

Optimal treatment sequence and mortality

Application of landmark analysis to real-world data

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INTRODUCTION

In survival analysis, time-dependent covariates often complicate the estimation of treatment effects or prognostic factors. Landmark analysis offers a pragmatic approach consisting of defining a fixed time point (the "landmark") and restricting the analysis to individuals still at risk at that point. The objective is to present a pragmatic framework for implementing landmark analysis in order to assess the associations between treatment sequences and subsequent all-cause mortality, and to illustrate its application through a study of the impact of treatment on mortality, using real-world data from the French National Health Data System (SNDS).

CONCLUSION

This work shows how landmark analysis makes it possible to estimate associations between the evolution of treatment sequences and subsequent mortality, while accounting for time-dependent exposures. In this illustration, single-treatment sequences were generally associated with lower risks compared with **treatment A** before 3 years, whereas combinations showed higher risks, with contrasts becoming more pronounced after 3 years. Although inference is limited to patients who survived up to each predefined time, landmark analysis is a simple, robust and widely accessible approach, offering clear and interpretable results, for handling time-dependent covariates in studies, as well as various potential outcomes.

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Abbreviations

CI: Confidence interval; KM: Kaplan-Meier; SNDS: French National Health Data System.

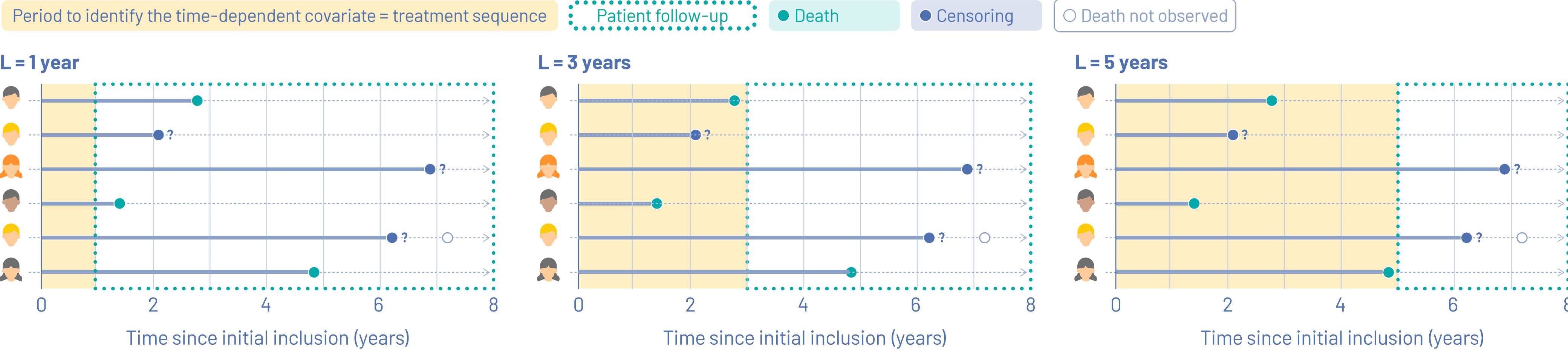
METHODS

The design of this landmark analysis aims to assess treatment effects at 1, 3 and 5 years after initiation. At each predefined landmark time **L**, the dataset comprised patients alive and uncensored at time **L**.

First, Kaplan-Meier curves were produced for each dataset. Only treatment sequences with at least one hundred patients at risk are shown on the KM curves (for better readability).

