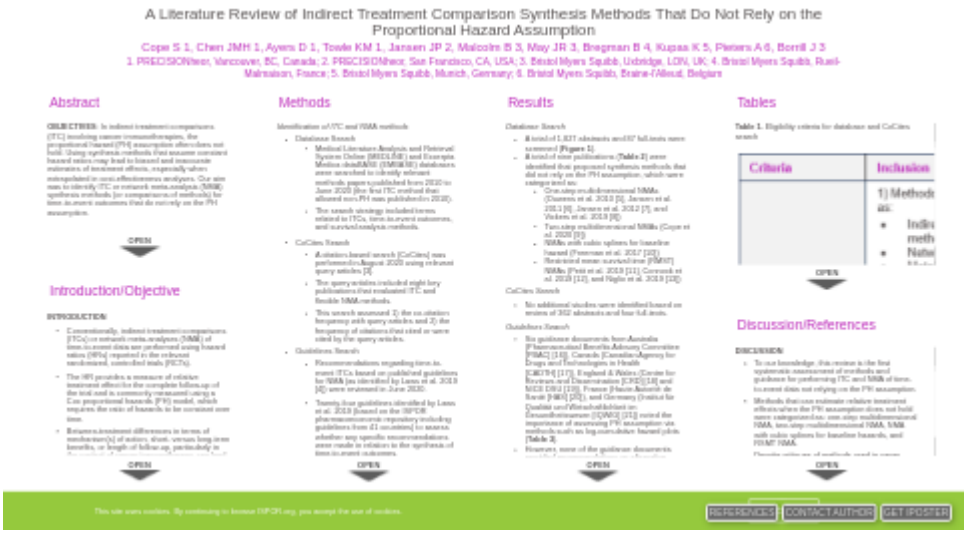
A Literature Review of Indirect Treatment Comparison Synthesis Methods That Do Not Rely on the Proportional Hazard Assumption



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ABSTRACT

OBJECTIVES: In indirect treatment comparisons (ITC) involving cancer immunotherapies, the proportional hazard (PH) assumption often does not hold. Using synthesis methods that assume constant hazard ratios may lead to biased and inaccurate estimates of treatment effects, especially when extrapolated in cost-effectiveness analyses. Our aim was to identify ITC or network meta-analysis (NMA) synthesis methods (or comparisons of methods) for time-to-event outcomes that do not rely on the PH assumption.

METHODS: A pre-defined search of EMBASE and MEDLINE from 2010 onwards was performed using terms related to ITCs, time-to-event outcomes, and survival methods. A search of citations and co-citations based on known methods papers was also performed using 'CoCites'. A search of recommendations regarding time-to-event analyses was also performed for ITC/NMA guidelines identified by Laws et al 2019. Relevant details were extracted from full-text publications, including the methodology to address non-PH and the mathematical notation of the model, the analyzed data source, the incorporation of between-study heterogeneity, and whether the analysis was implemented in a frequentist or Bayesian framework.

RESULTS: A total of nine publications were identified which were categorized as: 1) one-step multidimensional NMAs (Ouwens et al. 2010; Jansen 2011; Jansen et al. 2012; Vickers et al. 2019); 2) two-step multidimensional NMAs (Cope et al. 2020); 3) NMAs with cubic splines for baseline hazard (Freeman et al.2017); and 4) restricted mean survival NMAs (Petit et al. 2019; Niglio et al. 2019; Connock et al. 2019). No guidance was identified regarding appropriate synthesis models to adopt when confronted with this issue.

CONCLUSIONS: This study identified limited guidance on synthesis methods for NMA of survival data where the PH assumption is violated. Further evaluation of the methods that are available is warranted

INTRODUCTION/OBJECTIVE

INTRODUCTION

- Conventionally, indirect treatment comparisons (ITCs) or network meta-analyses (NMA) of time-to-event data are performed using hazard ratios (HRs) reported in the relevant randomized, controlled trials (RCTs).
- The HR provides a measure of relative treatment effect for the complete follow-up of the trial and is commonly measured using a Cox proportional hazards (PH) model, which requires the ratio of hazards to be constant over time.
- Between-treatment differences in terms of mechanism(s) of action, short- versus long-term benefits, or length of follow-up, particularly in the context of cancer immunotherapy, can lead to violation of the PH assumption.
- Ignoring variations in HRs over time can result in biased estimates of relative treatment effect. Moreover, when these estimates are incorporated into a cost-effectiveness analysis, fully extrapolated treatment effects can lead to substantial differences in expected qualty-adjusted life years (QALYs) per intervention [1,2].
- There is a need to identify and provide guidance regarding the alternative ITC/NMA methods available when the PH assumption is not valid across the trials.

