

Survival Model-based Meta-Analysis Framework for the Indirect Comparison of Anti-Cancer Therapy Efficacy

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Executive Summary

In the current work we present Bayesian model-based meta-analysis (MBMA) framework for the indirect comparison of survival data in oncology clinical trials. The modeling dataset was prepared via digitization of 140 Kaplan-Meier curves from 28 NSCLC clinical trial characteristics. Mixed-effects hierarchical parametrized survival model was developed and qualified using Stan statistical engine. The developed model was applied to perform indirect comparison between PD-1 and PD-L1 inhibitor treatments in NSCLC and after adjustment on the identified covariate effects was clinically non-inferior.

Introduction

Overall Survival (OS) is a gold standard clinical endpoint to assess efficacy of anticancer therapies. However, direct comparison of OS data between the novel therapies is often compromised due to the lack of head-to-head cohorts in pivotal clinical trials and difference in patient’s characteristics. Development of the modeling approaches able to perform indirect efficacy comparison of oncology clinical trials with precise quantification of patients’ population characteristics could enhance the applicability of survival model-based meta-analysis (MBMA) in drug development decisions making.

Objectives
The key aim of the presented work is a development of a methodology able to perform model-based meta-analysis using the individual survival data digitized from the published sources. In order to test the applicability of the proposed methodology we have applied it to quantitatively compare OS outcomes of PD-1 and PD-L1 immunotherapies in non-small cell lung cancer (NSCLC).

Materials and Methods

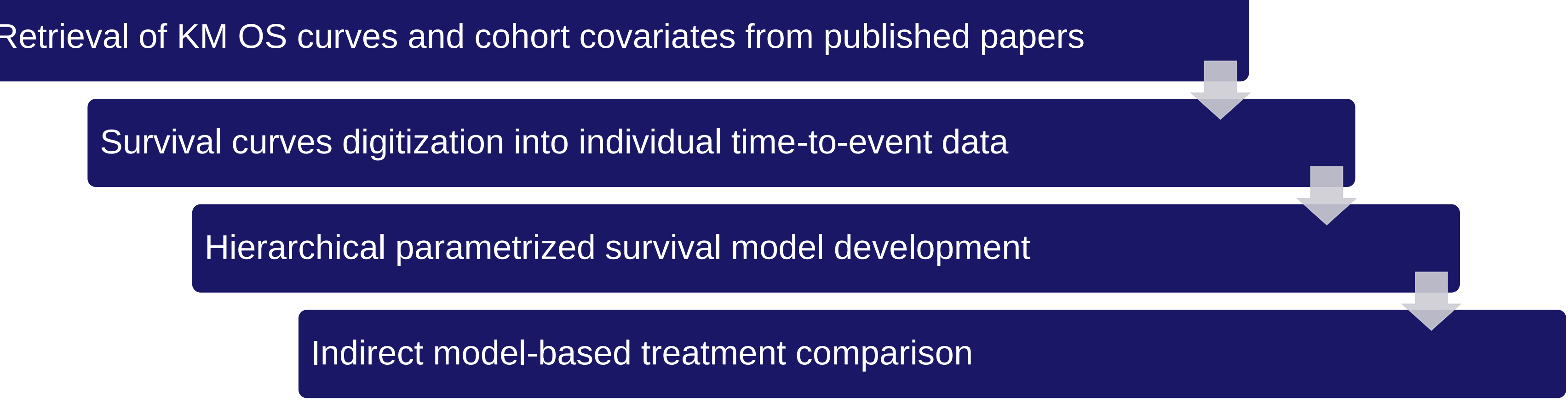


Fig 1. Subtasks of the Meta-Analysis Framework.

The main workflow of proposed framework is shown in Figure 1. The individual survival data were digitized using modified approach proposed by Guyot P. et al [1, 2]. Additionally, subgroup analysis Kaplan-Meier (KM) curves presented within the same clinical trial were used to extract specific covariate values such as the therapy line, PD-L1 expression level and others. Possible duplicates of patient entry were analyzed and excluded from the modeling dataset. At the next stage hierarchical parametrized survival model was developed and qualified using Stan statistical engine [3].

Materials and Methods

The structure of the developed model is presented in Figure 2. Individual hazard was parametrized using the cubic spline basis with 6 degrees of freedom. Each B-spline decomposition coefficient was defined using the linear regression of covariates and a study-level random effect.

Hazard(t) =

$$= \exp \left(\text{PDL1_min} * \begin{bmatrix} \text{'PD-L1' coef} \\ \text{'PD-1' coef} \\ \text{'Chemo' coef} \\ \text{'Atezolizumab' coef} \end{bmatrix} + \begin{bmatrix} \text{Chemotherapy} \\ \text{Durvalumab} \\ \text{Avelumab} \\ \text{Nivolumab} \\ \text{Pembrolizumab} \\ \text{Atezolizumab} \end{bmatrix} + \begin{bmatrix} \text{1 line} \\ \text{1+ lines} \\ \text{2+ lines} \\ \text{3+ lines} \end{bmatrix} + \text{ran_eff} \right) * \text{Spline_basis}(t)$$

Fig 2. Structure of the parametrized survival model.

