Bayesian joint modeling of bivariate longitudinal and competing risks data: An application to study patient-ventilator asynchronies in critical care patients

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Mechanical ventilation is a common procedure of life support in intensive care. Patient-ventilator asynchronies (PVAs) occur when the timing of the ventilator cycle is not simultaneous with the timing of the patient respiratory cycle. The association between severity markers and the events *death* or *alive discharge* has been acknowledged before, however, little is known about the addition of PVAs data to the analyses. We used an index of asynchronies (AI) to measure PVAs and the SOFA (sequential organ failure assessment) score to assess overall severity. To investigate the added value of including the AI, we propose a Bayesian joint model of bivariate longitudinal and competing risks data. The longitudinal process includes a mixed effects model for the SOFA score and a mixed effects beta regression model for the AI. The survival process is defined in terms of a cause-specific hazards model for the competing risks *death* or *alive discharge*. Our model indicates that the SOFA score is strongly related to vital status. PVAs are positively associated with *alive discharge* but there is not enough evidence that PVAs provide a more accurate indication of *death* prognosis than the SOFA score alone.

Keywords: Bayesian inference; Competing risks; Intensive care; Joint models; Model selection.

Additional supporting information including source code to reproduce the results may be found in the online version of this article at the publisher's web-site

1 Introduction

Mechanical ventilation (MV) is one of the most common procedures of life support in the intensive care unit (ICU). The goals of MV are to improve gas exchange, reduce the work of breathing, and improve patient comfort (Blanch et al., 2015). In critically ill patients, appropriate interaction with the mechanical ventilator is very important throughout ventilatory support. Patient-ventilator asynchronies (PVAs) appear when the timing of the ventilator cycle is not simultaneous with the timing of the

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patient's respiratory cycle. PVAs can occur during all phases of the respiratory cycle, including breath initiation, flow and pressure delivery, the transition from inspiration to expiration, and throughout expiration. PVAs are associated with longer duration of MV, longer stay in the ICU, higher incidence of respiratory muscle injury and tracheostomy, and lower probability of successfully wean from MV (Blanch et al., 2015; Bosma et al., 2007).

In the ICU setting, it is common to measure the severity of illness using severity scores (Vincent & Moreno, 2010). Scoring systems such as SAPS (simplified acute physiology score), MPM (mortality probability model), or APACHE (acute physiology and chronic health evaluation) measure severity at ICU admission. They are used to predict outcomes, with applications to inform patients or families, to risk-stratify patients (e.g., as inclusion criteria for clinical trials) or to evaluate quality of care. Instead, organ failure scores, such as the SOFA (sequential organ failure assessment) system, measure the degree of organ dysfunction and are used to assess evolution of the patient's severity over the ICU stay (Vincent et al., 1996). The longitudinal nature of the SOFA index and its strong association with illness severity and the two possible outcomes of interest at the ICU, death or alive discharge, are a suitable framework for quantitative studies that can assess these relationships to characterize patients' evolution and prognosis.

Joint models assess the association between repeatedly measured variables and time-to-event data (Rizopoulos, 2012). When the interest is in the longitudinal outcome, joint models use survival analysis tools to correct for nonrandom dropout. When the interest is in survival outcomes, they use longitudinal models to handle internal time-dependent covariates that are only known for specific time points and are typically measured with error (Verbeke & Davidian, 2009; Hogan & Laird, 1997a,b; Rizopoulos, 2012; Tsiatis & Davidian, 2004; Wulfsohn & Tsiatis, 1997). Sweeting and Thompson (2011) compared the shared random effects model with two approximate approaches, a naive proportional hazards model with time-dependent covariate and a two-stage joint model, which first fitted a mixed effects model to the longitudinal variable and then used plug-in estimates of the fitted values as covariates in a survival model. The authors showed that the shared random effects joint model outperformed the approximate approaches. In recent years, there has been an increase in the use of joint modeling in biomedical studies that have provided answers to many relevant questions that link the trajectory of longitudinal outcomes to risk of events (Andrinopoulou, Rizopoulos, Takkenberg, & Lesaffre, 2014, 2015b; Armero et al., 2016a; Serrat et al., 2015).

