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RESEARCH ARTICLE

Using marginal structural joint models to estimate the effect of a time-varying treatment on recurrent events and survival: An application on arrhythmogenic cardiomyopathy

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This article has earned an open data badge "**Reproducible Research**" for making publicly available the code necessary to reproduce the reported results. The results reported in this article were reproduced partially due to data confidentiality issues.

Abstract

In many clinical applications to evaluate the effect of a treatment, randomized control trials are difficult to carry out. On the other hand, clinical observational registries are often available and they contain longitudinal data regarding clinical parameters, drug therapies, and outcomes. In the past, much research has addressed causal methods to estimate treatment effects from observational studies. In the context of time-varying treatments, marginal structural models are often used. However, most analyses have focused on binary outcomes or time-to-the-first event analyses. The novelty of our approach is to combine the marginal structural methodology with the case where correlated recurrent events and survival are the outcomes of interest. Our work focuses on solving the nontrivial problem of defining the measures of effect, specifying the model for the time-dependent weights and the model to estimate the outcome, implementing them, and finally estimating the final treatment effects in this life-history setting. Our approach provides a strategy that allows obtaining treatment effect estimates both on the recurrent events and the survival with a clear causal and clinical interpretation. At the same time, the strategy we propose is based on flexible modeling choices such as the use of joint models to capture the correlation within events from the same subject and the specification of time-dependent treatment effects. The clinical problem which motivated our work is the evaluation of the treatment effect of beta-blockers in arrhythmogenic right ventricular cardiomyopathy (ARVC/D), and the dataset comes from the Trieste Heart Muscle Disease Registry.

KEYWORDS

Joint frailty models, marginal structural models, recurrent events, survival, time-varying treatment

1 | INTRODUCTION

To estimate the causal effect of a time-dependent treatment from retrospective observational registries, causal inference methods are required to control for confounders (Clare et al., 2019; Daniel et al., 2013). Cox marginal structural models are often used with survival outcomes. Nowadays, event-history analyses are also very often of interest in randomized controlled trials (RCT) as well as in observational studies. However, their application in the context of causal methods for the estimation of the effect of treatment with assignment switching has been limited. In this paper, we present a methodology to estimate the effect of a time-varying treatment on recurrent events and a terminal event from longitudinal data.

Marginal structural models (MSM) have been proposed by Hernán et al. (2000) and Robins et al. (2000), and they have been discussed in the counting process and martingale framework by Røysland (2011). A marginal structural model for recurrent events based on the Poisson process was proposed by Jensen et al. (2016). Joint frailty models for recurrent events and a terminal event were proposed by Liu et al. (2004), and their estimation was discussed by Rondeau et al. (2006). Mazroui et al. (2012) proposed a more general model allowing for two sources of heterogeneity.

The dataset that motivated this work is the Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC/D) Registry of Trieste (Cappelletto et al., 2018; Pinamonti, 2014; Pinamonti et al., 2011). ARVC/D is a genetically determined heart disease characterized by progressive loss of myocardium and fibro-fatty replacement (Thiene et al., 1988). Symptoms are predominantly caused by major ventricular arrhythmias (MVA), which cause cardiac arrest. This is the reason why the disease is a major cause of sudden cardiac death (SCD) among young individuals (Corrado et al., 2015). The aim of this study is to evaluate the effect of the use of beta-blockers (the time-dependent treatment) in preventing MVA which can recur over time. At the moment, no treatment has proven effective in stopping MVA from happening. In high-risk patients, an implantable cardioverter defibrillator (ICD) is an effective strategy only in avoiding the worst outcome for patients by stopping cardio-respiratory arrest (Corrado et al., 2015). There is no clear evidence of the effect of beta-blockers in preventing recurrent ventricular arrhythmias since no clinical trial has been carried out. This is due to the fact that it is a relatively rare disease; therefore, a trial would take a long time, and it would have a very high cost. The only scientific literature on the subject consists of few observational studies, which have been analyzed with standard statistical methods (i.e., time-dependent Cox regression; Marcus et al., 2009). However, it is well known that standard regression methods cannot address the problem of confounders when the treatment under study has a time-varying nature. Confounders represent a serious concern in this setting since cardiologists prescribe the drug on the basis of the current clinical status of the patients. Moreover, the history of the recurrent events process as well as past treatments is additional time-varying factors influencing the propensity of being treated over time.

Patients affected by ARVC can die as a consequence of a severe MVA or in time they can develop heart failure (HF) due to the progressive deterioration of the heart muscle. HF is incurable and eventually leads to either heart transplant or death. As a consequence, the process of the terminal event (i.e., death and heart transplant) and the process of the recurrent events run in parallel, introducing a semicompeting risk. Finally, beta-blockers can also be used to treat HF so the terminal event could also be of interest as a secondary endpoint.

Further details and the rationale of the motivating example used throughout the paper are given in Section 2. The notation and the observation scheme are introduced in Sections 3.1 and 3.2, respectively. Our approach aims at estimating the short-term average causal effect of beta-blockers comparing the expected counterfactual recurrent MVA outcomes when beta-blockers are assigned versus not assigned in a visit (Section 3.3). Moreover, our proposed approach allows us to contrast the counterfactual survival outcomes when patients are continuously assigned to beta-blockers versus never assigned to beta-blockers (Section 3.4). The treatment effect definition is given in Section 3.5. The marginal structural models on the two endpoints are discussed in Section 3.6, while in Section 3.7 it is explained how these models can be estimated from observational data. Both the MSM models and the models for the weights are flexible in their specification. The weights are estimated with a continuous-time model in order to take into account of the fact that information in clinical observational registries are typically collected on irregular time intervals as opposed to fixed time intervals. Flexible parametric survival models are used to estimate the joint frailty structural models. These models allow for both flexible parametric baseline intensity functions as well as time-dependent coefficients.

Our work brings forward the research on marginal structural models for recurrent events proposed by Jensen et al. (2016) in the context of vaccine regimes and hospitalizations due to infections in children. The novelty of this proposed strategy consists of applying the recent work by Liu et al. (2004), Mazroui et al. (2012), and Rondeau et al. (2006) in the marginal structural framework, extending the previous methodology to a more complex setting in which the outcome of interest are correlated recurrent events and time to a terminal event. The method is motivated by an application on

cardiomyopathies, but we believe it could be relevant to many different real-world applications. The implementation of this marginal structural model for a bivariate event process is possible thanks to recent developments in statistical software (Crowther et al., 2020). `R` and `STATA` were used for the implementation of this analysis.