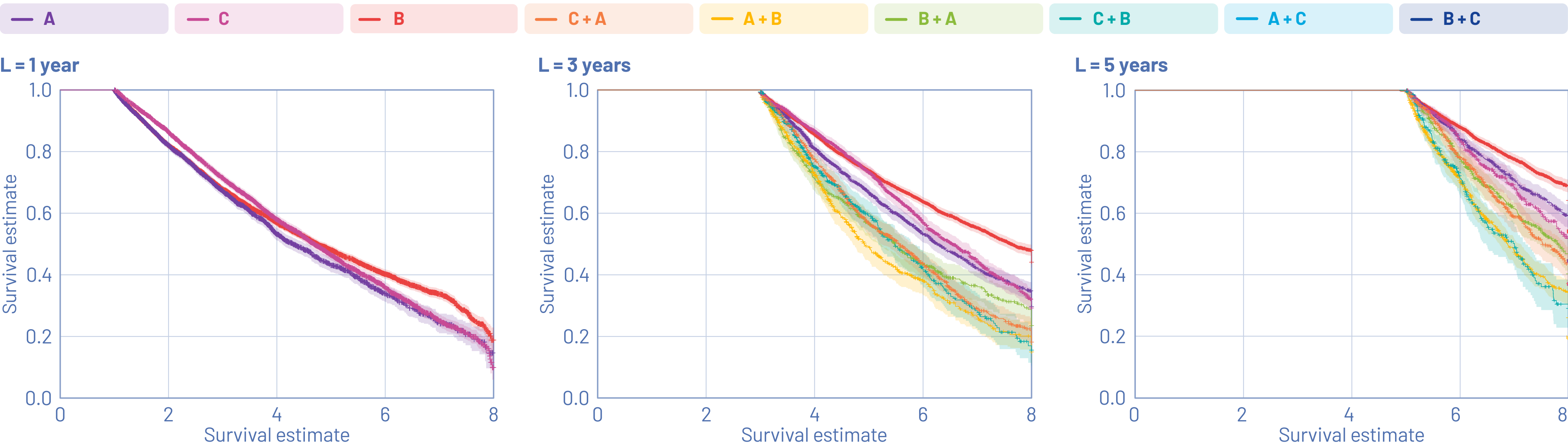
Next, Cox models adjusted for treatment sequence were used. The exposure of interest was the treatment sequence, defined as the two most recent treatments before the predefined landmark time **L**. In the main analysis, **treatment A** served as the reference; the sequences included treatments **B** and **C**, as well as combinations (e.g., A then B). At each predefined landmark time **L**, the estimate was the association between the treatment sequence at time **L** and all-cause mortality, among patients at risk at time **L**.

Representative diagram of the Landmark analysis



RESULTS

Kaplan-Meier curve



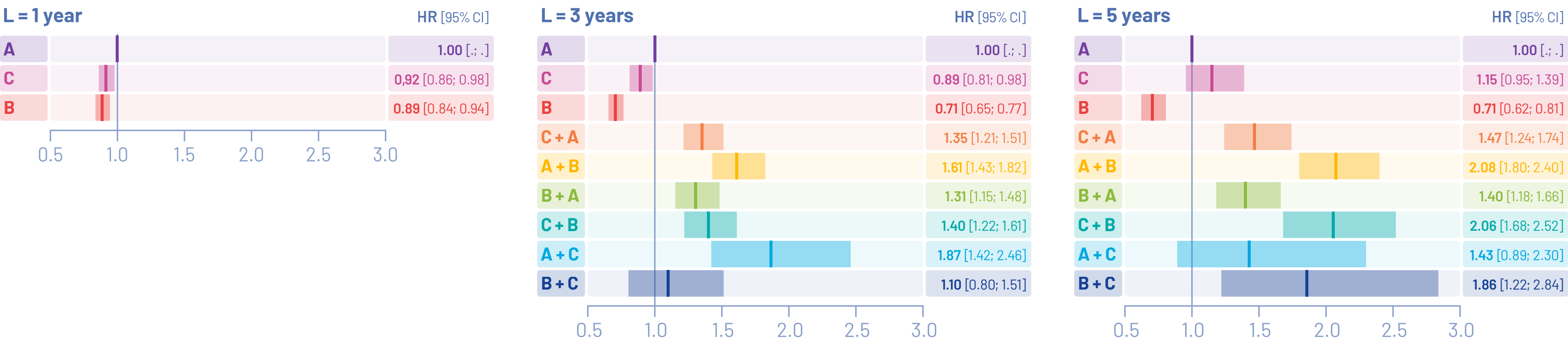
Number of patients at risk

L = 1 year									
Time in years	0	1	2	3	4	5	6	7	8
Total		15,549	11,112	7,656	5,063	3,132	1,723	699	7

