAPTER

FOUR

INCLUDED STUDIES

Table 4.1 presents the studies used in this NMA. In total, there were seven studies comparing GEM with one of six combination therapies. The studies were comparable in terms of median age and proportion male. The [Cunningham et al., 2009] study, compared GEM and GEM-CAP. The [Goldstein et al., 2015] study compared GEM and GEM-NAB. The [Gonçalves et al., 2012] study compared GEM and GEM-SOR. The [Kindler et al., 2011] and [Spano et al., 2008] studies compared GEM and GEM-AXI. The [Oettle et al., 2005] study compared GEM and GEM-PEM. The [Rocha Lima et al., 2004] study comapred GEM and GEM-IRI. All studies except Spano were phase III trials, however Spano was included as the OS data was quite mature. The [Conroy et al., 2011] study was the only study to not comapre GEM with a combination therapy; comparing GEM and FOLFIRINOX in a phase 2-3 trial.

Figure 4.1 and Figure 4.2 present forest plots of the median OS of the GEM arm in each study, and the comparator arm in each study, respectively. In particuar, the GEM arms in the Conroy, Cunningham, Oettle, Goldstein, and Rocha Lima studies were similar, while the Spano study was noted for having a large 95% CI. This was to be expected given there were only 34 patients in the GEM arm. For the comarator arms, there was more variation in the reported median OS. Large 95% CIs were present for the Spano and Goncalves studies, again due to the comparatively low number of patients in these studies. The efficacy of FOLFIRINOX iss clear from Figure 4.2. The median OS of FOLFIRINOX is above the upper bound of 95% credible interval of all compataors.

Study	Treatment	N	Medain Age	Proportion Male	Median OS (Months)
Conroy 2011	GEM	171	61.0	0.620	6.8 (5.5,7.6)
Conroy 2011	FOLFIRINOX	171	61.0	0.614	11.1 (9.0, 13.1)
Cunningham 2009	GEM	266	62.0	0.580	6.2 (5.5, 7.2)
Cunningham 2009	GEM-CAP	267	62.0	0.570	7.1 (6.2, 7.8)
Goldstein 2015	GEM	430	63.0	0.600	6.6 (6.0, 7.2)
Goldstein 2015	GEM-NAB	431	62.0	0.570	8.7 (7.9, 9.7)
Goncalves 2012	GEM	52	64.0	0.620	9.2 (7.7, 11.6)
Goncalves 2012	GEM-SOR	52	61.0	0.580	8.0 (6.0, 10.8)
Kindler 2011	GEM	316	61.0	0.590	8.3 (6.9, 10.3)
Kindler 2011	GEM-AXI	314	61.0	0.610	8.5 (6.9, 9.5)
Oettle 2005	GEM	282	63.0	0.535	6.3 (5.4, 6.9)
Oettle 2005	GEM-PEM	283	63.0	0.604	6.2 (5.4, 6.9)
Rocha Lima 2004	GEM	180	60.2	0533	6.6 (5.2, 7.8)
Rocha Lima 2004	GEM-IRI	180	63.2	0.572	6.3 (4.7, 7.5)
Spano 2008	GEM	34	61.0	0.470	5.6 (3.9, 8.8)
Spano 2008	GEM-AXI	69	65.0	0.510	6.9 (5.3, 10.1)

Table 4.1: Included studies with summary statistics

Figure 4.3 presents the KM curves for each treatment arm in each study. It was clear that the PHA would need to be relaxed when fitting NMA models from the shape of the curves in Figure 4.3, due to the amount of crossing. Most of the studies had mature data, however the Kindler and Concalves studies were noted for only dropping to an OS of aroun 0.25 at the end of the observation period.

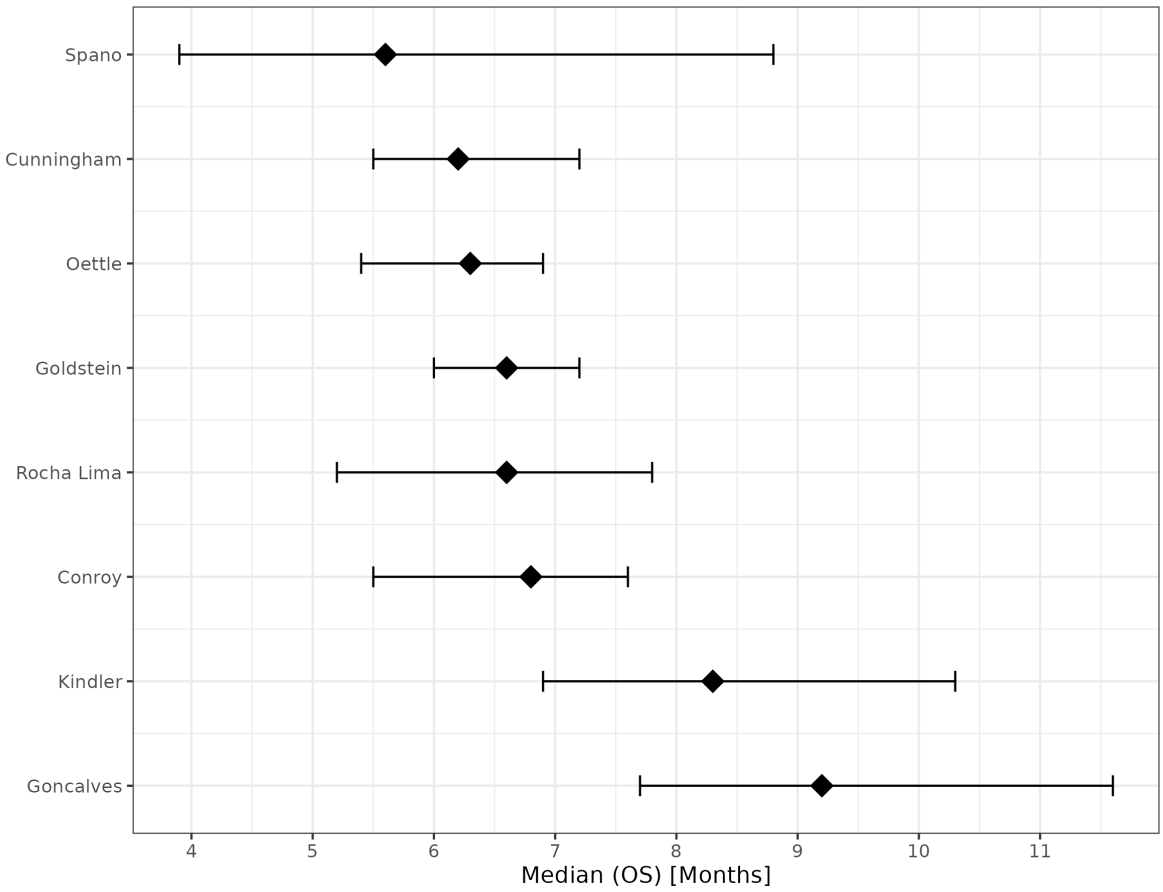

Figure 4.1: Forest plot for median OS of GEM in each study

4.1 Covariates

No IPD was available for any study in the network. For the ML-NMR model to fit, at least one study needs to have IPD. To deal with this, the sex of patients in the Golstein study was simulated based on the reported proportion of male patients in each treatment arm. For the GEM and NAB treatment arms, 60% and 57% of patients were assigned to be male, respectively.

4.2 Parametric Model Fitting

Figure 4.4 to Figure 4.11 present the extrapolation plots for each treatment arm in each study. The data was mature in all studies except the Kindler and Goncalves, which meant there was more variation in the survival models for treatments in these populations. The exponential model was noted for presenting poor visual fit in both treatments across both of these studies. For this reason, and due to the NMA not assuming the PHA held, the exponential model was left out of the NMA. Based on these plots, all other models were deemed to be appropriate for inclusion in the NMA.