2 | MOTIVATING EXAMPLE

We retrospectively analyzed 123 patients enrolled between 1990 and 2019 in the Trieste Heart Muscle Disease Registry fulfilling the current diagnostic criteria for definite ARVC (Marcus et al., 2010). After baseline assessment, patients were evaluated every 2 years or more frequently, as clinically indicated. Subjects were observed until 31st December 2019, death or heart transplant. Moreover, 10 patients were lost at follow-up and therefore they were censored at their last visit/ hospitalization. The study complies with the Declaration of Helsinki, and the ethics committee of our institution approved the study. At baseline and every follow-up evaluation, patients underwent detailed clinical assessment, including 12-lead electrocardiogram (ECG), signal-averaged electrocardiogram, 24-h electrocardiographic Holter monitoring, exercise-test, and transthoracic echocardiogram. Moreover, subjects could be evaluated during hospitalization due to a cardiovascular procedure (i.e. ICD implantation) or a sudden event (e.g. major arrhythmic event or syncope).

Over a median observation period of almost 11 (inter quartile range, IQR: 5–21) years, the median number of visits/contacts with the hospital per subject was six (IQR: 3–11). Forty-three patients initiated treatment with beta-blockers during the study period. Treatment switches were possible at each visit or during hospitalizations according to the cardiologist's decision. Their opinion could be influenced by fixed characteristics of the patients (e.g., family history of MVA) but most importantly by clinical status, concomitant medications, and history of past MVA.

In total 38 patients experienced MVA, and the total number of MVA observed in the cohort was 83. MVA was reported either because the patients were hospitalized or because they were recorded by the ICD. Patients who experienced an MVA were more likely to have other sudden cardiac arrests in the future, thus events from the same subject are highly correlated. Seven patients also died as a consequence of an MVA, and in addition 21 patients died and nine underwent heart transplant during the follow-up. The semicompeting risk of the terminal event is, therefore, biologically linked to the process of the recurrent MVA. Even though other causes of death cannot be excluded, death is either the immediate consequence of an MVA or most likely caused by progressive heart muscle deterioration. Therefore, the model strategy needs to take into account the presence of informative censoring due to the semicompeting risk and the possible correlation between the MVA and the semicompeting risk.

Baseline characteristics of the study population are reported in Table 1.

Following the criteria suggested by Hernán and Robins (2006), we report the protocol of our target trial:

(i) *Eligibility criteria*: Patients are to be diagnosed with ARVC/D according to the current diagnostic criteria for definite ARVC (2010)(Marcus et al., 2010) and not have used beta-blockers before the start of the study.
(ii) *Treatment strategy*: Randomization is performed at each visit/contact with the hospital, and patients are aware of the treatment strategy allocation. At each visit, patients can be randomized to either beta-blockers or no beta-blockers. (See the next section for details)
(iii) *Follow-up*: It starts at the first visit to the Hospital of Trieste (first randomization) and ends at death or heart transplant or last contact or on December 31, 2019, whichever comes first.
(iv) *Outcome*: The primary outcome of interest is recurrent MVA and secondarily death/heart transplant.
(v) *Causal contrast of interest*: It is per-protocol effect.
(vi) *Analysis plan*: It includes the joint frailty model for recurrent events and a terminal event (see the next section for details).

Finally, underlying the methodology presented in this work there are important assumptions that need to be remarked upon. In the context of our motivating example, first of all, we are assuming subjects have a non-zero and a non-one probability of receiving the prescription of beta-blockers over time (A1: Positivity). We are also assuming that cardiologist's decision to prescribe beta-blockers does not interfere with other subjects' potential outcome (A2: No interference) and that the observed outcome is the same as the potential outcome defined under the treatment regimen actually assigned (A3: Consistency). Last, as in all propensity score methods, we are assuming that all important confounders are measured (A4: No unmeasured confounders).

TABLE 1 Summary statistics of baseline characteristics in the cohort. Categorical variables are summarized with *n*(%), whereas either mean (*SD*) or median (Q1–Q3) are used for continuous variables as appropriate.

	Overall population (*N* = 123)
Clinical data	
Age (years)	39 (16)
Male (%)	86 (70)
Heart rate (bpm)	66 (12)
Systolic blood pressure (mmHg)	124 (16)
Year of enrolment: Before 2000	73 (59.4)
Year of enrolment: 2000–2010	31 (25.2)
Year of enrolment: >2010	19 (15.4)
MVA before the study period (%)	31 (25)
New York Heart Association Class>1 (%)	22 (18)
Proband (%)	92 (75)
Family history SCD (%)	25 (20)
Syncope (%)	19 (15)
ICD (%)	9 (7)
ECG/ 24-h Holter	
Epsilon waves (%)	18 (15)
Negative T waves (%)	30 (24)
Premature ventricular complexes (PVC) in 24 h	1005 (14–3780)
Premature ventricular complexes (PVC) >1000/24 h (%)	62 (50)
Positive late potentials (%)	31 (25)
Non-sustained ventricular tachycardia (NSVT) (%)	58 (47)
Echocardiography	
Left ventricular ejection fraction	55 (13)
Right ventricular fractional area change	30 (12)
Biventricular dysfunction (%)	28 (23)
Tricuspid regurgitation (TR) >1 (%)	14 (12)

3 | METHODS

3.1 | Notation

Time is considered continuous, and it is measured in months. All subjects' baseline corresponds to the first visit to the hospital. Observation times in the study are made at irregular intervals of follow-up and differ across individuals. Therefore, we use a common time grid for all subjects denoted with $t_0, t_1, \dots, t_k, \dots, t_T$, which includes all time points in which any contact with the hospital is observed in the cohort together with all the terminal events and censoring times. We use the notation from Hernán and Robins (2020) and denote exposure (current treatment assignment to either beta-blockers or no beta-blockers) at time t_k by B_k, confounders measured at time t_k by $\mathbf{L}_k$, baseline covariates by $\mathbf{Z}$, the occurrence of a recurrent arrhythmic event at time t_k by R_k, and the occurrence of the terminal event at time t_k by D_k. Moreover, $\bar{\mathbf{B}}_k = (B_1, \dots, B_k)$ corresponds to the treatment regimen history up to time t_k; $\bar{\mathbf{L}}_k = (\mathbf{L}_1, \dots, \mathbf{L}_k)$ corresponds to the history of time-dependent confounders up to time t_k, $\bar{\mathbf{R}}_k = (R_1, \dots, R_k)$ corresponds to the history of recurrent arrhythmic events up to time t_k. We use capital letters to denote random variables and lowercase letters to denote their realizations.