A set of graphical model diagnostics were proposed to assess the quality of posterior prediction for the developed models. Indirect comparison for the PD-1, PD-L1 and Chemotherapy OS outcome was performed in order to adjust the population model prediction on the effects of significant covariates and assess level of uncertainty of the estimated parameters.

Results

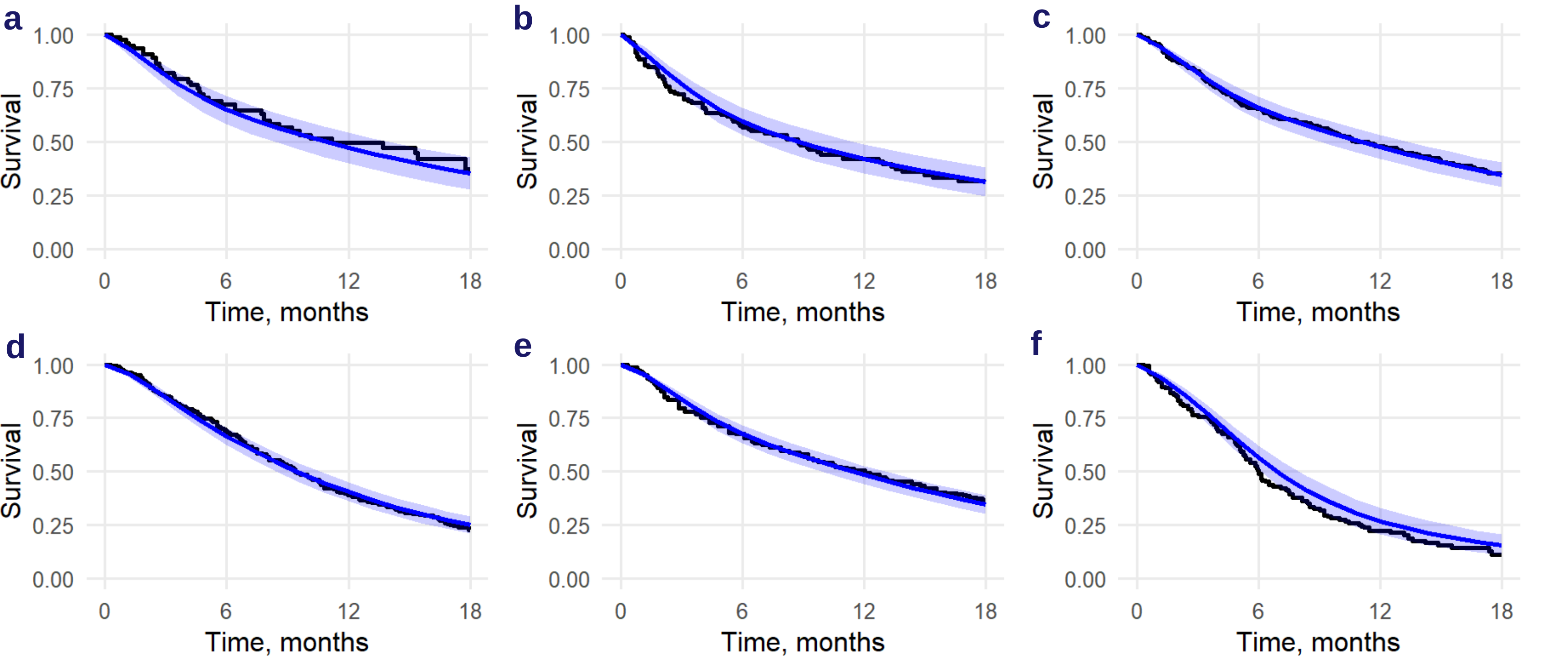


Fig 3. Graphical diagnostics example. Actual survival KM vs. predicted survival. **a, b** - Antonia S., et al. doi: 10.1016/S1470-2045(15)00544-6; **c** - Barlesi F, et al. doi: 10.1016/S1470-2045(18)30673-9; **d, e** - Borghaei H, et al. doi: 10.1056/NEJMoa1507643; **f** - Brahmer J, et al. doi: 10.1056/NEJMoa1504627.

We reconstructed individual time-to-event data from 140 published OS Kaplan-Meier curves from 28 NSCLC clinical trials with PD-1 inhibitors (Nivolumab, Pembrolizumab), PD-L1 inhibitors (Durvalumab, Avelumab, Atezolizumab) and chemotherapy control arms. The proposed parametric survival model was able to adequately describe the existing OS outcome data on the population and individual-study level. Figure 3 shows the example of proposed Visual Prediction Check diagnostics. Actual KM curve (black line) is compared to the predicted survival curve (blue line), colored range represents the 95%CI for predictions.

Results

Figure 4 shows the results of model-based indirect comparison for chemotherapy and immunotherapy. Simulations were performed for the first line and for the mixed lines starting from the second (2+). Two levels of PD-L1 expression level were tested: 0 (negative) and 5 (common threshold for positive status). The differences between PD-1 and PD-L1 inhibitor treatments after adjustment on the identified covariate effects was clinically non-inferior.