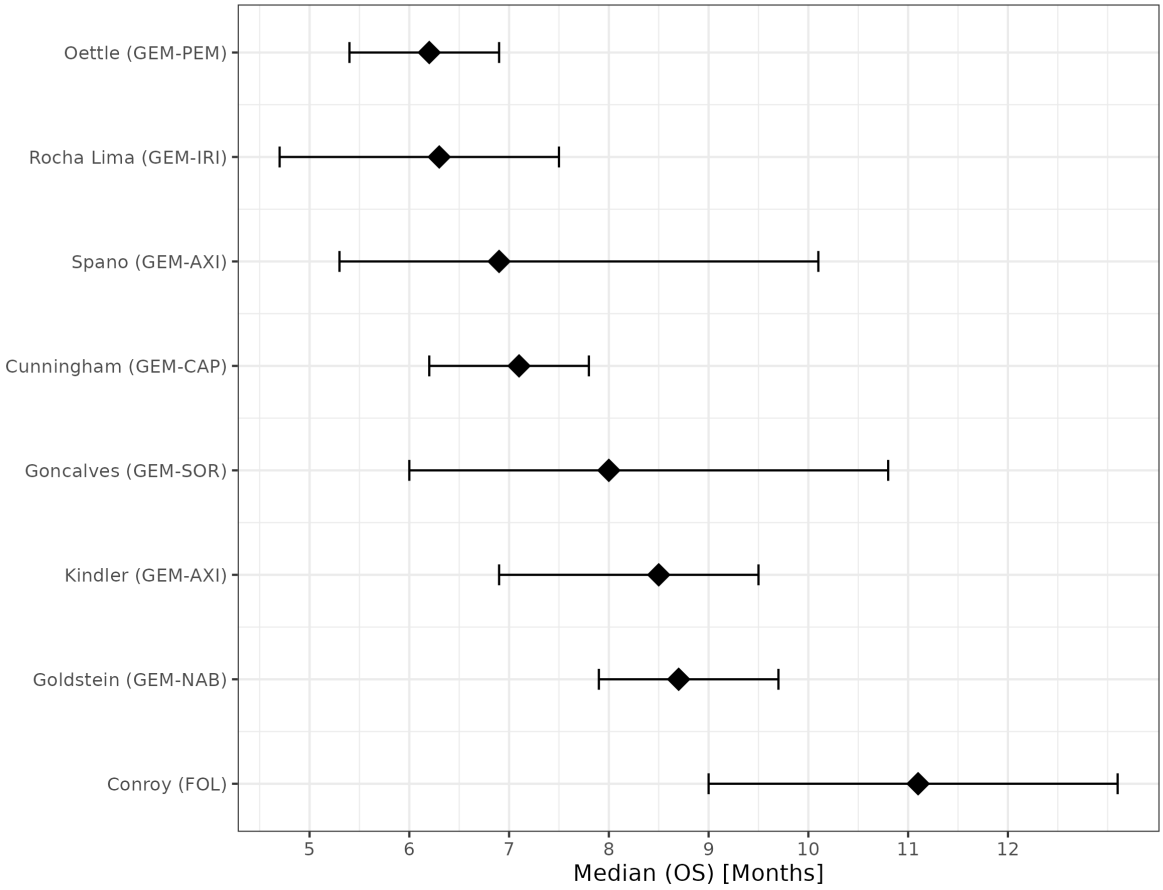

Figure 4.2: Forest plot for median OS of the comparator in each study

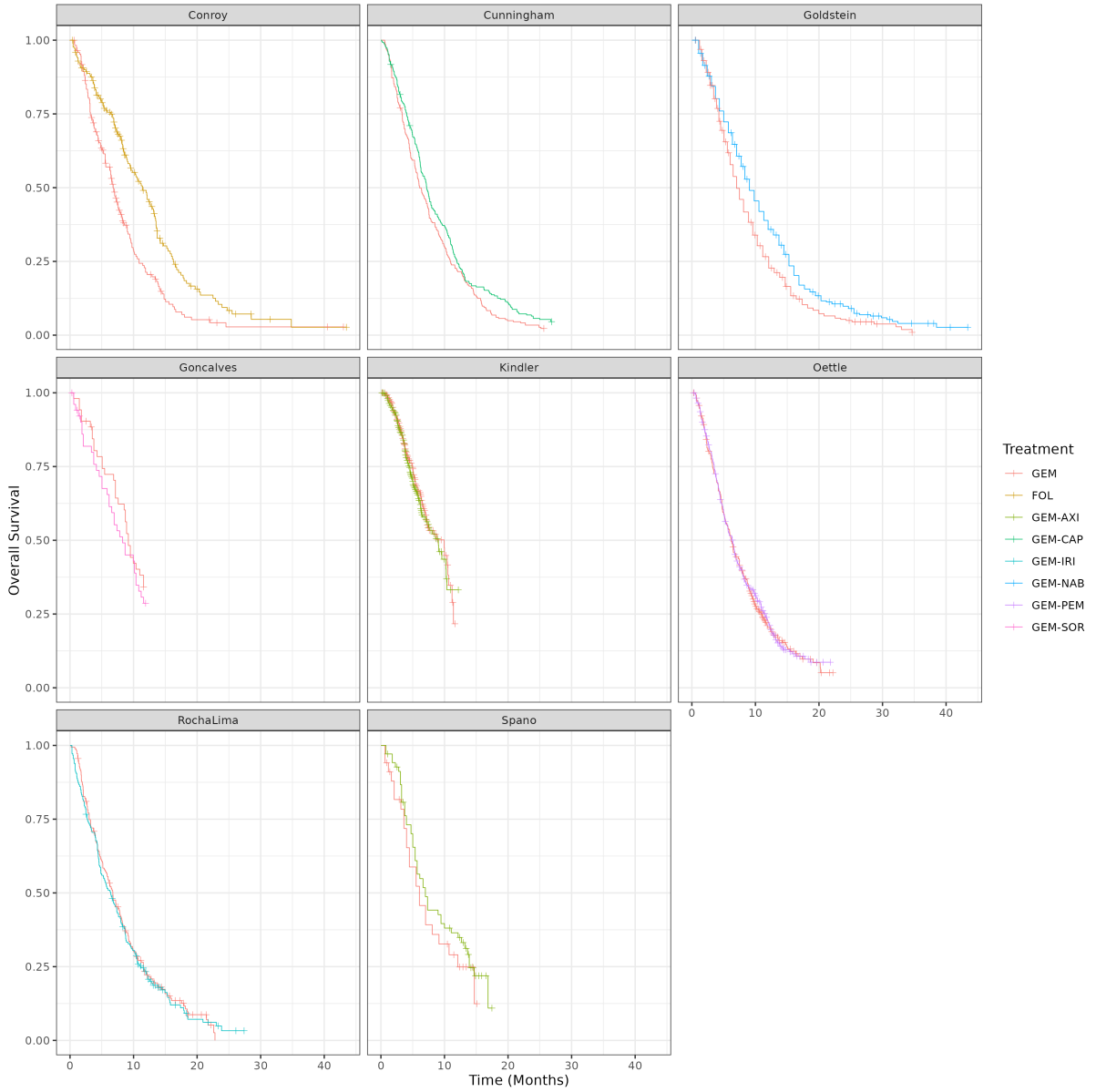

Figure 4.3: KM curves for each study

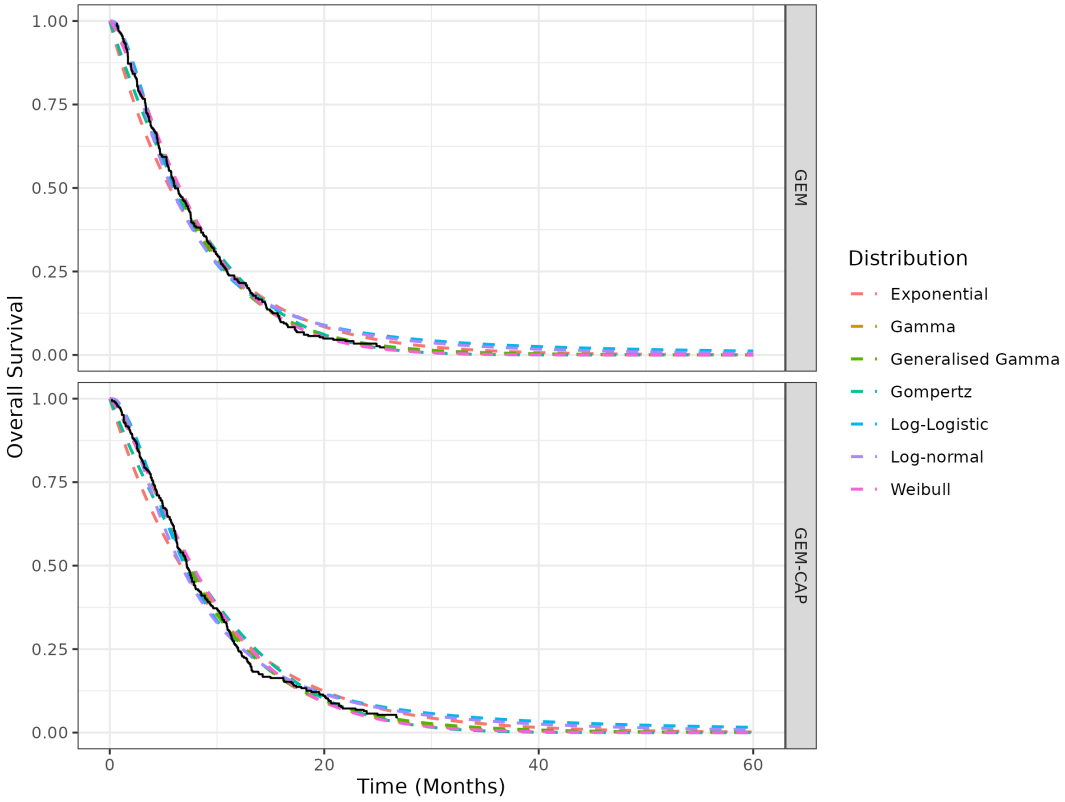

Figure 4.4: Cunningham (2009) parametric model extrapolations

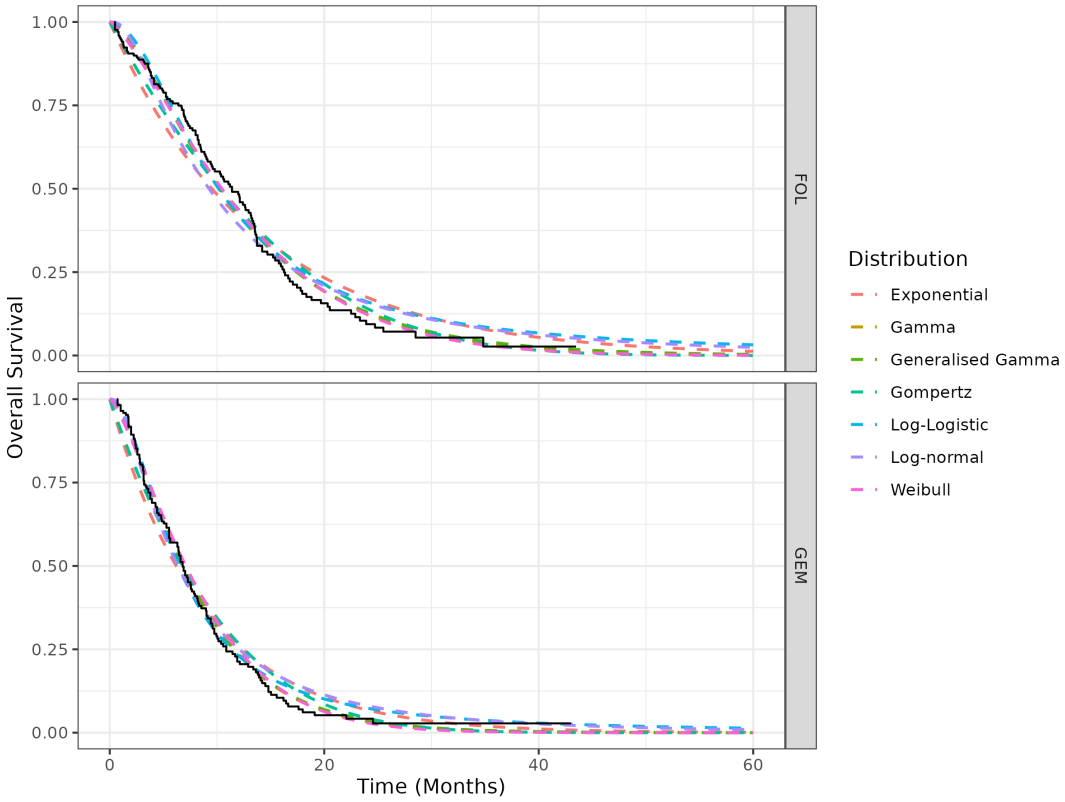

Figure 4.5: Conroy (2011) parametric model extrapolations

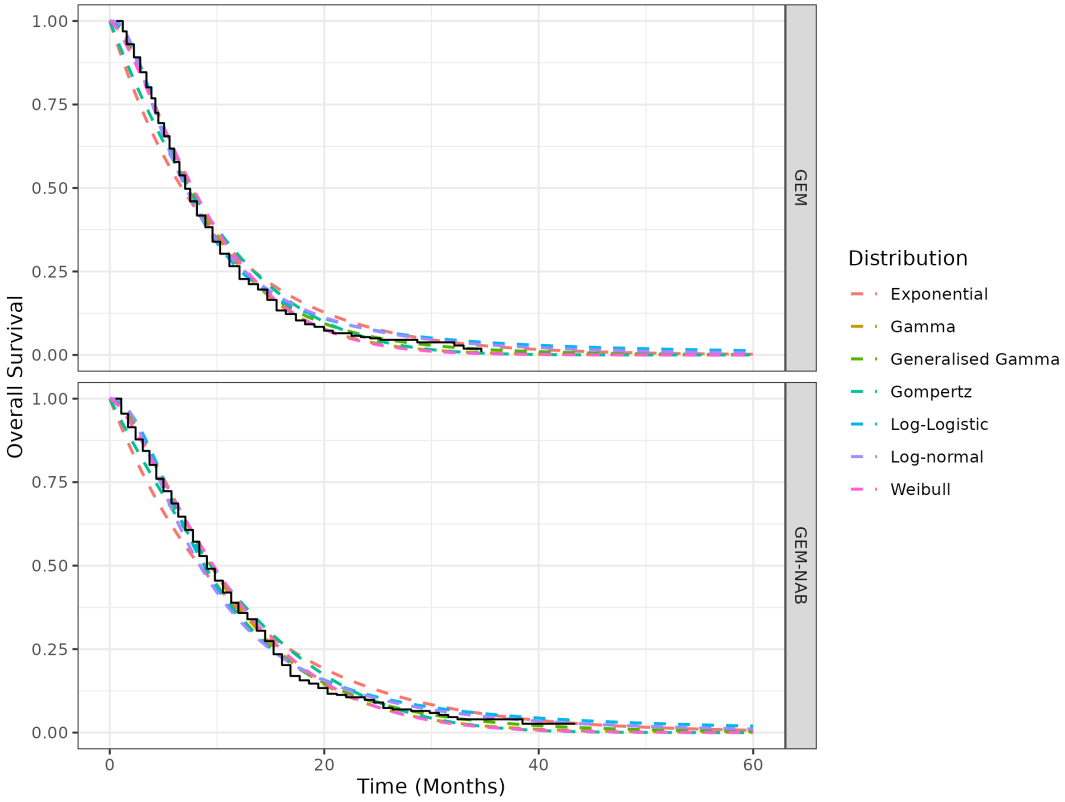

Figure 4.6: Goldstein (2015) parametric model extrapolations

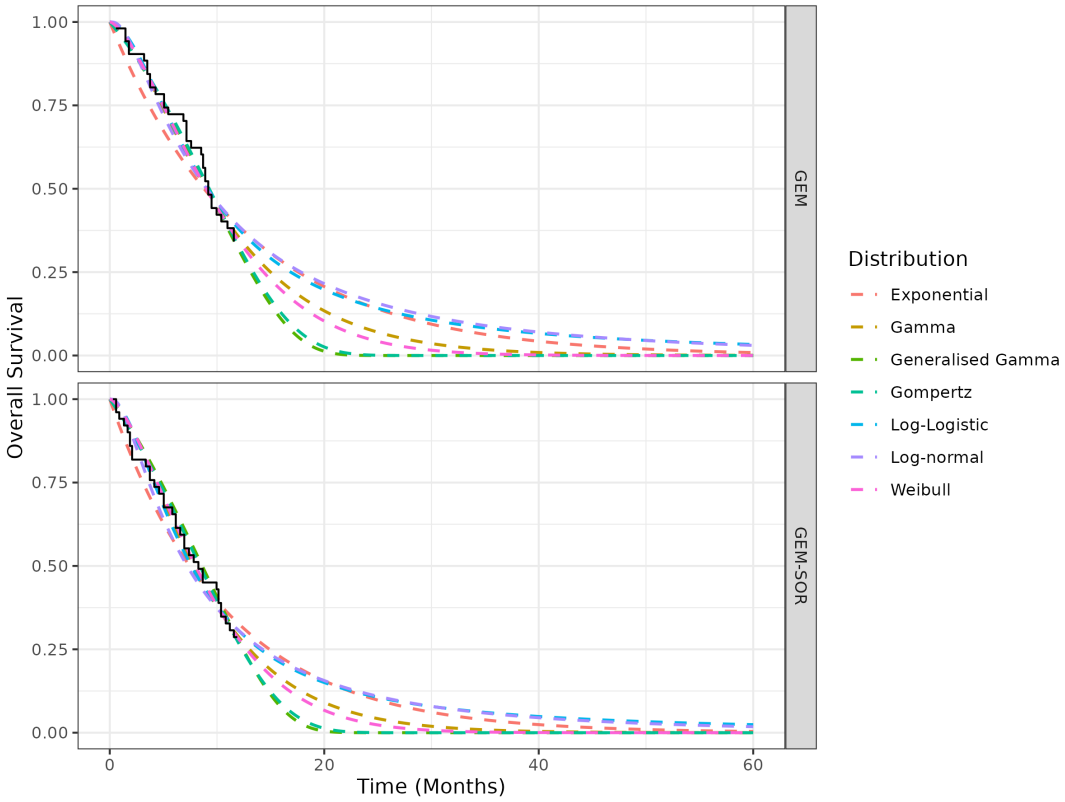

Figure 4.7: Goncalves (2012) parametric model extrapolations

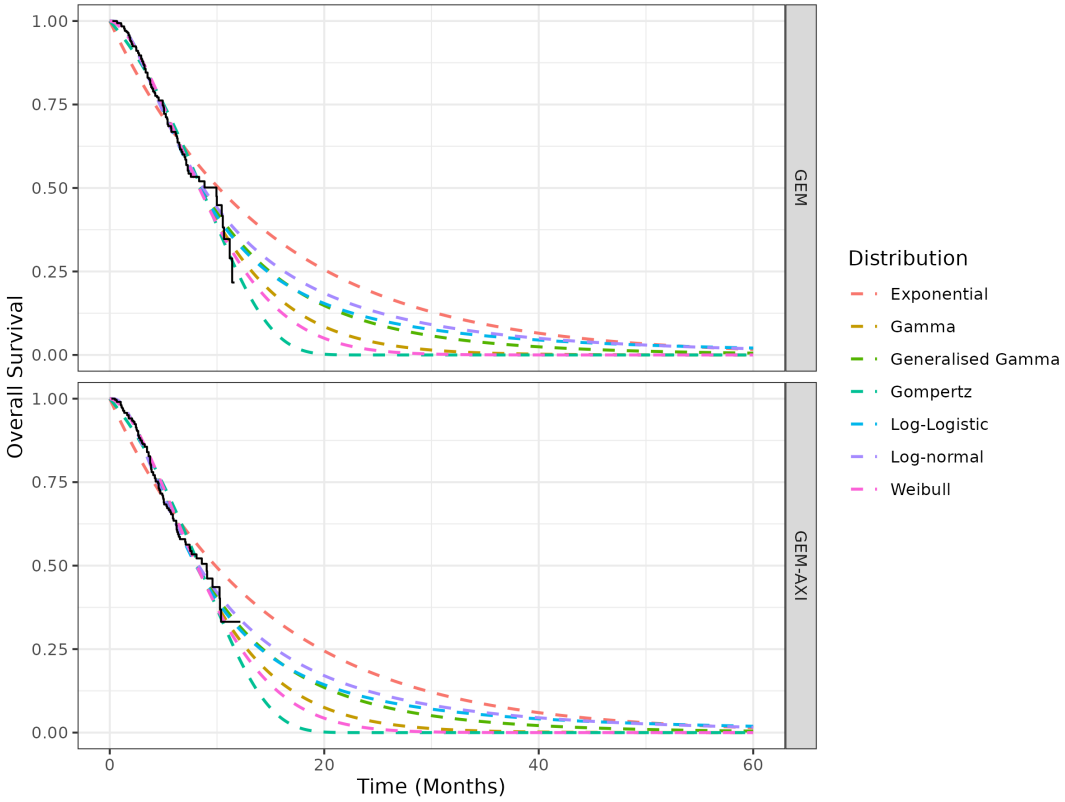

Figure 4.8: Kindler (2011) parametric model extrapolations

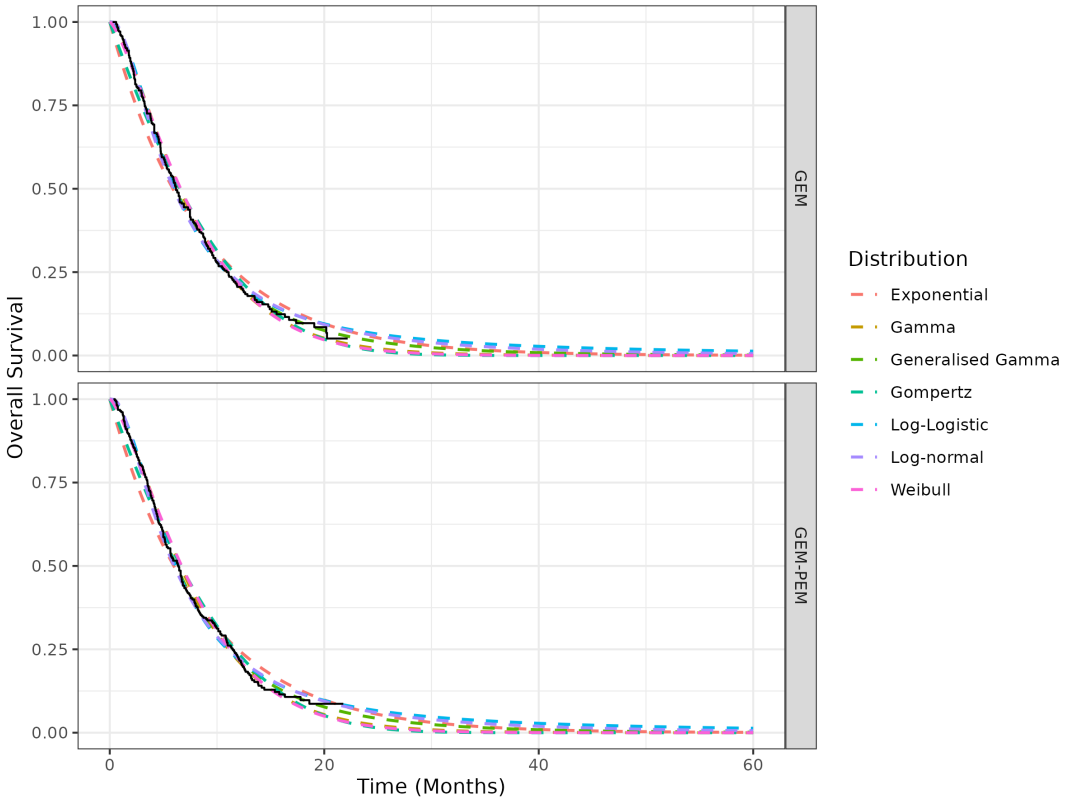

Figure 4.9: Oettle (2005) parametric model extrapolations

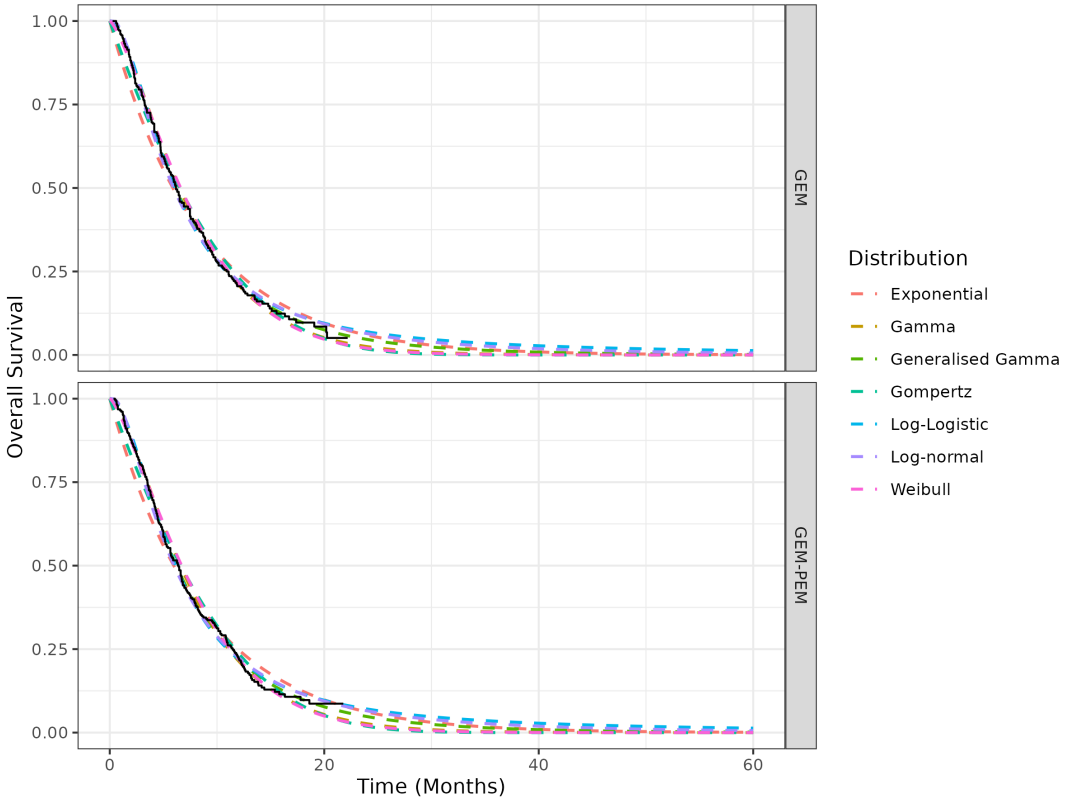

Figure 4.10: Rocha Lima (2004) parametric model extrapolations

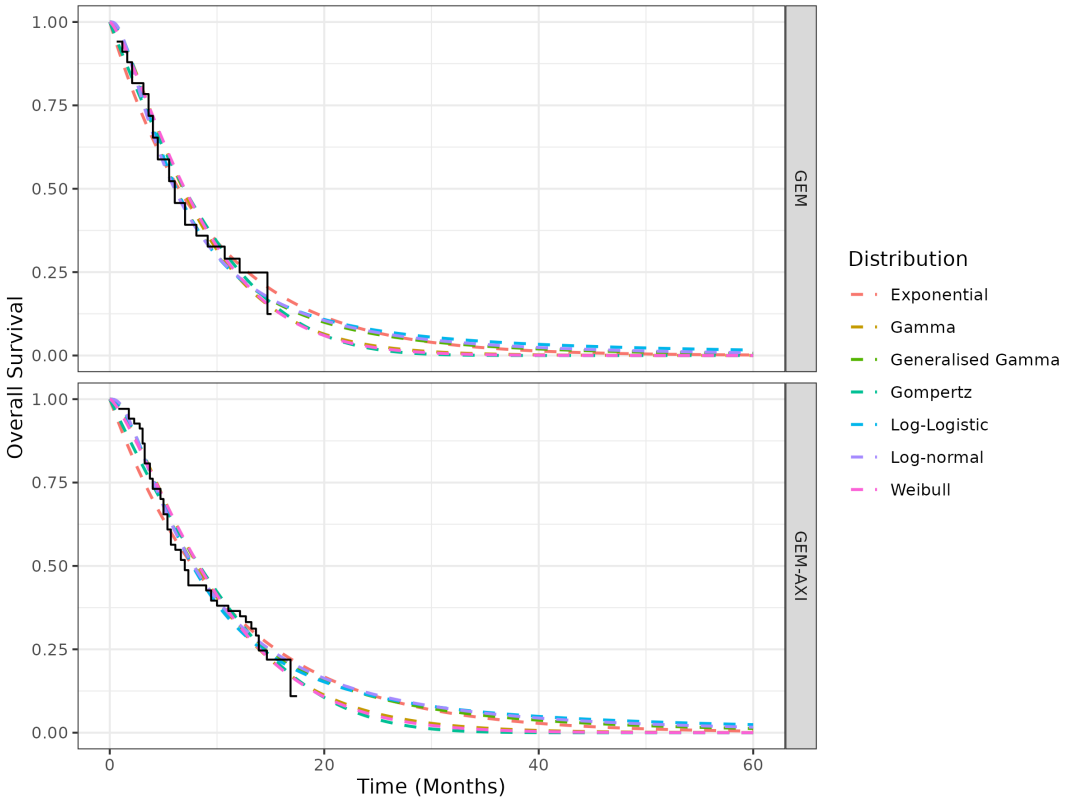

Figure 4.11: Spano (2008) parametric model extrapolations

CHAPTER

FIVE

NMA OF PANCREATIC CANCER TRIALS

5.1 Network of Evidence

Figure 5.1 presents the network of evidence for this NMA. There were two studies comparing GEM with GEM-AXI, but only one study for each other comparison. As indicated by the size of each node, GEM-SOR was the treatment with the lowest sample size, and GEM-NAB was the comparator with the highest. The GEM → GEM-NAB edge is a different colour due to being an IPD trial.

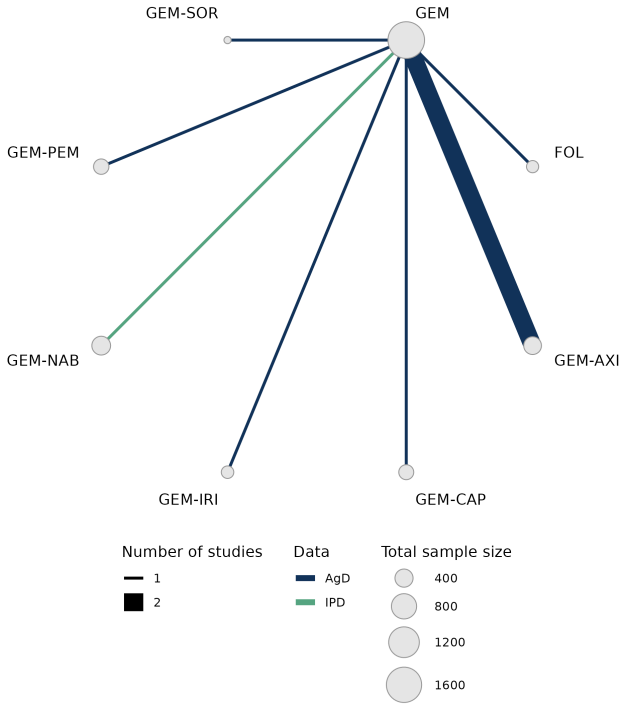

Figure 5.1: Network of evidence

5.2 Model Fitting and Selection

Both FE and RE models were fit using gamma, generlaised gamma, Gompertz, log-logistic, log-normal, and Weibull likelihoods. Vague priors were used for each model. Namely, the intercept prior was $N(0, 100)$, the treatment prior was $N(0, 10)$, the auxiliary prior was $hN(0, 5)$, and auxiliary regression prior was $N(0, 10)$. Here, hN denotes a *half-normal distribution*, as defined in Defintion A.2. For each model, sampling was done using 1000 iterations on four chains. The first 500 iterations were