3.2 | Observation scheme

Each subject i is observed only in a subset of time points $t_{1i}, \dots, t_{ki}, \dots, t_{li}$, with $t_{li} \leq t_T$ being her/his end time of observation. We assume that B_{ik} remained constant and $R_{ik} = 0$ between two observations. We can also assume that some $\mathbf{L}_{ik}$ remained

constant between contacts with the hospital. For time-dependent confounders whose such assumption did not hold we specified generalized mixed effects models to impute subject-specific values of the covariate at time points other than measurement times. More details on the specification of the imputation models are given in Appendix A.2.

3.3 | Estimand of interest and measure of effect for recurrent events

With regard to the timescale, that is the metric on which the risk sets are constructed and times to event are measured (Klein & Moeschberger, 2003), so far we have referred to time T as the time in months since the study entry.

In recurrent events settings, this is not the only timescale possible. We now define a different timescale, $\Delta T = T_{k+1} - T_k$, as the time in months since the last hospital contact. This corresponds to a "clock-reset" formulation in which every time a patient has contact with the hospital the clock is reset to 0. We use this timescale for the recurrent events outcome. Since we assume that after a major arrhythmia the subject has some sort of contact with the hospital, this timescale corresponds to an extension of the "gap-time" formulation for recurrent events. Under this timescale, we are interested in comparing the treatment strategy "treat with beta-blockers at visit k" versus "do not treat with beta-blockers at visit k." We denote the first strategy by $\{b_k = 1\}$ and the second one $\{b_k = 0\}$. The average treatment effects of B_k on the primary outcome can be defined as the contrast between the counterfactual expected outcomes $R_{\Delta t}^{b_k=1}$ and $R_{\Delta t}^{b_k=0}$, that is, the counterfactual time-varying indicator for the recurrent event under the two treatment strategies assigned at time t_k. The average causal treatment effect we aim to estimate is a point treatment effect, but since there are multiple visits it corresponds to a treatment effect averaged across visits. Therefore, we are not interested in distinguishing between visits since we assume that the treatment effect on the recurrent events endpoint does not significantly differ between one visit and the other. The above causal effect has been previously defined by Keogh et al. (2018), and it is also referred to as the"short-term effect." As a measure of effect for the primary endpoint, we consider the cumulative hazard, $\Lambda(\Delta t)$. The causal contrast of interest is $\Lambda(\Delta t)^{b_k=1}$ versus $\Lambda(\Delta t)^{b_k=0}$ for $\Delta t = 1, \dots, 24$ months. $\Lambda(\Delta t)^{b_k=1}$ and $\Lambda(\Delta t)^{b_k=0}$ are the cumulative hazards specified in terms of the counterfactual outcomes:

$$\Lambda(\Delta t)^{b_k} = \int_0^{\Delta t} \lim_{u \to 0} \frac{Pr(R_{s+u}^{b^k} = 1 | R_s^{b^k} = 0)}{u} ds. \tag{1}$$

3.4 | Estimand of interest and measure of effect for the terminal event

For the terminal event, which is by definition a long-term outcome, we are interested in estimating the joint effect of treating with beta-blockers at each visit over the follow-up versus never treating with beta-blockers. We denote the first treatment strategy by $\bar{\mathbf{b}} = (1, 1, \dots, 1) = \bar{\mathbf{1}}$ and the second one by $\bar{\mathbf{b}} = (0, 0, \dots, 0) = \bar{\mathbf{0}}$. The average treatment effects of $\bar{\mathbf{B}}$ on the secondary outcome can be defined as the contrast between the counterfactual expected survival outcomes under the two treatment strategies.

We now define $D_k^{\bar{\mathbf{b}}}$ as the counterfactual time-varying indicator for the terminal event under treatment strategy $\bar{\mathbf{b}}$. In this case, our causal estimand of interest is the survival probability at time t_k, $S_{t_k}^{\bar{\mathbf{b}}} = Pr(D_k^{\bar{\mathbf{b}}} = 0)$ and our causal contrast of interest is

$$Pr(D_k^{\bar{\mathbf{1}}} = 0) \text{ versus } Pr(D_k^{\bar{\mathbf{0}}} = 0) \text{ for } t_k = 1, \cdots, 60 \text{ months}. \tag{2}$$

3.5 | Treatment effect definition

For both outcomes, as treatment effects, we consider the ratio and the difference of the measures of effect previously defined in terms of counterfactual outcomes, $\Lambda_{\Delta t}^{b_k}$ and $S_{t_k}^{\bar{\mathbf{b}}}$.

Specifically, these average treatment effects correspond to the following questions:

(i) What would be the average difference/ratio in the cumulative hazard of a new MVA up to 24 months from a previous visit if everyone received the treatment at that visit compared with if everyone did not receive the treatment?

(ii) What would be the difference/ratio in the survival up to 5 years from the start of follow-up if everyone continuously received the treatment compared with if everyone never received the treatment?

3.6 | Marginal structural models for recurrent events and a terminal event

To estimate the causal effects of interest, we need to specify a joint structural model for the hazard of the counterfactual recurrent events outcome and the hazard of the counterfactual death outcome for each subject i, according to the treatment strategies b_k and $\bar{\mathbf{b}}$, respectively. Specifically, we assume a structural joint frailty model (Model 1) as follows (Liu et al., 2004; Rondeau et al., 2006):

$$\begin{aligned}\lambda_i^{b_k}(t_{k+1}-t_k|u_i) &= \lambda_0(t_{k+1}-t_k)\exp\{b_{it_k}\boldsymbol{\beta}(t_{k+1}-t_k)+u_i\}\\ \gamma_i^{\bar{\mathbf{b}}}(t_k|u_i) &= \gamma_0(t_k)\exp\{b_{it_k}\boldsymbol{\alpha}(t_k)+ru_{i1}\}\end{aligned} \tag{3}$$

where b_{it_k} are the time-dependent covariates indicating the current treatment at time t_k; $\boldsymbol{\beta}(t_{k+1}-t_k)$ and $\boldsymbol{\alpha}(t)$ are the possibly time-dependent regression coefficients for beta-blockers; the individual frailty terms, u_i, are independently and identically distributed random variables with $u_i \sim \mathcal{N}(0,\sigma^2)$, and $\lambda_0(t_{k+1}-t_k)$ and $\gamma_0(t_k)$ are the baseline hazard functions of the Royston–Parmar (Royston & Parmar, 2002) survival model.

All observations from the same subject share the frailty term u_i, which can affect both the risk of recurrent events and the risk of the terminal event. When $r \neq 0$, the model assumes the existence of a common source variation for both the association between recurrent events and between recurrent events and the terminal event.

