



Universiteit
Leiden
The Netherlands

Statistical modelling of time-varying covariates for survival data

Spreafico, M.

Citation

Spreafico, M. (2022, October 12). *Statistical modelling of time-varying covariates for survival data*. Retrieved from <https://hdl.handle.net/1887/3479768>

Version: Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/3479768>

Note: To cite this publication please use the final published version (if applicable).

Statistical modelling of time-varying covariates for survival data

Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Leiden,
op gezag van rector magnificus prof.dr.ir. H. Bijl,
volgens besluit van het college voor promoties
te verdedigen op woensdag 12 oktober 2022
klokke 13.45 uur

door

Marta Spreafico
geboren te Bellano, Italië
in 1993

Promotor:

Prof.dr. M. Fiocco

Universiteit Leiden, Leids Universitair Medisch Centrum,
Prinses Máxima Centrum

Co-promotor:

Dr. F. Ieva

Politecnico di Milano, Human Technopole

Promotiecommissie:

Prof.dr. P. Stevenhagen

Universiteit Leiden

Prof.dr. P. Grünwald

Universiteit Leiden, Centrum Wiskunde & Informatica

Prof.dr. A. Farcomeni

Università degli Studi di Roma Tor Vergata

Dr. E. Musta

Universiteit van Amsterdam

Prof.dr. H. Putter

Leids Universitair Medisch Centrum, Universiteit Leiden



POLITECNICO
MILANO 1863



Universiteit
Leiden
The Netherlands

This doctoral dissertation was part of a cotutelle agreement and was presented to Politecnico di Milano (Italy) in fulfillment of the requirements for the degree of Doctor in *Mathematical Models and Methods in Engineering* (Metodi e Modelli Matematici per l'Ingegneria), and to Universiteit Leiden (The Netherlands) in fulfillment of the requirements for the degree of Doctor in *Mathematics* (Wiskunde).

*A mio nonno Ermanno[†]
con infinito amore*

“Uau”

Contents

Introduction	1
I.1 Basics of Survival Analysis	3
I.2 Epidemiological and clinical framework	6
I.2.1 Pharmacoepidemiology in Heart Failure	6
I.2.2 Chemotherapy in Osteosarcoma	8
I.3 Overview of the thesis	9
 PART I Pharmacoepidemiology in Heart Failure	 13
 1 A new method for measuring adherence to polypharmacy	 15
1.1 Materials and Administrative data	16
1.1.1 Study setting	16
1.1.2 Data sources	16
1.1.3 Study population	17
1.2 Methodologies	18
1.2.1 Target dosages according to guidelines	18
1.2.2 Adherence measures	18
1.2.3 Adherence to polypharmacy	19
1.2.4 Outcome measure	20
1.2.5 Survival Analysis: multivariable Cox regression models	20
1.3 Results	21
1.3.1 Cohort selection	21
1.3.2 Standardized Daily Dose	25
1.3.3 Patients' adherence measures	25
1.3.4 Multivariable Cox models for survival outcome	27
1.4 Final remarks	29
 2 Joint modelling of time-varying adherence to medication and survival	 33
2.1 Statistical Methodologies	35
2.1.1 Pharmacological time-varying covariates	35
2.1.2 Joint model specification	37
2.2 Materials and Administrative data	39
2.2.1 Study setting	39
2.2.2 Administrative data sources	40
2.2.3 Pharmacological time-varying covariates for ACE/ARB therapy	41

2.2.4	Outcome measure	42
2.3	Results	42
2.3.1	Study cohort	42
2.3.2	Joint models for time-varying consumption and adherence to ACE/ARB therapy	43
2.4	Final remarks	52
3	Functional modelling of recurrent events on time-to-event processes	55
3.1	Materials and Administrative data	57
3.1.1	Administrative data sources	57
3.1.2	Study design and outcome measure	58
3.2	Statistical Methodologies	59
3.2.1	Marked point process formulation for recurrent events	59
3.2.2	Functional linear Cox regression model with multiple functional compensators	62
3.3	Data application	64
3.3.1	Step 1: Data preprocessing & clinical history	64
3.3.2	Step 2: Modelling compensators of marked point processes	65
3.3.3	Step 3: Summarize compensators through Functional Principal Com- ponent Analysis	69
3.3.4	Step 4: Predictive functional Cox model for overall survival	71
3.4	Final remarks	72
A.	Appendix to Chapter 3	75
PART II	Chemotherapy in Osteosarcoma	77
4	Modelling time-varying covariates effect on survival via Functional Data Analysis	79
4.1	Statistical Methodologies	81
4.1.1	Time-varying covariates and survival frameworks	81
4.1.2	Time-Varying covariate Cox Model	83
4.1.3	Functional covariate Cox Model	83
4.2	MRC BO06 randomized clinical trial data	86
4.2.1	Trial protocol	86
4.2.2	Sample cohort selection and baseline characteristics	87
4.3	Results	88
4.3.1	Time-varying characteristics	88
4.3.2	Time-Varying covariate Cox Model	91
4.3.3	Functional covariate Cox Model	92
4.4	Final remarks	98
5	A novel longitudinal method for quantifying multiple overall toxicity	103
5.1	BO06 data	104
5.1.1	Treatment-related factors	105

5.2	Statistical Methodologies	107
5.2.1	Longitudinal Multiple Overall Toxicity (MOTox) scores and outcomes	107
5.2.2	Statistical analysis	108
5.3	Results	109
5.3.1	Non-haematological longitudinal Overall Toxicity scores	109
5.3.2	Multivariable logistic regression models for high overall toxicity over cycles	111
5.4	Final remarks	112
B.	Appendix to Chapter 5	117
6	Modelling longitudinal profiles of latent probability and relative risk via latent Markov models and compositional data	119
6.1	Statistical Methods	121
6.1.1	Motivations for latent Markov models for longitudinal toxicity data	121
6.1.2	Latent Markov model with covariates	122
6.1.3	Model selection	124
6.1.4	Longitudinal profiles: latent probability and relative risk	125
6.2	Data application	127
6.2.1	Longitudinal toxicity data: item-response categories	127
6.2.2	Latent Markov model for longitudinal toxicity data	128
6.2.3	Longitudinal profiles of Latent Overall Toxicity	133
6.3	Final remarks	135
C.	Appendix to Chapter 6	138
7	Investigating the causal effects of joint-exposure on survival outcome in presence of time-varying confounders	139
7.1	Data description	141
7.1.1	Control arms protocol and Cohort selection	142
7.1.2	Complexity of chemotherapy data	143
7.1.3	Chemotherapy exposure characteristics	146
7.2	Causal inference structure and methods	150
7.2.1	Event-Free Survival Outcome	151
7.2.2	Causal inference assumptions for marginal structural models	151
7.2.3	Causal structure of chemotherapy data	153
7.2.4	Joint-exposure and marginal structural Cox model for DAG-1	156
7.2.5	Joint-exposure and marginal structural Cox model for DAG-2	158
7.3	Results	161
7.3.1	Joint-exposure descriptive and association with EFS	161
7.3.2	IPTW diagnostics	162
7.3.3	Causal inference through marginal structural Cox models	165
7.4	Final remarks	167
D.	Appendix to Chapter 7	170
	Conclusions	178

Contents

Bibliography	192
Summary	193
Samenvatting	195
Sommario	197
List of Publications	199
Acknowledgments	201
Curriculum Vitae	203