warmup iterations.

Table 5.1 presents the selection statistics for each model. The fixed effect model was also deemed to be clinically appropriate due to homogeneity in the patient population. The FE gamma, FE and RE generalised gamma models failed to converge, meaning no DIC or LOOIC estimates could be obtained. The RE gamma and RE Gompertz models gave LOOIC and DIC scores so high that they were classified as Inf, indicating poor fit. The log-logistic, log-normal, and Weibull models gave similar LOOIC and DIC scores. In each case, the FE model had slightly lower LOOIC than the RE model for each likelihood. The FE log-normal model gave the lowest LOOIC and DIC score, indicating it was the best fitting model. The trace plot for this model is available in Appendix B, Figure B.1, and indicated good convergence due to consistent peaks and troughs across each treatment arm.

Likelihood	Effect	DIC	LOOIC
Gamma	Fixed	NA	NA
Gamma	Random	Inf	Inf
Gen Gamma	Fixed	NA	NA
Gen Gamma	Random	NA	NA
Gompertz	Fixed	15388.1764	15381.1184
Gompertz	Random	Inf	Inf
Log-logistic	Fixed	15176.9789	15176.0719
Log-logistic	Random	15175.2325	15176.2254
Log-normal	Fixed	15172.3036 ←	15173.0542 ←
Log-normal	Random	15172.7801	15173.3975
Weibull	Fixed	15200.20470	15200.1331
Weibull	Random	15199.29711	15200.6538

Table 5.1: Model selection statistics for each model

5.3 Results

Figure **??** and Figure **??** present the predicted survival and hazard of each treatment in study population, respectively. GEM-NAB and GEM-CAP had the highest OS and lowest hazard in each study population. The hazard curves for each study in each population followed a similar pattern, with peaks in the hazard just before ten months, before declining. GEM-SOR had the highest peak-hazard in each population, but crossed the GEM hazard curve in each population shortly after the peak, finishing with a lower hazard than GEM by the end of the observation period in each population. Further, in terms of hazard, the GEM-AXI and GEM-PEM curves were almost identical in each population.