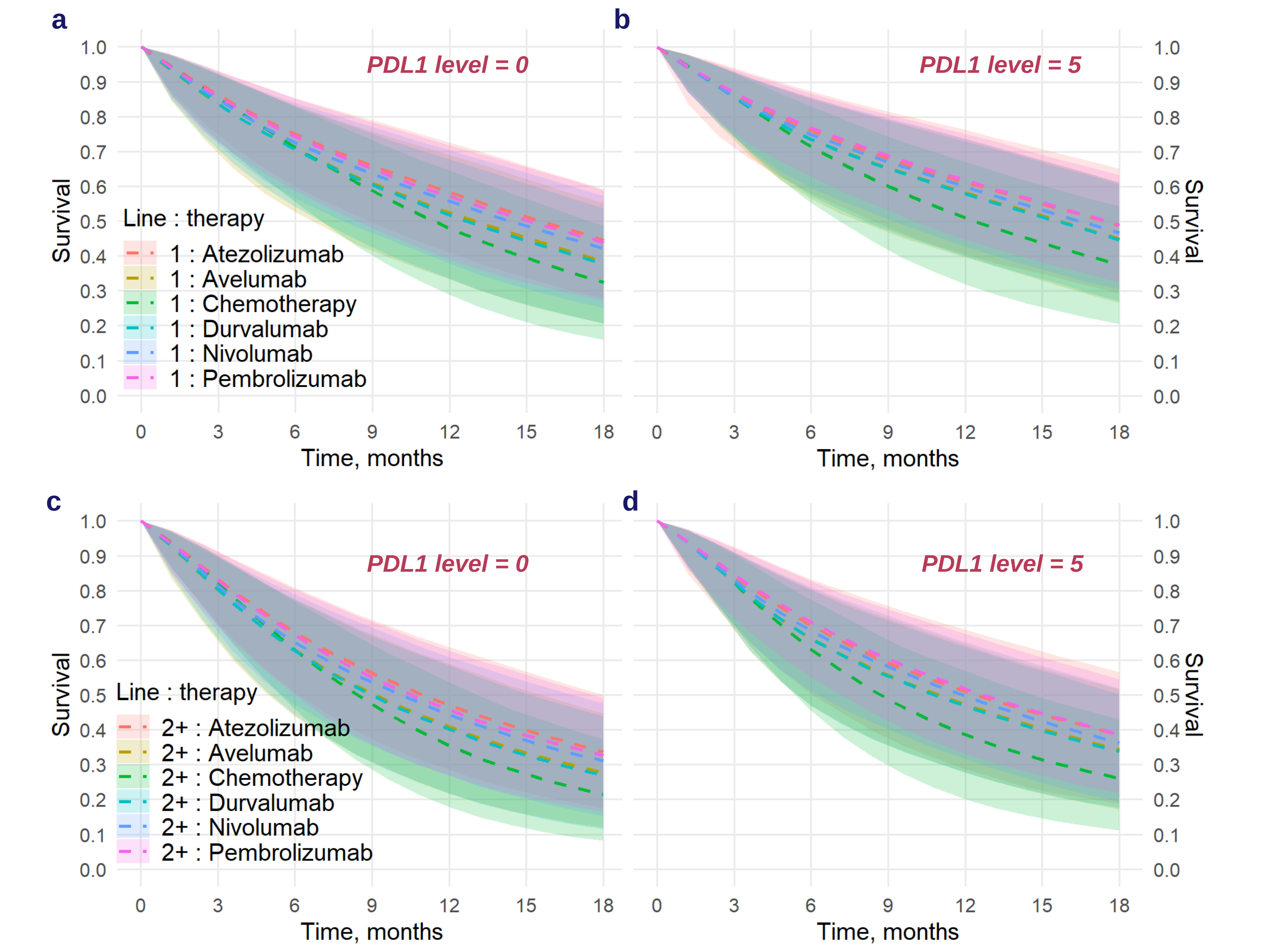


Fig 4. Simulated survival curves with 95%CI for different types of therapy. **a** – first line of therapy and PD-L1 level=0; **b** – first line of therapy and PD-L1 level=5; **c** – 2+ line of therapy and PD-L1 level=0; **d** – 2+ line of therapy and PD-L1 level=5;

Conclusions

The developed survival MBMA approach could be generalized and applied to any type of time-to-event outcome and disease. The reduction to individual patient level dataset allows to use complex parametrized baseline hazard models for survival description and to avoid cohort size correction, which can provide a model-based tool for the more precise indirect comparison of oncology clinical trials.

References
[1] Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol. 2012 Feb 1;12:9. doi: 10.1186/1471-2288-12-9.
[2] Wei Y, Royston P. Reconstructing time-to-event data from published Kaplan-Meier curves. Stata J. 2017;17(4):786-802.
[3] Carpenter B, Gelman A, Hoffman M. et al. Stan: A Probabilistic Programming Language. Journal of Statistical Software. 76 (1): 1–32. doi:10.18637/jss.v076.i01