OBJECTIVE

- The objective of this study was to systematically identify and summarize ITC or NMA evidence synthesis methods for time-to-event outcomes that do not rely on the PH assumption.

METHODS

Identification of ITC and NMA methods

- Database Search
  - Medical Literature Analysis and Retrieval System Online (MEDLINE) and Excerpta Medica dataBASE (EMBASE) databases were searched to identify relevant methods papers published from 2010 to June 2020 (the first ITC method that allowed non-PH was published in 2010).
  - The search strategy included terms related to ITCs, time-to-event outcomes, and survival analysis methods.
- CoCites Search
  - A citation-based search (CoCites) was performed in August 2020 using relevant query articles [3].
  - The query articles included eight key publications that evaluated ITC and flexible NMA methods.
  - This search assessed 1) the co-citation frequency with query articles and 2) the frequency of citations that cited or were cited by the query articles.
- Guidelines Search
  - Recommendations regarding time-to-event ITCs based on published guidelines for NMA (as identified by Laws et al. 2019 [4]) were reviewed in June 2020.
  - Twenty-four guidelines identified by Laws et al. 2019 (based on the ISPOR pharmacoeconomic repository including guidelines from 41 countries) to assess whether any specific recommendations were made in relation to the synthesis of time-to-event outcomes.
  - Additionally, the National Institute for Clinical Excellence (NICE) Decision Support Unit (DSU) website was searched for relevant guidance.

Methods selection and data extraction

- Pre-defined study eligibility criteria were used to guide the title/abstract and full-text selection (**Table 1**).
- The following information was extracted for included studies: summary of the method description, how the issue of non-PH was addressed, data used, incorporation of between-study heterogeneity, standardized mathematical notation of the model, and implementation in a frequentist or Bayesian framework.

RESULTS

Database Search

- A total of 1,827 abstracts and 87 full-texts were screened (**Figure 1**).
- A total of nine publications (**Table 2**) were identified that proposed synthesis methods that did not rely on the PH assumption, which were categorized as:
  - One-step multidimensional NMAs (Ouwens et al. 2010 [5], Jansen et al. 2011 [6], Jansen et al. 2012 [7], and Vickers et al. 2019 [8])
  - Two-step multidimensional NMAs (Cope et al. 2020 [9])
  - NMAs with cubic splines for baseline hazard (Freeman et al. 2017 [10])
  - Restricted mean survival time (RMST) NMAs (Petit et al. 2019 [11], Connock et al. 2019 [12], and Niglio et al. 2019 [13])