Figure 5.4 presents the estimated RMST of each treatment in each population. The GEM-SOR arm had large credible intervals in each population due to the lower number of patients for which GEM-SOR data was available. Further, GEM-SOR and GEM-IRI had the lowest and second-lowest RMST estimates in each population, respectively. The RMST estimates for GEM, GEM-AXI, and GEM-PEM were similar in each population, as were GEM-CAP, and GEM-NAB. GEM-NAB and GEM-CAP had the highest and second-highest RMST estimates respectively in every study population.

Figure 5.5 presents the estimated median OS of each treatment in each population. The median OS estimates followest the same pattern as the RMST estimates. Namely, GEM-SOR and GEM-IRI gave the lowest and second-lowest estimates for median OS in each study population, GEM, GEM-AXI, and GEM-PEM gave similar estimates, and GEM-NAB and GEM-CAP gave the highest and second-highest estimates of median OS, respectively. The median OS estimates of GEM-NAB and GEM-CAP were further apart than the RMST estimates for the same two treatments.

Figure 5.2: OS of each treatment in each population

Figure 5.3: Hazards of each treatment in each population

Figure 5.4: RMST of each treatment in each population

5.4 Considerations for the ISPOR Good Practice Task Force

The Progessional Society for Health Economics and Outcomes Research (ISPOR) developed a 26-item questionnaire for assessing the credibility of an NMA [Jansen et al., 2014]. This NMA was performed inline with these practices. While each question is not answered individually here, the themes of the guidance, and how this NMA aligns with it, are discussed.