Alternatively, the general shared frailty model (Model 2) allows for two distinct origins of heterogeneity: one for the recurrent events' dependency and one for the association between the two intensity functions. The model is defined by (Mazroui et al., 2012)

$$\begin{aligned}\lambda_i^{b_k}(t_{k+1}-t_k|u_{i1},u_{i2}) &= \lambda_0(t_{k+1}-t_k)\exp\{b_{it_k}\boldsymbol{\beta}(t_{k+1}-t_k)+u_{i1}+u_{i2}\}\\ \gamma_i^{\bar{\mathbf{b}}}(t|u_{i2}) &= \gamma_0(t)\exp\{b_{it}\boldsymbol{\alpha}(t)+u_{i2}\}.\end{aligned} \tag{4}$$

In this case, two mutually independent individual frailty terms are introduced in the model: $u_{i1} \sim \mathcal{N}(0,\sigma_1^2)$, $u_{i2} \sim \mathcal{N}(0,\sigma_2^2)$, $\forall i = 1,\ldots,123$.

Of note, both models allow for time-dependent coefficients to relax the assumption of proportional hazards which in practice is often violated. Specifically, time-dependent coefficients were obtained by adding an interaction term between the treatment coefficient and time. For the latter, a restricted cubic spline transformation was used to allow for nonlinearity. In Appendix A.2, we show how the marginal models are used to obtain the causal estimands of interest.

3.7 | Model for the weights

In Figure 1, a directed acyclic graph (DAG) is used to represent the causal problem under study. The fixed (green) and time-dependent (blue) confounders specific to the example are also listed. An important aspect of the DAG representing our causal problem is that there is treatment-confounders feedback for the terminal event outcome as it can be seen from the lines going from $\mathbf{L}_0$ to B_1 and from B_1 to $\mathbf{L}_2$. Moreover, it is important to note that we are assuming that treatments only affect the outcomes at the subsequent time since there are no paths between arrhythmic events and past treatments (e.g., between B_0 and R_2) and between the terminal events and past treatments (e.g., between B_0 and D_2). The rationale behind this assumption relies on the pharmacodynamics of beta-blockers which are known to have no cumulative effect. In order to control for confounding, we need to construct the inverse probability of treatment weights.

This methodology was previously described by Hernán et al. (2000) and Robins et al. (2000). The inverse probability of treatment weight (IPTW) is based on the probability for subject i of being assigned to a specific treatment at time t_k,

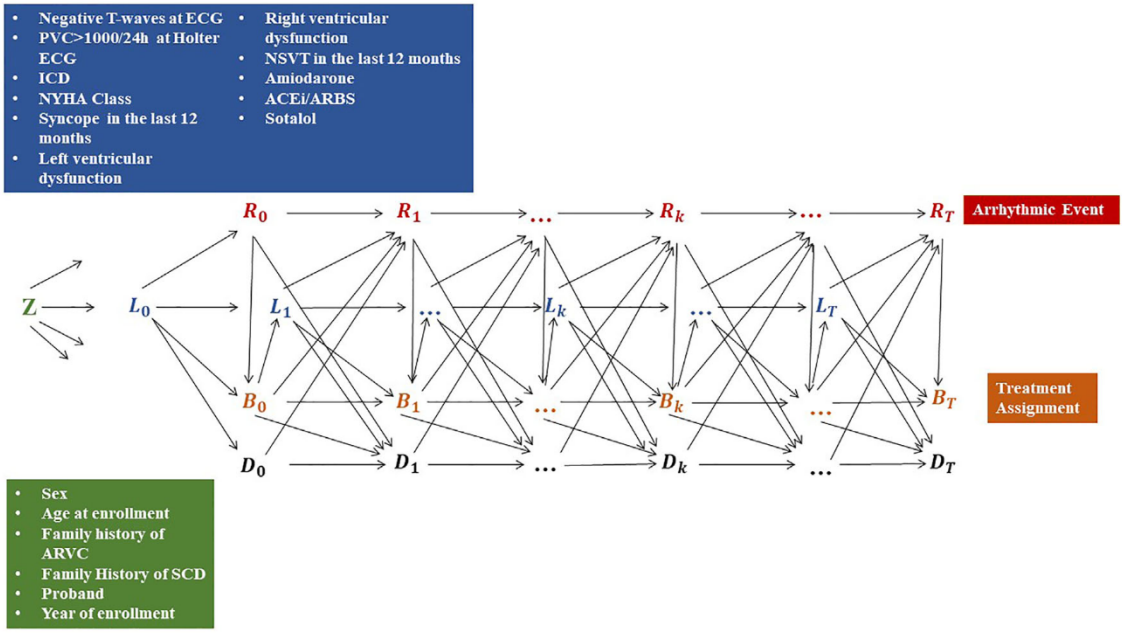

FIGURE 1 Causal direct acyclic graph. **Z** represents fixed confounders, **L** represents time-dependent confounders, B is the treatment indicator, R is the recurrent-event indicator, and D is the terminal event indicator. Subscripts represent the time points at which random variables can be measured

conditionally to the subject's previous history:

$$PS_i(t_k) = \mathrm{P}(B_k = b_{ik} | \bar{\mathbf{B}}_{k-1} = \bar{\mathbf{b}}_{i(k-1)}, \bar{\mathbf{L}}_k = \bar{\mathbf{l}}_{ik}, \bar{\mathbf{R}}_k = \bar{\mathbf{r}}_{ik}, \mathbf{Z} = \mathbf{z}_i, D_k = 0). \tag{5}$$

The probability defined in (5) is also known as the *propensity score*, and in observational studies it is an unknown quantity which, therefore, needs to be estimated from the data. We now define the treatment weights, $w_i^{(T)}$, which differ between the two outcomes because of the differences between the treatment effect we aim to estimate. For the terminal event, we want to estimate a *joint* effect; therefore, the weights need to take into account of time-dependent confounding:

$$w_i^{(T)}(t_k) = \prod_{j=0}^{k} \frac{1}{PS_i(t_j)} \tag{6}$$

To reduce the weights' variability and hence to increase the precision of the estimates, a *stabilized* version of the weights is used (Hernán et al., 2000; Robins et al., 2000):

$$sw_i^{(T)}(t_k) = \prod_{j=0}^{k} \frac{\mathrm{P}(B_j = b_{ij} | \bar{\mathbf{B}}_{j-1} = \bar{\mathbf{b}}_{i(j-1)})}{PS_i(t_j)}. \tag{7}$$