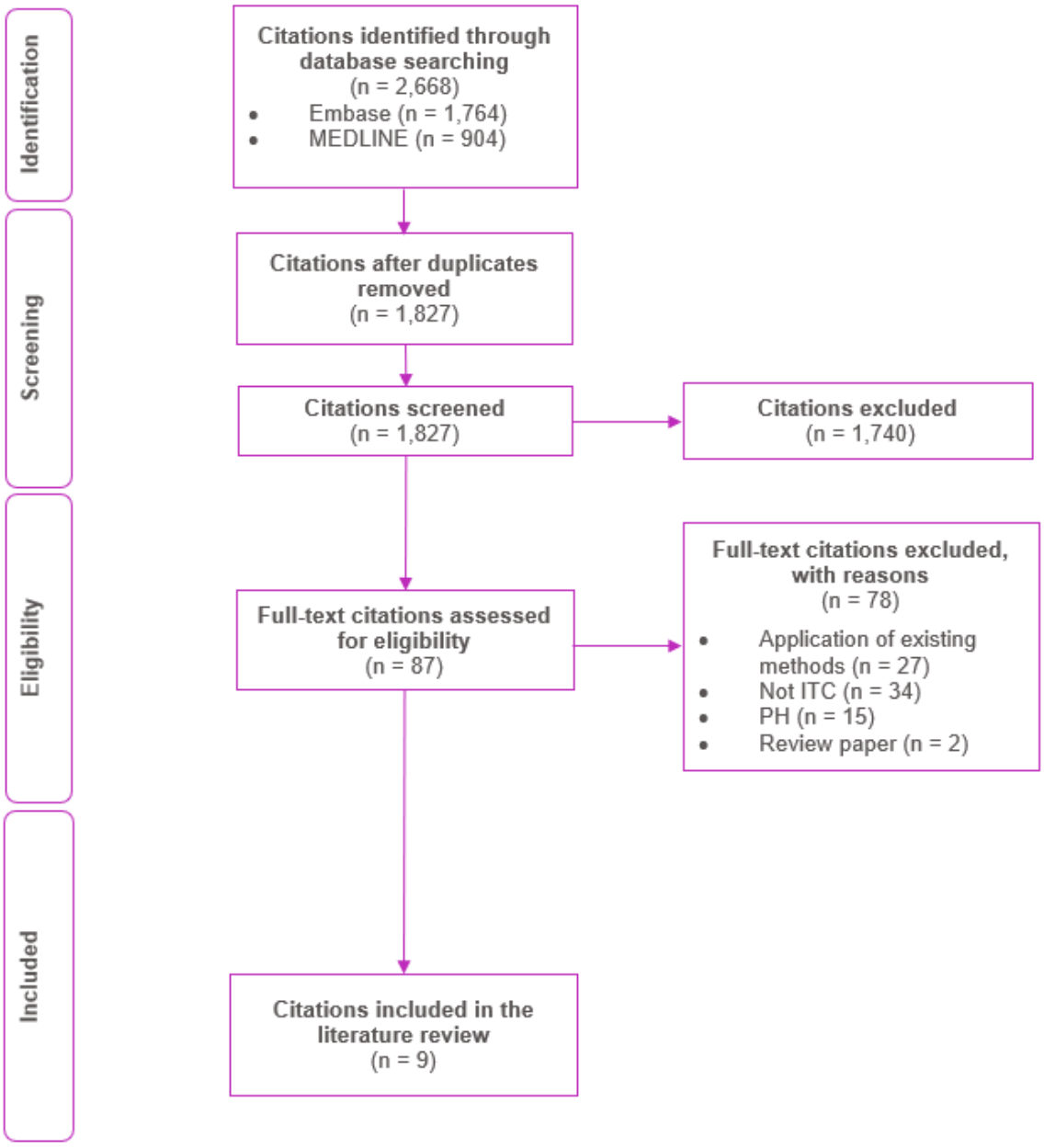
CoCites Search

- No additional studies were identified based on review of 362 abstracts and four full-texts.

Guidelines Search

- Six guidance documents from Australia (Pharmaceutical Benefits Advsory Committee [PBAC] [16]), Canada (Canadian Agency for Drugs and Technologies in Health [CADTH] [17]), England & Wales (Centre for Reviews and Dissemination [CRD] [18] and NICE DSU [19]), France (Haute Autorité de Santé [HAS] [20]), and Germany (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [IQWIG] [21]) noted the importance of assessing PH assumption via methods such as log-cumulative hazard plots (**Table 3**).
- However, none of the guidance documents provided recommendations on alternative methods or models when the PH assumption is violated.

Figure 1. Study identification and selection diagram for database search



***Notes**: no additional citations were identified through the CoCites search. **Abbreviations**: ITC, indirect treatment comparison; PH, proportional hazard*

TABLES

Table 1. Eligibility criteria for database and CoCites search

Criteria	Inclusion	Exclusion
Study design *Note:* study must have met all four (#1-4) inclusion criteria to be eligible	1) Methodology for indirect comparison, such as: • Indirect comparison (i.e. Bucher method) • Network meta-analysis (NMA) • Matching-adjusted indirect comparison (MAIC) • Simulated treatment comparison (STC)	The following study designs were not of interest: • Studies performing between-study comparisons and only estimating treatment effects where head-to-head evidence exists (i.e. meta-analysis) • Studies collecting and analyzing primary data (i.e. no between-study comparisons)
	2) Methodology that did not rely on PH assumptions, such as: • Parametric models • Restricted means • Flexible models (splines, piecewise, cure, mixture, etc.)	Methodology that relied on PH assumption, such as: • Exponential models • PH models
	3) Methodology that allowed for synthesis of time-to-event outcomes (e.g. OS, PFS, DOR, time to response etc.)	No further restrictions
	4) At least one of the following: • Methodology was introduced transparently in terms of math or corresponding code; • Methodological comparison of ≥2 relevant non-PH methodologies; or • Methodological comparison of ≥1 relevant non-PH methodology with PH methodology	• Applied studies using a previously published non-PH methodology. • Methods not presented transparently (i.e. no formula or code)
Language	English language	No further restrictions
Publication type	Full-text publication	Abstracts and posters
Time restriction	Publications from 2010 onwards	Publications prior to 2010

Abbreviations: *DOR, duration of response; PFS, progression-free survival; PH, proportional hazards; OS, overall survival*