The first set of questions in the guidance concerns the evidence base. This NMA was performed on a fully-connected network of evidence (Figure 5.1), and included no poor-quality studies. Indeed, the study populations and trial characteristics were similar, meaning there was no systematic differences in treatment effect modifiers across the comparisons. The only aspect of this NMA that could be considered not to follow these guidelines was that not all available RCTs were included. The Greshem study, for example included 23 studies obtained by seaching several databases. This NMA was not conducted based on results of a systematic literature review or database search. Studies were selected for this NMA based on a brief literature search for trials comparing GEM with another therapy. Since all the KM curves from published papers had to be digitised, which takes a considerable amount of time, there was always to be a limit on how many studies could be included.

The second set of questions concerns the analysis. No naïve comparisons were made, which preserve within-study randomisation. As there were no cases of both direct and indirect evidence for any treatments, questions eight and nine were not deemed relevant. Question ten concerns imbalance of the distribution of effect modifiers, and how this was accounted for. Since the ML-NMR is a meta-regression model, this was directly accounted for. In terms of FE and RE models, both were fit, and the best fitting model selected in terms of robust selection statistics. Since the studies included in this NMA were not diverse in terms of methodology, FE models were deemed to be clinically appropriate. The guidance generally reccomends RE models, but it was deemed clinically appropriate to consider FE models in this case. Were more trials to be included, more consideration would need to be given to the similarity assessment to determine the suitability of FE models.