L = 3 years									
Time in years	0	1	2	3	4	5	6	7	8
Total				11,326	8,012	5,510	3,642	2,256	1,306

L = 5 years									
Time in years	0	1	2	3	4	5	6	7	8
Total						6,154	4,177	2,720	1,696

Cox model

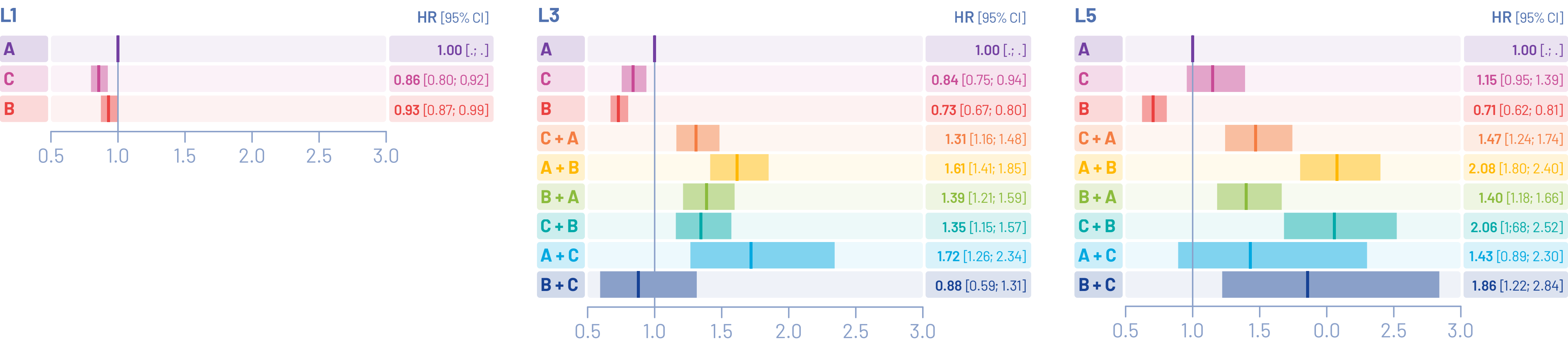


Patients who followed **treatment B** consistently showed better survival than those who followed **treatment A**, with a hazard ratio (HR) ranging between 0.89 and 0.71. Patients who followed **treatment C** showed better survival than those who followed **treatment A** at 1 year and at 3 years, with a hazard ratio (HR) around 0.90. Patients who followed **treatment A + B** showed a higher risk of death than those who followed **treatment A** at 3 years and at 5 years, with a hazard ratio (HR) of 1.61 and 2.08.

CHECKS (MODEL DIAGNOSTICS)

Proportional hazards

Proportional hazards were assessed using Schoenfeld residuals. The effect of each covariate remained constant over a 3-year period, except for **treatment C**. The hazard ratios from the Cox models truncated at 3 years are relatively close to those of the initial model.



At 1 year, the hazard ratio for **treatment B**, computed over the whole follow-up period, was 0.89 [0.84; 0.94]; when restricting the analysis to a maximum follow-up of 3 years, the association is slightly stronger, with a hazard ratio of 0.93 [0.87; 0.99].

Sensitivity analyses

The sensitivity analysis consisted of excluding patients who died within the month following their inclusion at the predefined landmark time **L**, these deaths being considered to have occurred shortly after the reference time. All results remain consistent. At 1 year, the HR for **treatment B** is 0.89 [0.84; 0.94] with a p-value of 0.0001, and the sensitivity analyses show an HR of 0.89 [0.84; 0.95] with a p-value of 0.0002.