On the other hand, for the recurrent event outcome we are estimating the effect of beta-blockers proximal to a visit, that is, a point treatment effect, so the treatment weights are simply defined as

$$w_i^{(T)}(t_k) = \frac{1}{PS_i(t_k)}. \tag{8}$$

To stabilize them, we use the marginal probability of getting the treatment he/she has received at time t_k:

$$w_i^{(T)}(t_k) = \frac{Pr(B_k = b_{ik})}{PS_i(t_k)}. \tag{9}$$

TABLE 2 Summary statistics of stabilized treatment weights

Treatment weights	Min	1st quartile	Median	Mean	SD	3rd quartile	Max
Recurrent events	0.18	0.78	0.86	0.93	0.48	1.02	3.18
Terminal event	0.60	1.00	1.00	1.01	0.10	1.00	1.52

In addition to treatment weights, also censoring weights (C) can be defined in the same way in order to adjust for possible dependent censoring different from death/heart transplant (Hernán et al., 2000; Robins et al., 2000):

$$sw_i^{(C)}(t_k) = \prod_{j=0}^{k} \frac{\mathrm{P}(C_j = 1|\bar{\mathbf{C}}_{j-1} = \mathbf{0}, \bar{\mathbf{B}}_{j-1} = \bar{\mathbf{b}}_{i(j-1)}, D_{j-1} = 0)}{\mathrm{P}(C_j = 1|\bar{\mathbf{C}}_{j-1} = \mathbf{0}, \bar{\mathbf{B}}_{j-1} = \bar{\mathbf{b}}_{i(j-1)}, \bar{\mathbf{L}}_j = \bar{\mathbf{l}}_{ij}, \bar{\mathbf{R}}_j = \bar{\mathbf{r}}_{ij}, \mathbf{Z} = \mathbf{z}_i, D_{j-1} = 0)}. \tag{10}$$

However, in our application the fraction of censoring due to possibly informative drop-out is small and therefore weights in (10) were not estimated.

Typically, to estimate the probabilities required to obtain the weights logistic regression models are used. However, most recently time-to-event models have been proposed when constructing weights in marginal structural models (Jensen et al., 2016; van der Wal & Geskus, 2011). The main advantage of using survival models is that they do not require to discretize time, and they are particularly useful in case data are not recorded at fixed intervals of time (e.g., yearly visits), but information can be gained at irregular time intervals as it is our case.

Specifically, we used a modulated Cox Poisson model to estimate the instantaneous risk of starting/continuing using beta-blockers at time t_k since the entry in the study is measured in months:

$$r_i(t_k|\mathbf{z}, \mathbf{l}, \bar{\mathbf{r}}, \bar{\mathbf{b}}) = r_0(t)\exp\{\mathbf{z}_i^T\boldsymbol{\gamma}_1 + \mathbf{l}_{ik}^T\boldsymbol{\gamma}_2 + f_1(\bar{\mathbf{b}}_{i(k-1)})^T\gamma_3 + f_2(\bar{\mathbf{r}}_{ik})^T\gamma_4\}. \tag{11}$$

The hazard model defined in (11) corresponds to the extension of the Cox model by Andersen and Gill (1982) for recurrent events in which recurrent events for subject i (i.e., use of beta-blockers at each time t_k) are considered independent conditionally on fixed baseline covariates and time-varying covariates. In the models fixed, $\mathbf{z}_i$, and time-dependent covariates, $\mathbf{l}_{ik}$, are used to take into account the characteristics of the subjects at time t_k. Moreover, we need to choose how to simplify the history of the recurrent events and the treatment history in order to model them as a time-varying covariate. As $f_1(\bar{\mathbf{b}}_{k-1})$, the treatment regimen assigned at the previous contact with the hospital (Karim et al., 2014) was used, whereas the number of past major arrhythmic events was used as $f_2(\bar{\mathbf{r}}_k)$. From the predicted values of the model, it is straightforward to obtain the estimated probabilities needed to define the weights. The probability in (5) can be obtained as

$$PS_i(t_k) = \begin{cases} 1 - \exp\{-\int_{t_{k-1}}^{t_k} r_i(s|\mathbf{z}, \mathbf{l}, \bar{\mathbf{r}}, \bar{\mathbf{b}})\}ds & \text{if } b_{ik} = 1 \\ \exp\{-\int_{t_{k-1}}^{t_k} r_i(s|\mathbf{z}, \mathbf{l}, \bar{\mathbf{r}}, \bar{\mathbf{b}})\}ds & \text{if } b_{ik} = 0 \end{cases}. \tag{12}$$

A similar model can also be used to estimate the probabilities of the numerator in (7). Detailed R code on the weights estimation and the structure of the dataset are available as Supporting Information on the journal's web page.

4 | RESULTS

4.1 | Weights diagnostics

Weights were obtained using the procedure explained in Section 3.7 and the R software (see the Supplementary Information). The distribution of the stabilized weights over 21 years of follow-up is reported in Figure 2 together with the corresponding number of subjects under observation. Summary statistics are reported in Table 2. Overall, weights for the terminal event have a small variability and they have a mean and median of around 1. Their behavior over time is also satisfying. With regard to the recurrent events weights, they show higher variability compared to the terminal event ones but their behavior is still acceptable.

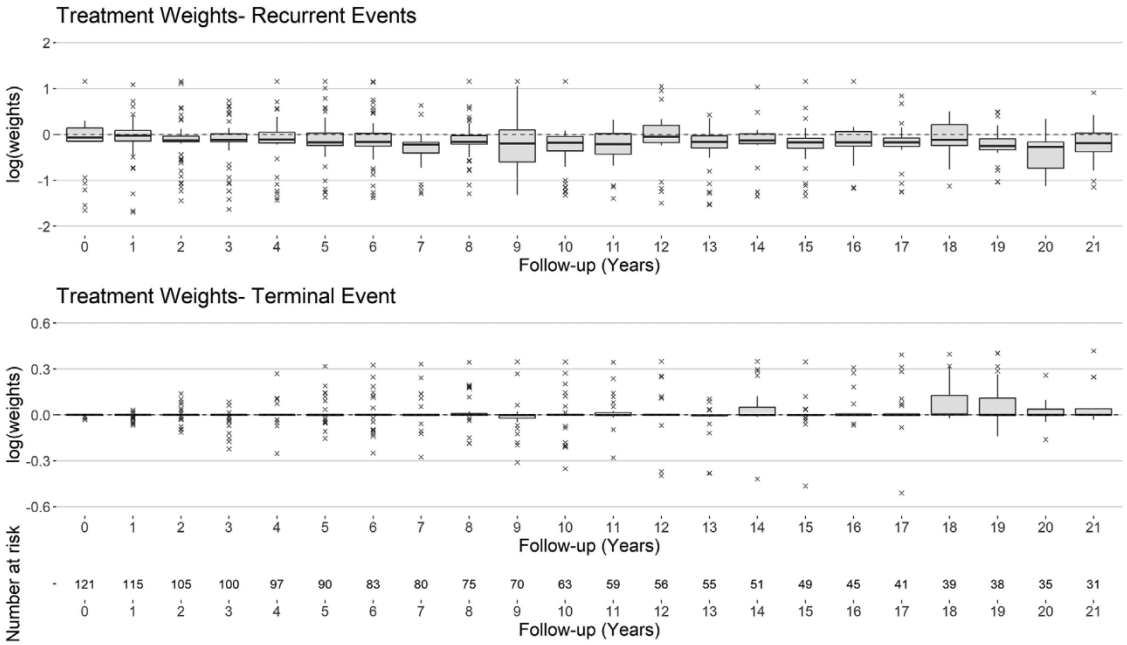

FIGURE 2 Distribution of the stabilized weights on the log scale over an observation period of 21 years. The number of subjects still under observation is reported below