The third set of questions relates to the reporting quality. while all the studies used, and indeed the associated KM curves were presented, the actual TTE data was not presented. This is due to the form of the data, although it is available within `PCNMA` R package. Individual study results were provided in Figures 5.2- 5.5. Considerations did not have to be made for direct and indirect comparisons since there were no closed loops. Rankings were reported to address the main project aim, and pairwise comparisons were reported. In particular, the pairwise comparison between GEM-CAP and GEM-NAB was important to clarify the uncertainty mentioned by NICE in NG85. No consideration was given to the effect of important patient characteristics due to the homogeneity in the trial populations and further because of a lack of IPD available for this study. It is not sound for those involved in the study to assess the fairness of the conclusions and interpretation, but every attempt was made to perform this NMA with integrity and interpret the results in line with the evidence.

Figure 5.5: Median OS of each treatment in each population

CHAPTER
SIX

CONCLUSION AND DISCUSSION

6.1 Conclusion

6.2 Discussion and Further Work

The results obtained in this dissertation align with an NMA conducted by [Gresham et al., 2014], which also found GEM-NAB and GEM-CAP offered improvements in OS compared to GEM monotherapy. This NMA included fewer studies than that of [Gresham et al., 2014], so future work to expand the number of trials would be good to solidfy the place of GEM-NAB and GEM-CAP as the best treatment options for advanced/pancreatic cancer.

In 2017, NICE published TA476 [National Institute for Health and Care Excellence, 2017], which recommended GEM-NAB as an option for untreated metastatic pancratic cancer in adults only if other combination chemotherapies are unsuitable and the patient would otherwise recieve GEM monotherapy. The TA claimed that GEM-NAB was more effective in increasing than GEM monotherapy, similarly effctive to GEM-CAP, but was less effective than FOLFIRINOX. The comparison to GEM-CAP was stated as "uncertain".

Given the poor prognosis of pancreatic cancer, even a small improvement in median OS of a couple of months is of immense emotional value to patients and their families, and should not be overlooked for looking like small improvements out of context.

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Appendices

APPENDIX

A

SUPPLAMENTARY DEFINITIONS

This chapter contains several definitions used in the main project.

A.1 Model Selection

Definition A.1.1: Deviation Information Criterion (DIC)

Let y be the data on which a model was fitted. Further, let θ and $p(y|\theta)$ be the unknown paramaeters and likelihood function respectively. Let $E(\theta) = \bar{\theta}$ be the expectationi of θ. The deviance is defined as in Equation A.1.

$$D(\theta) = -2\log(p(y|\theta)) + C \tag{A.1}$$

Here, C is an unknown constant. C cancels in all model comparisons so is of no importance, but is included here for completeness. Further, the effective number of parameters is given by Equation A.2.

$$p_D = \bar{D(\theta)} - D(\bar{\theta}) \tag{A.2}$$

The **Deviation Information Criterion (DIC)** is then given by Equation A.3.

$$DIC = p_D + \bar{D(\theta)} \tag{A.3}$$

Definition A.1.2: Leave-One-Out Information Criterion

Begin by defining the expected log pointwise predictive density (elpd) as in Equation A.4 for data y,

$$elpd_{loo} = \sum_{i=1}^{n} \log(p(y_i|y_{-i}) \tag{A.4}$$

Here, $p(y_i|y_{-i})$ is the LOO predictive density given the data y with the i^{th} data point removed.

$$p(y_i|y_{-i}) = \int p(y_i|\theta)p(\theta|y_{-i})d\theta \tag{A.5}$$

Define the **Leave One Out Information Criterion (LOOIC)** score as in Equation A.6.

$$LOOIC = -2elpd_{loo} \tag{A.6}$$

A.2 Probability Distributions

Definition A.2.1: Half Normal Distribution

Let X be a normal distribution such that $X \sim N(0, \sigma^2)$. Then $Y = |X|$ follows a half-normal distribution. In particular, the half-normal distribution has PDF

$$f(x, \sigma) = \frac{\sqrt{2}}{\sigma\sqrt{\pi}} \exp\left(-\frac{x^2}{2\sigma^2}\right)$$

With $x \in [0, \infty)$, and $\sigma > 0$.

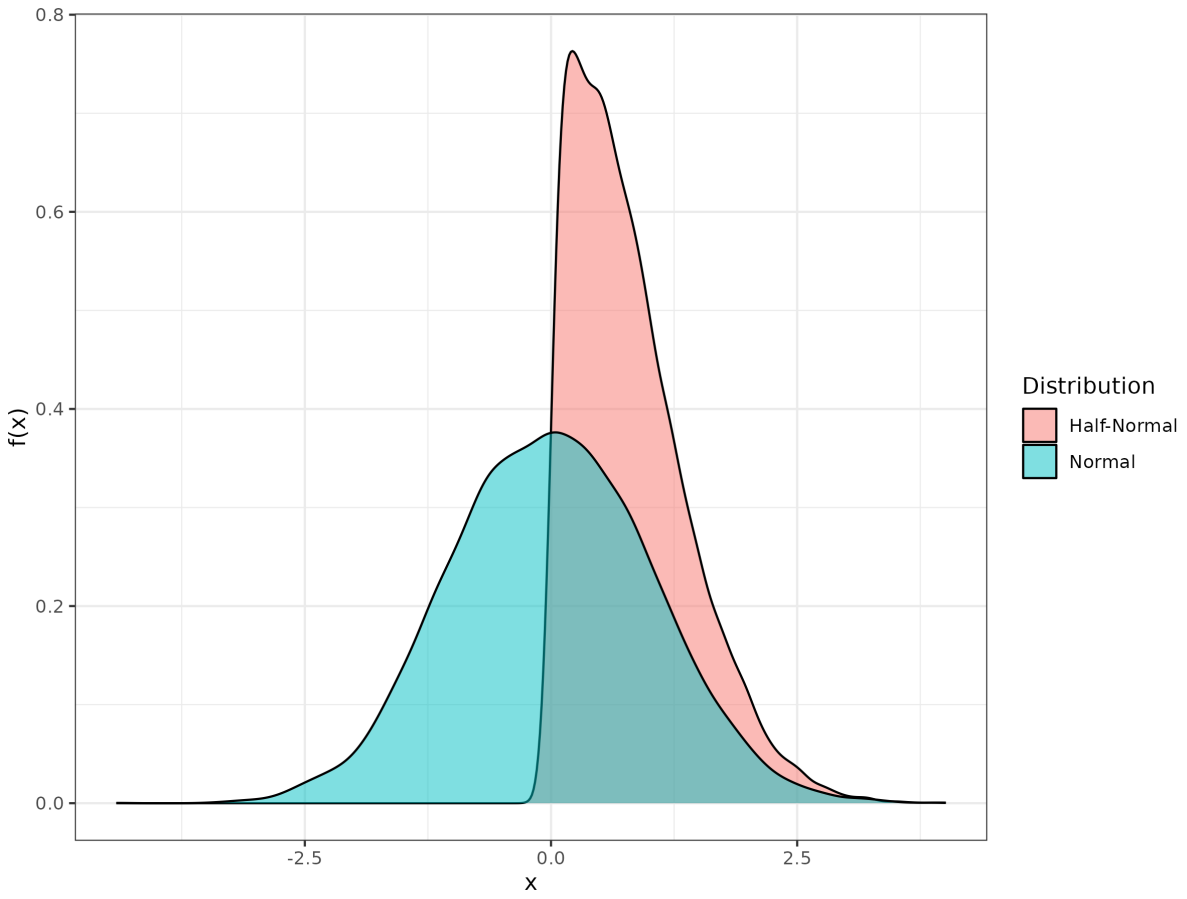

Figure A.1: Half-normal and normal distribution (taken from 100 samples of $N(0, 1)$)

APPENDIX
B

ADDITIONAL NMA RESULTS

This appendix presents some additional NMA results for the FE log-normal ML-NMR model.