Table 2 (Part I). Summary of evidence synthesis methods for ITCs and NMAs that do not rely on PH assumption

Method	Articles	Description of NMA model	Survival distribution/function	One or two-step	Framework	Likelihood*	Treatment effect and how non-PH is addressed	Between-study hetero-geneity	Inconsis-tency models
One-step multidimensional NMA	Ouwens et al. 2010 [5]	Uses a multidimensional treatment effect as an alternative to the synthesis of the trial-specific constant HRs. The hazard functions of the interventions in a trial are modeled using parametric distribution and the difference in the parameters are considered the multi-dimensional treatment effect, which are synthesized (and indirectly compared) across studies.	Weibull, Gompertz, log-normal, log-logistic	One-step (trial level specific treatment effects and pooled effects are estimated simultaneously)	Bayesian	Approximation with piecewise constant hazards (discrete hazards) according to a binomial likelihood	Multivariate relative treatment effect parameters regarding scale and shape related factors of the survival distribution/function. These relative treatment effect parameters are used to describe time-varying HRs (or odds ratios in case of log-logistic models).	Yes	Yes
	Jansen et al. 2011 [6]		First (Weibull, Gompertz) and second-order fractional polynomials describing the log-hazards over time						
	Jansen et al. 2012 [7]								
	Vickers et al. 2019 [8]								
Two-step multidimensional NMA	Cope et al. 2020 [9]	For each arm of every RCT in the network, (recreated), IPD are used to estimate alternative survival distributions. Next, for each distribution, its scale and shape parameters are included in a multivariate NMA to obtain time-varying estimates of relative treatment effects between competing interventions.	Weibull, Gompertz, lognormal, log-logistic describing the log-hazards over time	Two-step (Arm specific survival function parameters are estimated first. Subsequently, these are incorporated in the multivariate NMA)	Step 1 – Frequentist; Step 2 – Bayesian	Exact likelihood corresponding to survival distribution selected	Multivariate relative treatment effect parameters regarding scale and shape related factors of the survival distribution/function. These relative treatment effect parameters are used to describe time-varying HRs (or odds ratios in case of log-logistic models).	Yes	Yes

Table 2 (Part II). Summary of evidence synthesis methods for ITCs and NMAs that do not rely on PH assumption

Method	Articles	Description of NMA model	Survival distribution/function	One or two-step	Framework	Likelihood*	Treatment effect and how non-PH is addressed	Between-study hetero-geneity	Inconsis-tency models
NMA with cubic splines for baseline hazard	Freeman et al. 2017[10]	An IPD Royston-Parmar Bayesian NMA model, which provides flexible alternative modeling approach that can accommodate time-dependent effects. The baseline log-cumulative hazard is modeled with restricted cubic splines. HRs are either fixed over time or can be modeled as a function of ln(time).	Restricted cubic splines describing the cumulative hazard of the baseline of each trial	Two-step (Described as one-step but requires orthogonalized basis function of study-specific splines as input for NMA)	Bayesian framework for NMA but first step in frequentist framework	General likelihood using 'zeros trick' using probability density function of Poisson distribution***	Constant HRs represented with a single basic parameter by treatment. As an extension, HR can vary over time by adding extra parameters for the interaction between treatment and ln(time)	Yes	Yes
Restricted mean survival NMA	Petit et al. 2019 [11]	A two-step analysis to estimate restricted mean survival (RMS) based on (reconstructed) IPD from KMs; then evaluated mean difference in RMS in NMA model	RMS estimated based on a) trial-specific KM method; b) AUC of KM + exponential tail	Two-step	Frequentist	Normal likelihood for NMA model and exact likelihood corresponding to parametric distribution selected (if extrapolation involved)	Difference in RMS (AUC up to specific time point) between treatments	Yes	Yes
	Connock et al. 2019 [12]		RMS estimated based on a) AUC Weibull/gen gamma per arm; b) mean survival using Weibull; c) AUC of KM + exponential tail		Bayesian			No	No
	Niglio et al. 2019 [13]		RMS estimated based on a) pseudo values based on KM; b) Poisson-gamma frailty model		Frequentist			No	No