TABLE 3 Coefficients with relative standard errors, hazard ratios, and percentile bootstrap 95% CI from the structural marginal models with fixed coefficients

	Recurrent events			
	$\hat{\beta}$	$\hat{se}$	$\hat{HR}$	**95% CI**
Model 1	−1.31	1.17	0.27	0.008–0.55
Model 2	−2.16	1.20	0.12	0.005–0.573
	Terminal event			
	$\hat{\alpha}$	$\hat{se}$	$\hat{HR}$	**95% CI**
Model 1	−0.06	0.70	0.94	0.116–1.799
Model 2	0.10	0.77	1.10	0.177–3.147

4.2 | Treatment effect estimates

Using the weighted dataset, the two different models described in Section 3.6 were fitted using the `merlin` package in STATA (Crowther et al., 2020) (see the Supplementary Information). All standard errors and confidence intervals were obtained through 150 nonparametric bootstrap replicates. By using bootstrap, we took into account for the fact that the dataset was weighted and, therefore, observations could not be considered independent (Ali et al., 2014). Moreover, the uncertainty of the weights estimation process was incorporated in the treatment effect estimates.

The degree of freedom of the baseline hazard functions was selected using the akaike information criterion (AIC). First, the two models with fixed coefficients were obtained and the hazard ratios are reported in Table 3. Beta-blockers appear to reduce the risk of arrhythmias. It can be observed that different specifications for the random effect structure of the model influence the estimates for the recurrent events. Indeed, the protective effect of beta-blockers is greater in Model 2, where two independent frailty terms are used to model the correlation between events of the same subjects. On the other hand, there is not enough evidence in support of a reduction of the risk of the terminal event in patients continuously treated with beta-blockers.

Both models were then extended to include time-varying coefficients. The hazard ratio (HR) in function of time is shown in Figure 3.

From the time-dependent hazard ratios, it can be observed that the protective effect of beta-blockers with respect to the recurrent events is significant after 6 months since contact with the hospital in both models (panels a and b) even though

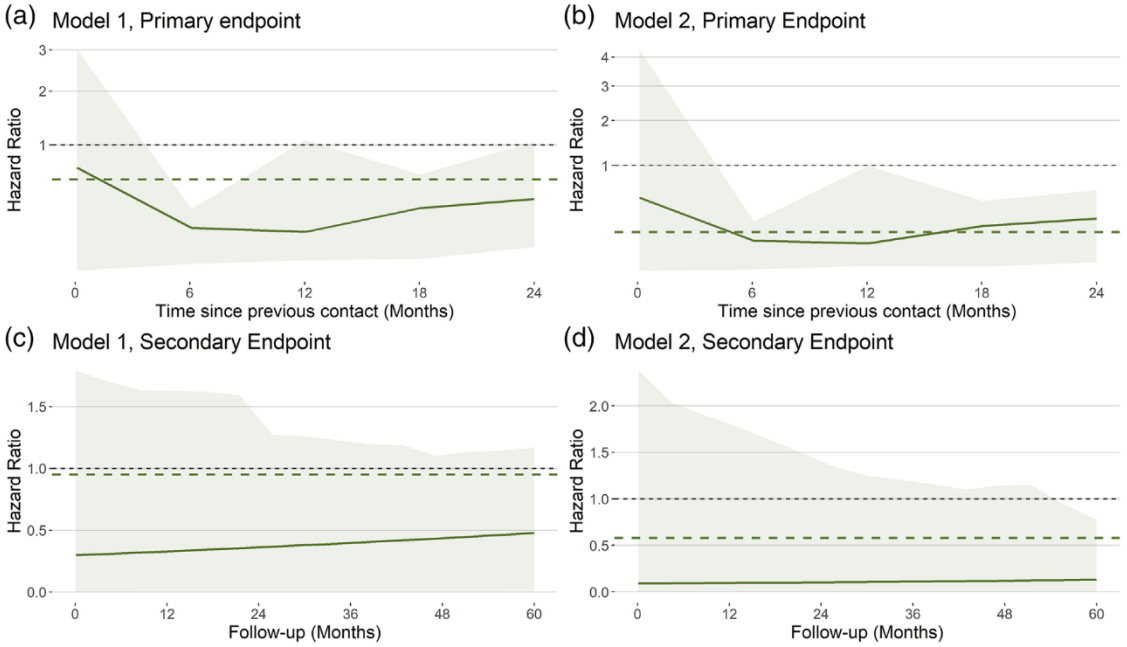

FIGURE 3 Solid lines represent time-dependent HR estimates for the primary endpoint (panels a and b) and the secondary endpoint (panels c and d) obtained with Model 1 and Model 2, respectively. Shaded areas represent the 95% percentile bootstrap confidence interval. For comparison, the corresponding fixed HR is indicated with a green dashed line. Black dashed lines represent HR = 1

TABLE 4 Frailty terms parameters estimated from the marginal structural models along with 95% percentile bootstrap confidence intervals and AIC

Model 1	$\hat{\sigma}$	$\hat{r}$	**AIC**
Fixed coefficients	0.79 (0.46 to 1.62)	0.04 (−0.03 to 0.9)	1467
Time-varying coefficients	0.79 (0.41 to 1.51)	0.06 (−0.02 to 1.35)	1466
Model 2	$\hat{\sigma}_1$	$\hat{\sigma}_2$	
Fixed coefficients	0.83 (0.38 to 1.43)	0.29 (0.04 to 1.32)	1424
Time-varying coefficients	0.46 (0.4 to 1.5)	0.6 (0.39 to 1.32)	1415

the effect is weaker in Model 1. For the terminal event, the lack of effect is also confirmed when the effect is allowed to be time varying (panels c and d).