B.1 Model Convergence

Figure B.1: Trace plot for the FE log-normal model ML-NMR

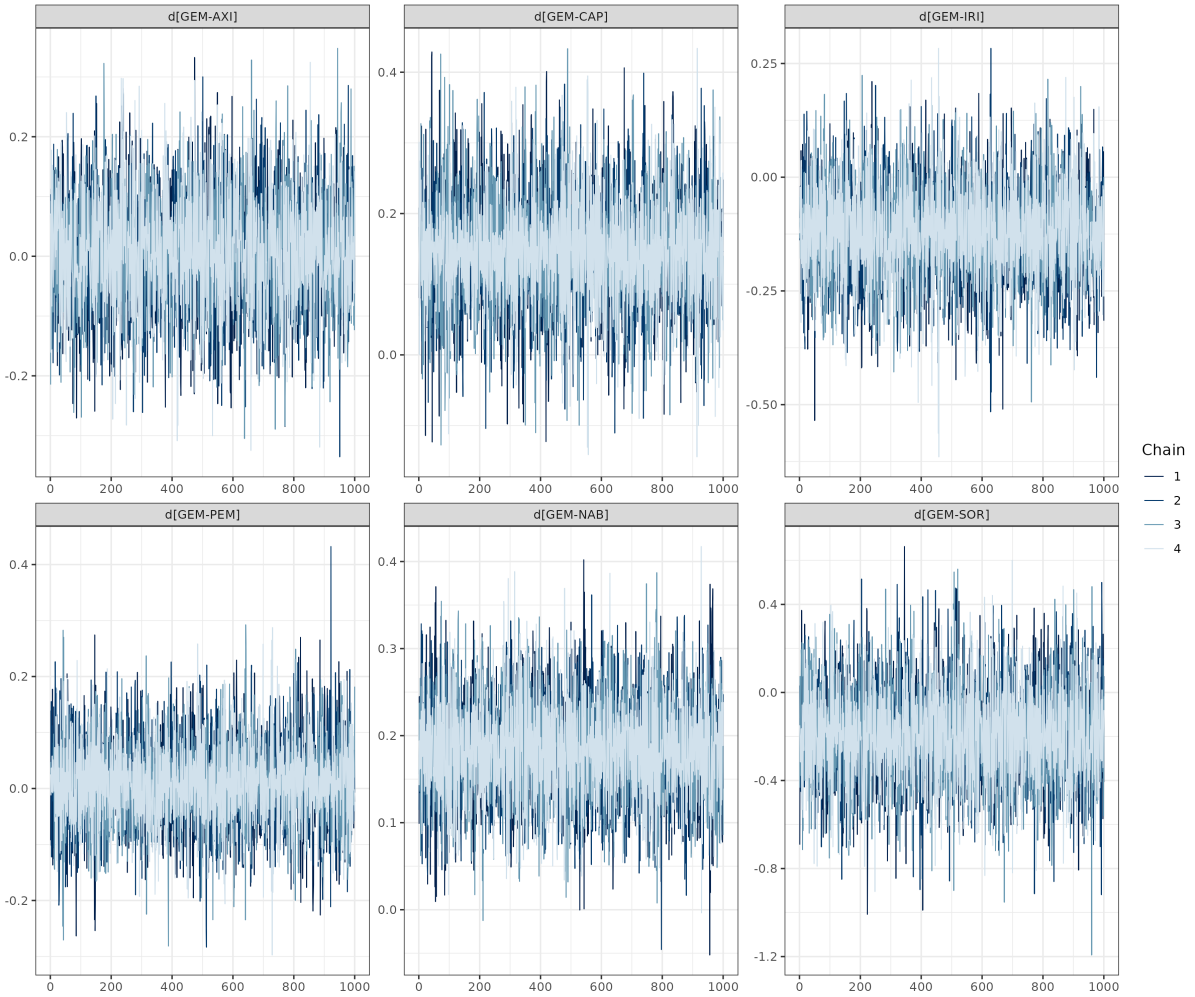

Figure B.2: Trace plot for the FE log-normal model ML-NMR

APPENDIX

C

THE PCNMA PACKAGE

To facilitiate the analysis conducted in this project, an `R` package was constructed. Performing the analysis in this way ensures easy reproducibility for further analysis in the future. The package is roughly split into two parts: survival code, and NMA code.

C.1 Survival Functions

The central function in the package for survival analysis is the *fit_distribution* function. This function is a wrapper around the *flexsurvreg* function from `flexsurv`. It is designed to take a list object containing the names of distributions and the associated argument to pass that distribution to `flexsurv`. For example,

```
distributions <- list("Weibull" = "weibull")
```

The reason for defining the distributions in this way is because the default `flexsurv` arguments look untidy by default when plotting. For example, the exponential distribution is passed as just "exp". The beauty of the *fit_distribution* function is that several distributions can be passed with a tidier name, which *flexsurvreg* never sees. This purely aesthetic change can be seen by comparing Figure C.1, and Figure C.2.

Any default `flexsurv` distribution will work with *fit_distribution*, it just needs a suitable name in the list object . The *fit_distribution* function itself doesn't actually fit any distributions. There is a sub-function, *.fit_distribution* which takes a single distribution as an argument, and some data on which to fit that distribution. This function takes the "weibull" element of the above list and passes it to flexsurv. The *fit_distribution* function maps *.fit_distribution* across the list of distributions, using the `purrr::map` function [Wickham and Henry, 2023]. After some data cleaning, the object that is returned by *fit_distribution* is given the class "fitted_distribution".

Several S3 methods exist for objects of class "fitted_distribution", these are *plot.fitted_distribution*, *summary.fitted_distribution*, and *coef.fitted_distribution*. These functions allow for plotting fitted models, accessing information such as AIC scores, and accessing the model coefficients respectively.

C.2 NMA Functions

The NMA part of the `PCNMA` package is a wrapper around `multinma`. In particluar, the *fit_model* function is a wrapper around *multinma::nma*.

Package 'PCNMA'

June 16, 2024

Type Package

Title Parametric and Non-Parametric Survival Models in Pancreatic Cancer Trials

Version 0.1

Date 2023-06-27

Author Matthew Knowles

Maintainer Matthew Knowles <mattknowles314@gmail.com>

Description This package contains the functions and data for my MSc Thesis, concerning the use of parametric and non-parametric models for survival in pancreatic cancer

License MIT + file LICENSE

RoxygenNote 7.2.3

Encoding UTF-8

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`.fit_distribution` *Fit a single survival distribution*

Description

This function is a wrapper on ‘flexsurv::flexsurvreg‘, and fits a single distribution to the specified data.

Usage

```
.fit_distribution(distribution, data, strata = "Treatment")
```

Arguments

`distribution`	A single distribution
`data`	An IPD dataset
`strata`	Strata for the RHS of the ‘survival::Surv‘ function

Value

A [flexsurv::flexsurvreg] object

`boxTid` *Box-Tidwell Transformation*

Description

Box-Tidwell Transformation

Usage

```
boxTid(x, p)
```

Arguments

`x`	A real value
`p`	The p-value to raise x to

coef.fitted_distribution *Coefficients of fitted models*

Description

Returns the model coefficients for a given survival model

Usage

```
## S3 method for class 'fitted_distribution'
coef(fit, studies, ...)
```

Arguments

fit	A [PCNMA::fitted_distribution] object
...	for S3 consistency

fit_distribution *Fit survival distributions to a dataset.*

Description

This function extends the 'PCNMA:::.fit_distribution' function, by fitting a given set of distributions to a TTE dataset.

Usage

```
fit_distribution(
  distributions = nice_parametric_dists,
  data,
  strata = "Treatment",
  maxT = 60
)
```

Arguments

distributions	A list of distributions
data	An IPD dataset
strata	Stratification variables
maxT	maximum time to calculate fitted values at

Value

A dataframe with fitted values

fit_model *Run an NMA*

Description

Run an NMA

Usage

```
fit_model(network, effects, seed = 1, chains = 4, llhood = "weibull")
```

Arguments

network	A [multinma::nma_data] object
llhood	Character string specifying a likelihood function
link	Character string specifying a link function (defaults to "log")
...	Other parameters to pass to [multinma::nma]

gen_network *Generate a network of evidence*

Description

Generate a network of evidence

Usage

```
gen_network(net_data, ref, covs)
```

Arguments

net_data	A dataset created by [PCNMA::gen_network_data]
ref	A character reference treatment

Value

A [mutlinma::nma_data] object

gen_network_data *Generate network data*

Description

Generate network data

Usage

```
gen_network_data(data, ref)
```

Arguments

data	A date extraction dataset
ref	A character reference treatment

Value

A dataframe

H *H-function for FPs*

Description

H-function for FPs

Usage

```
H(x, P, zeta, j)
```

Arguments

x	A real value
P	A vector of powers
zeta	A vector of zeta values
j	The index

hr *Hazard Ratio*

Description

Hazard Ratio

Usage

```
hr(TTE, strata = "1")
```

Arguments

TTE	A TTE dataframe
strata	A strata variable

km_estimates *Generate KM estimates*

Description

Generate Kaplan-Meier estimates from a TTE object. Uses ‘ggsurvfit::survfit2‘ to generate KM estimates. Only requires strata to be specified.

Usage

```
km_estimates(TTE, strata = "1")
```

Arguments

TTE	A TTE dataframe

Value

A [PCNMA::km_obj] object

phi *Fractional Polynomial Function*

Description

Fractional Polynomial Function

Usage

```
phi(x, m, P, zeta)
```

Arguments

x	A real valye
m	The degree of the polynomial
P	A vector of powers
zeta	A vector of zeta values

plot.fitted_distribution *Plot a fitted distributions object*

Description

Creates a plot for a result of 'PCNMA::fit_distribution'.