Abbreviations: *AUC, area under the curve; HR, hazard ratio; IPD, individual patient data; KM, Kaplan-Meier; NMA, network meta-analysis; PH, proportional hazards; RCT, randomized control trial; RMS, restricted mean survival. *All methods utilize time-to-event data based on individual patients either reconstructed from KM using Guyot algorithm or based on observed IPD; **"Allow treatment effects to vary by covariates independently of the other treatments in the network of evidence. The treatment effect remains constant for any treatment not specified within a hierarchical exchangeable structure…In addition, where possible, different doses also were included as a hierarchical structure with an overall treatment class effect. Constraints were imposed to ensure that the efficacy increased with dose intensity" adapted from Owen et al. [14] *** If we wish to implement a likelihood representing the flexible fractional polynomials or cubic splines in WinBUGS, we can use the "zeros" trick [15] where a dataset comprising entirely of zeros is given a Poisson distribution with its parameter defined equal to the negative log-likelihood (plus a sufficiently large constant). The log-likelihood function corresponding to the fractional polynomial or spline is then written algebraically in the WinBUGS code*

Table 3. Summary of recommendations from guidelines search

Nation	Reimbursement bodies and HTA agencies	Recommendations on PH and time-to-event outcomes
Australia	PBAC 2016 [16]	• PH: Discuss whether the results are consistent with the assumption of constant PH. Present results of testing for PH. Where the assumption of constant PH is not reasonable, present alternative methods for estimating comparative effectiveness. • Pooled time-to-event: Data from multiple trials involving a particular time-to-event outcome may be statistically combined in a number of ways. The preferred method is to pool individual patient data from a Cox PH model. If individual patient data are not available, pool the HRs from the trial-level data to present the pooled HR with its 95% CI. If HRs with their standard errors are not all available, pool dichotomised data based on a common duration of follow-up. • ITC: For time-to-event outcomes, present the results of each individual randomised trial as the HR with its 95% CI between the common reference, and the proposed medicine and the main comparator. Also report the median event-free survival in each arm of the common reference, proposed medicine and main comparator.
Canada	CADTH 2017 [17]	• Extrapolation: Suggested to follow the Survival Model Selection Process Algorithm developed by DSU (NICE). • Time-to-event: Where researchers have access only to summary-level data, they may consider the use of methods to recreate patient-level data. For methods related to the synthesis of time-to-event (survival) data based on either summary or individual participant data, researchers are referred to Cooper et al (section 9.3). o *Discussed constant hazard violations and other time-to event data complications; publications cited included Woods 2010, Welton 2010, Ouwens 2010, Guyot 2011, Jansen 2011, Welton 2008*
England & Wales	CRD 2008 [18]	• Recommended to estimate HRs by using methods described in Tierney 2007.
	DSU 2011 [19]	• Detailed discussion on different survival analysis methodologies • Mean time-to-event should be estimated rather than medians • PH modelling should only be used if the PH assumption can be clearly justified using log-cumulative hazard plots • Guidance on model selection is given
France	HAS 2020 [20]	• Highlights that NMA model assumptions should be described, such as PH assumption (no mention of alternative methods or models)
Germany	IQWIG 2017 [21]	• If a HR is neither available nor calculable, or if the available HR cannot be interpreted meaningfully (e.g. due to relevant violation of the PH assumption), it should be examined whether a relative risk (referring to a meaningful time point) can be calculated. It should also be examined whether this operationalization is adequate in the case of transient outcomes for which the outcome of time-to-event was chosen.

DISCUSSION/REFERENCES

DISCUSSION

- To our knowledge, this review is the first systematic assessment of methods and guidance for performing ITC and NMA of time-to-event data not relying on the PH assumption.
- Methods that can estimate relative treatment effects when the PH assumption does not hold were categorized as: one-step multidimensional NMA, two-step multidimensional NMA, NMA with cubic splines for baseline hazards, and RSMT NMA.
- Despite critiques of methods used in cases where the PH assumption was questioned or found to be violated, no recommendations or guidelines on methods to address the issue of non-PH in ITCs or NMAs evaluating time-to-event outcomes were provided by the reimbursement bodies and health technology assessment (HTA) agencies included in this study.
- A multi-faceted approach was employed to identify articles in databases and to validate findings using a citation-based search approach.
- Potential limitations of this review include:
  - Our research question focused on full-text methods papers, with conference abstracts being excluded due to the insufficient details regarding specific methodological approaches or analysis code.
  - Additional studies may have been published since the dates of the search.
  - It was challenging to differentiate applications of synthesis methods from new methods in some cases where population-adjusted ITCs applied methods that did not rely on PH assumption.
  - We did not include all possible methods that have been applied in the meta-analysis framework, which theoretically could be extended to evaluate NMAs.
- A study designed to evaluate the strengths and limitations of these alternative synthesis methods and their suitability for HTA economic modelling and decision making is warranted.

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