All models confirm the positive correlation between the recurrent events. Model 1 exhibits a very small correlation between the recurrent events process and the terminal event process. On the other hand, the correlation between the recurrent events and the terminal event is better captured by Model 2, which shows that the two processes are positively correlated (Table 4). This could be explained by the fact that the data-generating mechanism contains two distinct sources of dependencies: the inter-recurrences one and the one between the terminal and recurrent events.

Moreover, as shown in Table 4, Model 2 seems to better describe the correlation structure of the problem under study because it has a lower AIC compared to Model 1. Therefore, in Figure 4 we show the measures of effect and the treatment effect estimates from Model 2 with time-varying coefficients, which display the lowest AIC.

In panel a of Figure 4, it can be noted that 24 months after contact with the hospital the cumulative hazard of an arrhythmic event reaches 16% if patients were not assigned to beta-blockers on that occasion, whereas it is estimated to be around 4% if, on the contrary, they were assigned to beta-blockers. As explained in the Methods section, these measures of effect are marginal with respect to the individual frailty terms as opposed to the hazard ratio which is conditioned on them. We can conclude that the difference in the cumulative hazard of an arrhythmic event significantly decreases when subjects have been assigned to beta-blockers at the visit (panel b of Figure 4). Specifically, after 24 months the difference in the cumulative hazard is −0.14,95% confidence interval, (CI) [−0.82, −0.03]. The treatment effect is highlighted using a relative measure of effect such as the ratio (panel c of Figure 4). In fact when beta-blockers are prescribed to a patient, on average, 24 months from that visit, his/her cumulative hazard will be 82% smaller than with respect to the same patient

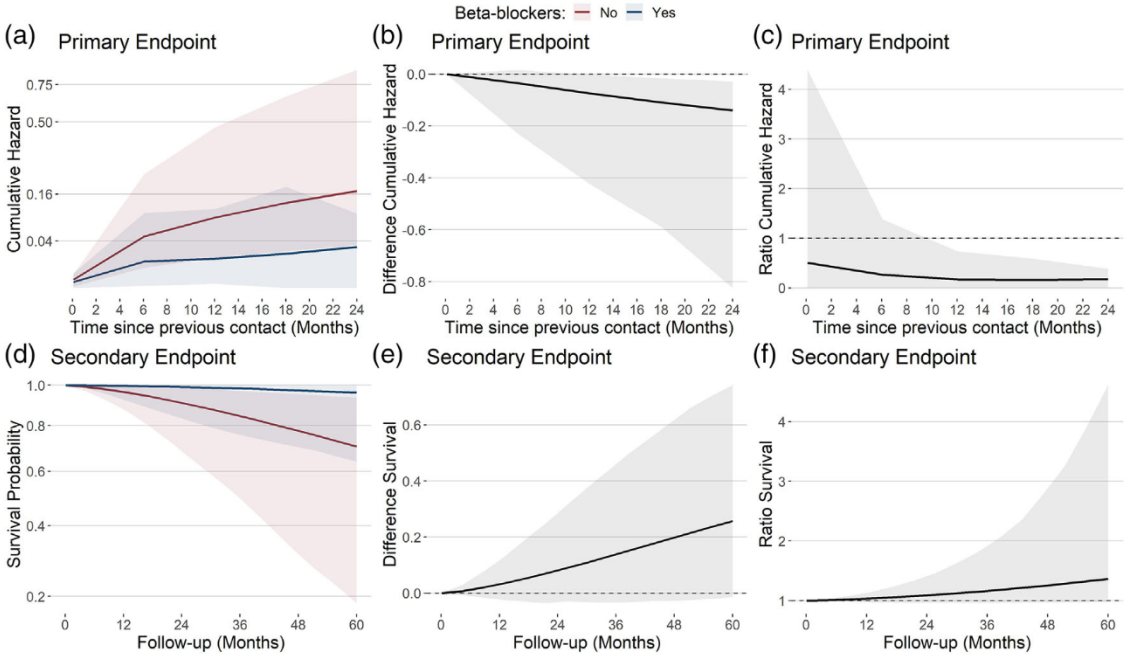

FIGURE 4 Measures of effect and average treatment effects estimates for the primary endpoint (panels from a to c) and the secondary endpoint (panels from d to f). Shaded areas represent the 95% percentile bootstrap confidence intervals

without the prescription. On the contrary, no significant difference (panel e of Figure 4) nor ratio (panel f of Figure 4) between the survival probabilities can be seen.

5 | DISCUSSION

In this paper, we presented a marginal structural model for a recurrent events process and a terminal event. The methodology was motivated by the need of estimating the treatment effect of beta-blockers on recurrent MVA and survival with a causal interpretation in a retrospective clinical registry. Together with the problem of controlling for both fixed and time-dependent confounders, including the history of MVA, we faced the issue of modeling the correlation among events from the same subject which are biologically related. To overcome the many disadvantages of the hazard as a measure of effect discussed by Hernán (2010), we used the cumulative risk of recurrent major arrhythmic events and the survival probability.

To model the recurrent event process, many different approaches have been proposed for both counts and gap times (Amorim & Cai, 2015). In contrast with marginal methods, shared frailty models add individual non-observable random effects called *frailty* into the model to take into account the unobserved heterogeneity. In addition, when a semicompeting risk is present, shared frailty models can be extended to jointly model the recurrent event process and the terminal event when the two are correlated. It should be pointed out that by modeling the process of the recurrent events jointly with the process of the terminal event, our method allows estimating the direct effect on the recurrent events. Specifically, it can be defined as the treatment effect on the recurrent events not mediated by the semicompeting event (Young et al., 2020). Furthermore, the joint frailty model specified has the advantage of using a baseline intensity function based on regression splines and time-dependent coefficients which greatly increase the flexibility of the proposed approach.

As in most observational studies, the observation times are informative since patients in worse conditions are more likely to have contact with the hospital. In order to make our analysis less dependent on the subject-specific observation times as possible, we have considered a common, irregular, time grid. In the weights estimation, using a time-dependent model we were able to estimate IPTW weights using such a time grid. We made this choice since using an artificial fixed-length time grid is not appropriate for settings such as the one of the ARVC registry, which is characterized by a long observation period and the granularity of the data. Furthermore, as a consequence of the irregular observation scheme of our study, we had missing data in some of the time-dependent confounders at times different than the observed ones that required the use of generalized mixed models for the imputation of the missing values.

The "gap-time" formulation for recurrent events represents a meaningful way of measuring time with nonincidental recurrent events (i.e. events that alter the event process itself) (Cook & Lawless, 2007). It is also rooted in the pharmacodynamics knowledge about the short-term effect of beta-blockers on the arrhythmic episode. Therefore, it justifies the choice of estimating an average point-treatment effect across visits. Moreover, it reflects the analysis we would have performed in the corresponding target trial where subjects would have been assigned to the treatment at each visit/contact with the hospital.