Usage

```
## S3 method for class 'fitted_distribution'
plot(
  fit,
  CI = FALSE,
  km = FALSE,
  km_alpha = 1,
  linewidth = 0.75,
  linetype = "dashed",
  theme = "bw",
  facet_by = "Treatment",
  ...
)
```

Arguments

fit	A ‘PCNMA::fitted_distribution‘ object
CI	Include a confidence interval?
km	Add the original KM curve?
...	For S3 consistency

---

plot.fitted_model *Plots for an NMA modelr*

Description

Plots for an NMA modelr

Usage

```
## S3 method for class 'fitted_model'
plot(
  model,
  type = "trace",
  pars = parsForStan,
  prob = 0.95,
  ordered = FALSE,
  xLims = NULL
)
```

Arguments

model	A [PCNMA::fitted_model] object
type	Type of plot to produce

---

plot.km_obj *Plot a KM curve*

Description

Plot a KM curve

Usage

```
## S3 method for class 'km_obj'
plot(
  fit,
  type = "survival",
  risk.table = TRUE,
  break.x.by = 5,
  xMax = 40,
  risktable.height = 0.3,
  ...
)
```

Arguments

fit	A 'PCNMA::km_obj' object
type	See 'ggsurvfit::ggsurvfit' for details.
risk.table	Add numbers at risk?
break.x.by	A numeric value for splitting x axis
xMax	The maximum time value to plot
risktable.height	The proportion of the figure to be taken up by the risk table
...	For S3 consistency

Value

A plotted km curve

---

plot_network *Plot a network of evidence*

Description

Plot a network of evidence

Usage

```
plot_network(network, ...)
```

Arguments

network	A network dataset

rmst *Hazard ratios of a fitted model*

Description

Hazard ratios of a fitted model

Usage

```
rmst(fit, x, ...)
```

Arguments

fit	A [PCNMA::fitted_distribution] object
x	Time to calculate RMST for
...	For S3 consistency

summary.fitted_distribution *Summary of a set of fitted models*

Description

Summary of a set of fitted models

Usage

```
## S3 method for class 'fitted_distribution'
summary(fit, AIC = FALSE, median = FALSE)
```

Arguments

fit	A [PCNMA::fitted_distribution] object.
AIC	Returns the AIC scores for a set of models
median	Returns a table of median estimates for a set of models

summary.fitted_model *Summary of an NMA model*

Description

Summary of an NMA model

Usage

```
## S3 method for class 'fitted_model'
summary(model, likelihood, effect)
```

Arguments

model	A [PCNMA::fitted_model] object

summary.hr_obj *Summarise a Hazard Ratio*

Description

Summarise a Hazard Ratio

Usage

```
## S3 method for class 'hr_obj'
summary(hr)
```

summary.km_obj *Summarise KM data*

Description

Summarise KM data

Usage

```
## S3 method for class 'km_obj'
summary(fit, ...)
```

Arguments

fit	A ‘PCNMA::km_obj‘ object

Value

A summary table of the KM data

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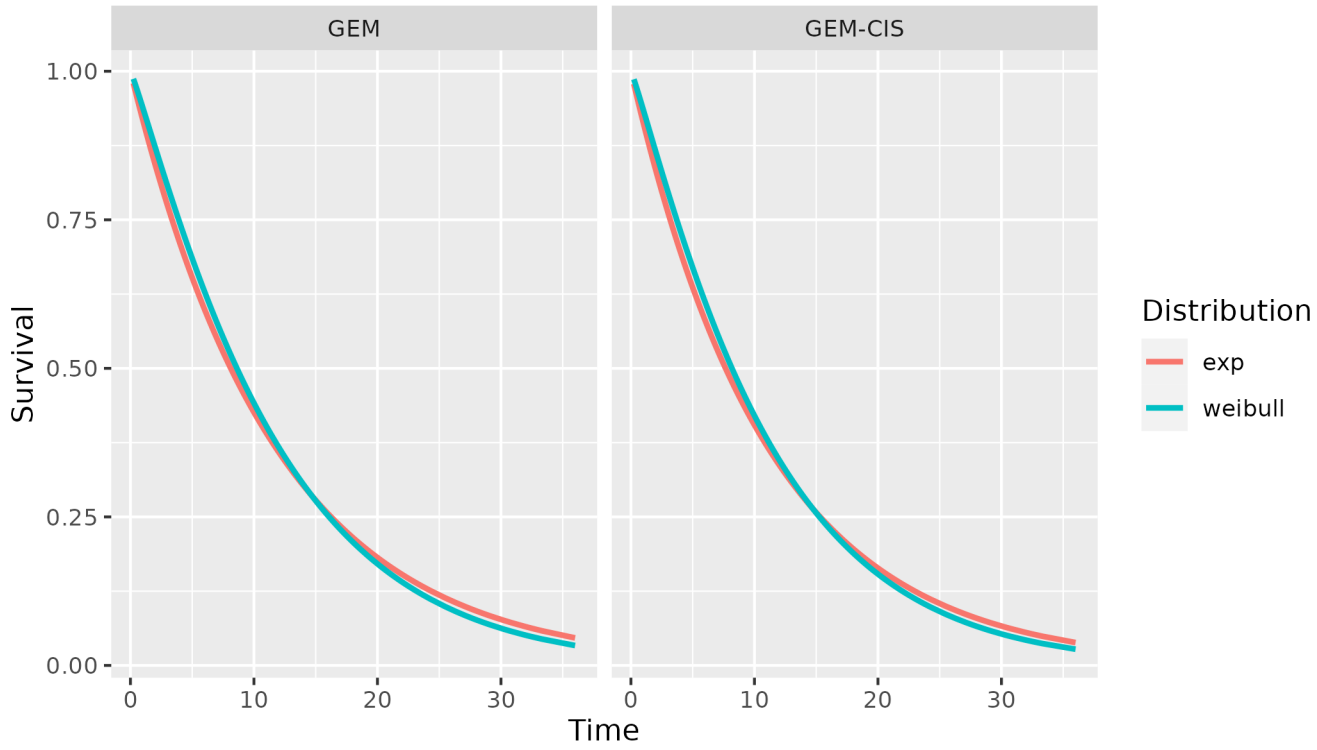

Figure C.1: Fitted Models as in Flexsurv

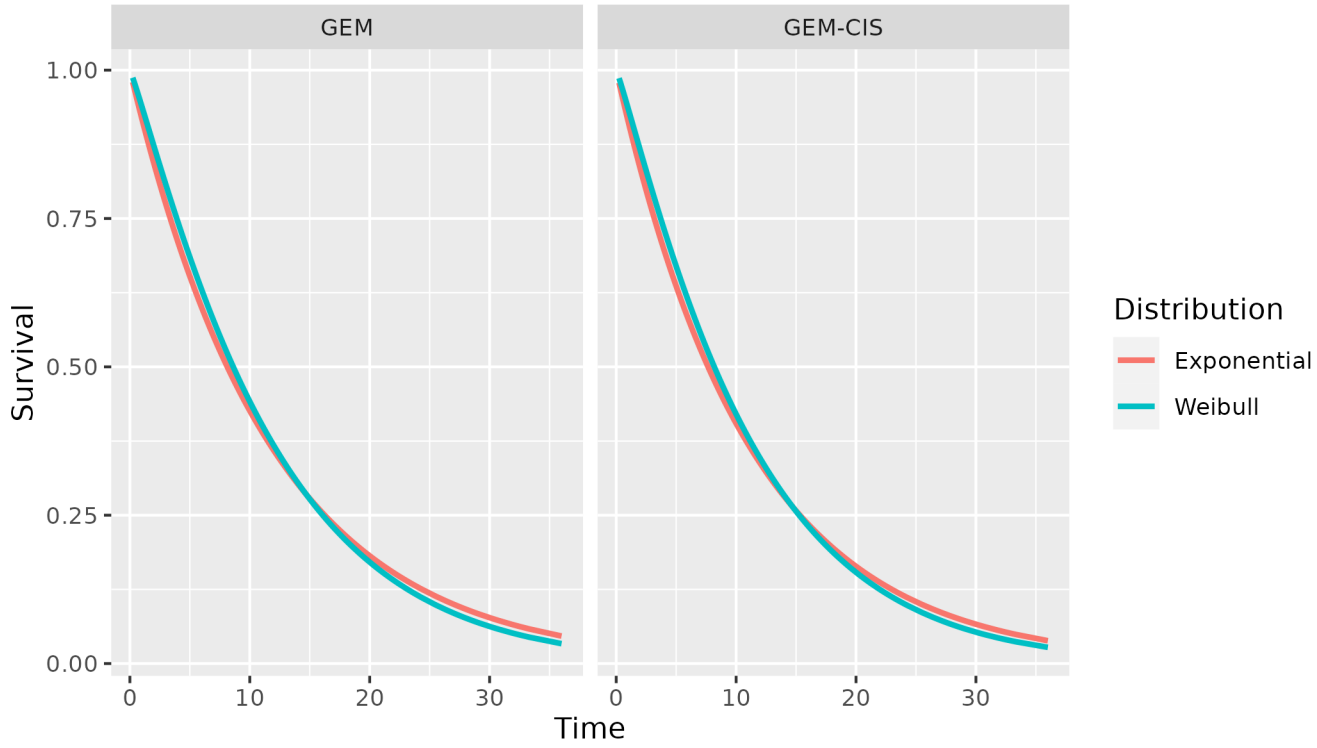

Figure C.2: Fitted Models with *fit_distribution*