Nevertheless, it would be possible to define different timescales for the recurrent events and define different measures of effects, such as the expected number of recurrent events per subject up to time t, similarly to Jensen et al. (2016). The issue with an approach based on counts for the recurrent events is that it requires the use of a counting process format in the part of the joint frailty model for the recurrent event as well. The counting process format was used for the terminal event of the model. We found that adding the start-stop times format also for the recurrent events dramatically increased the complexity of the estimating procedure (i.e., the quadrature of the integrals needed for the frailty terms) to the point that it did not allow us to obtain valid estimates from the model. The complexity related to the use of the counting process format in joint models has been previously discussed by Crowther et al. (2016).

Moreover, we were able to obtain standard errors and confidence intervals through bootstrap which has the advantage of taking into account the uncertainty due to the whole estimation process and the use of a weighted dataset.

With regard to the assumptions underlying this work, we believe that they are met since all patients could potentially receive a beta-blockers prescription since none of them was intolerant to the drug (A1); the fact that a patient received beta-blockers would not impact another patient's risk of having an MVA the next day (A2); the event MVA is not different according to the treatment regimen assigned (A3). With regard to A1, it has to be noted that we cannot exclude positivity violations due to chance in finite samples and this is the reason why we have implemented stabilized weights in our IPTW estimator since they are known to weaken this assumption. Obviously, the last one is the most difficult to rule out (A4). In our example, we used all the factors which to the best of our scientific knowledge of this disease could represent a confounder in the treatment–outcome relationship. An important unmeasured factor is the genetic characterization of subjects. However, its prognostic role has still to be completely understood (Corrado et al., 2020). Moreover, because too little is known in this regard, gene mutations are not used for the assignment of patients to beta-blockers. Even though genetics is an important yet partly unknown aspect of this disease and it will probably play an important role in the treatment of patients affected by ARVC in the future, at the moment it cannot be considered a confounder.

As already mentioned, we did not have the data regarding the purchases of beta-blockers by the patients. Therefore, even though our analysis is a per-protocol effect since it considers changes in the treatment made by the cardiologists during the follow-up, the calculation of patients' adherence between visits cannot be obtained. In future work, it could be of interest to consider the adherence of patients and compare its effect to the one obtained here.

In conclusion, our approach based on marginal structural models for event-history data was able to produce a marginal estimate of the treatment effect in analogy with the one that would have been estimated from a RCT. However, in many real-world applications, as the one presented, RCT is highly unfeasible due to the rarity of the disease and the long observation period required to observe the clinically relevant outcomes. In conclusion, we believe that applying methods such as the one proposed for this application could represent a valid alternative to RCT in many life-history settings.

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CONFLICT OF INTEREST

The authors have declared no conflict of interest.

DATA AVAILABILITY STATEMENT

Research data cannot be shared since they are the property of the Trieste Hospital.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX A

A.1 | Mixed effect models for the imputation of time-dependent confounders

For the time-dependent confounders that could not be assumed to remain constant between observations (Negative T waves at ECG, PVC>1000/24 h at Holter ECG, NYHA class, right ventricular dysfunction, left ventricular dysfunction), the following generalized mixed effect model was fitted for each of them to impute values other than the measurement times:

$$g[E(L_i(t_k))] = \alpha_0 + a_{i0} + \sum_{j=1}^{4}(\alpha_j + a_{ij})BB_j(t_k), \tag{A.1}$$

where $BB_j(t_k)$, $j = 1, \dots, 4$ is the B-basis for a natural cubic spline of follow-up time t_k with three internal knots placed at the 25th, 50th, and 75th percentiles of follow-up times. $\boldsymbol{\alpha}$ is the vector of the fixed effect, and $a_i \sim \mathcal{N}(\mathbf{0}, \mathbf{D})$ is the vector of the subject-specific random effects, with $\mathbf{D}$ unstructured variance covariance matrix. Since all time-dependent confounders considered were dichotomous variables, the *logit* function was used as link function $g(\cdot)$.

A.2 | Treatment effect estimation from MSM

An estimate of the counterfactual measures of effect under the treatment strategies can then be obtained from Model 3 as follows:

$$\begin{aligned}
\hat{\Lambda}_{\Delta t}^{b_k=0} &= \int \left\{ \int_0^{\Delta t} \hat{\lambda}_0(s)\exp\{u\}ds \right\} du. \\
\hat{\Lambda}_{\Delta t}^{b_k=1} &= \int \left\{ \int_0^{\Delta t} \hat{\lambda}_0(s)\exp\{\hat{\beta}(s) + u\}ds \right\} du. \\
\hat{S}_{t_k}^{\bar{\mathbf{0}}} &= \int \exp\left\{ -\int_0^{t_k} \hat{\gamma}_0(s)\exp\{\hat{r}u\}ds \right\} du. \\
\hat{S}_{t_k}^{\bar{\mathbf{1}}} &= \int \exp\left\{ -\int_0^{t_k} \hat{\gamma}_0(s)\exp\{\hat{\alpha}(s) + \hat{r}u\}s \right\} du.
\end{aligned} \tag{A.2}$$

Similarly from Model 4:

$$\hat{\Lambda}_{\Delta t}^{b_k=0} = \int \left\{ \int \left\{ \int_0^{\Delta t} \hat{\lambda}_0(s) \exp\{u_1 + u_2\} ds \right\} du_1 \right\} du_2,$$

$$\hat{\Lambda}_{\Delta t}^{b_k=1} = \int \left\{ \int \left\{ \int_0^{\Delta t} \hat{\lambda}_0(s) \exp\{\hat{\beta}(s) + u_1 + u_2\} ds \right\} du_1 \right\} du_2,$$

$$\hat{S}_{t_k}^{\bar{\mathbf{0}}} = \int \exp\left\{ -\int_0^{t_k} \hat{\gamma}_0(s) \exp\{u_2\} ds \right\} du_2,$$

$$\hat{S}_{t_k}^{\bar{\mathbf{1}}} = \int \exp\left\{ -\int_0^{t_k} \hat{\gamma}_0(s) \exp\{\hat{\alpha}(s) + \hat{r} u_2\} ds \right\} du_2. \tag{A.3}$$

The estimates of the baseline intensity functions are easily obtained since Model 1 and Model 2 are both flexible parametric survival models. The frailty terms are integrated out using mean-variance adaptive Gauss–Hermite quadrature. Therefore, these measures of effect are fully marginal, that is, at the average population level.

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