In the ICU setting, a previous study has illustrated how joint models permit a useful analysis of complex data and perform better than other more standard approaches (Deslandes & Chevret, 2010). The aim of the study focused on the longitudinal behavior of the SOFA score when comparing two treatments. They used a competing risks model to overcome the complication of nonignorable dropout caused by the events *death* or *alive discharge*. In the present study, we propose a Bayesian joint model with bivariate longitudinal information and competing risks data for patients in critical care. This study was initiated with the goal of better understanding the role of PVAs in patients prognosis and advancing toward personalized medicine in critical care. Specifically, the primary objective is to assess if the addition of an asynchrony index (AI) to the SOFA score could provide a more accurate and up-to-date indication of patients' severity and prognosis. Although this study was designed primarily to answer a clinical question, it also contains some methodological contributions with regard to the longitudinal modeling, including the use of a mixed effects beta regression model. Moreover, by extending the standard clinical modeling, the study shows the potential of joint models in the critical care setting.

This paper is organized as follows. Section 2 presents the motivating data; Section 3 describes the Bayesian joint model for the multiple longitudinal outcomes and the competing risks process, as well as the criteria used for model selection; Section 4 introduces longitudinal posterior profiles for generic individuals of the population and posterior updated estimation of the cumulative incidence function for specific individuals; Section 5 presents the results of the ICU study; and Section 6 closes with a discussion.

2 The ICU data

We studied 139 mechanically ventilated patients admitted to four Spanish ICUs (Parc Taulí University Hospital, Sabadell; Hospital Sant Joan de Deu-Fundació Althaia, Manresa; Hospital Central de Asturias, Oviedo, and Complejo Hospitalario Universitario de Granada, Granada) from July 2009 to May 2016. The institutional review board of the Parc Taulí University Hospital approved the protocol and waived informed consent because the study was noninterventional, posed no added risk to the patient, and did not interfere with usual care. All patients were followed from the first day in MV until ICU discharge or day 30 after MV initiation, whichever occurred first. Two main outcomes were of interest in the study: dead in the ICU or discharge alive from the ICU. Of the 139 studied patients, 28 (20.1%) died, 97 (69.8%) were discharged alive, and 14 (10.1%) were administratively censored.

During the time in MV, patients' breaths were recorded continuously and PVAs were captured digitally from the ventilator and processed using the software Better Care^{TM} (Barcelona, Spain). The AI was defined as the proportion of asynchronous events among the total number of ventilator cycles. Patients' overall severity was measured using the SOFA (Vincent et al., 1996) which assigns from 0 (normal) to 4 (most abnormal) points to the function of each of the following six organ systems: respiratory, circulatory, renal, hematology, hepatic, and central nervous system, giving a possible score of 0 to 24. Both the AI and the SOFA scores were measured daily.

Figure 1 shows the longitudinal trajectories of the AI and the SOFA indices for 20 patients, 10 randomly selected among those discharged alive (top) and 10 randomly selected among those that died in the ICU (bottom). The figure shows that the SOFA trajectories for patients discharged alive were generally lower than those for patients who died. However, the AI trajectories present high and low levels, and fluctuate more, for both types of patients.

Figure 2 presents the estimated cumulative incidences of the two studied outcomes, dying in the ICU or being discharged alive. They were obtained using the `survfit` function of the `survival` `R` package, with the option `mstate` for the censoring type. The first 10 days after MV initiation represent a critical time period with higher rates of *death* or *alive discharge*. At day 10, the cumulative incidences of *death* and *alive discharge* were 14.4% and 42.5%, respectively, at day 20, 18.7% and 62.6%, and at day 30, 20.1% and 69.8%, respectively.

3 Joint modeling

Joint models assume a full joint distribution for the longitudinal ($\boldsymbol{y}$) and the survival processes ($\boldsymbol{s}$). Bayesian inference expresses uncertainties for parameters and hyperparameters by means of probabilistic distributions. Consequently, a Bayesian joint model is a joint probability distribution for $\boldsymbol{y}$, $\boldsymbol{s}$, the subject-specific random effects ($\boldsymbol{b}$), and the parameters and hyperparameters ($\boldsymbol{\theta}$) of the model defined as follows

$$f(\boldsymbol{y}, \boldsymbol{s}, \boldsymbol{b}, \boldsymbol{\theta} \mid \boldsymbol{x}) = f(\boldsymbol{y}, \boldsymbol{s} \mid \boldsymbol{x}, \boldsymbol{b}, \boldsymbol{\theta})\, f(\boldsymbol{b} \mid \boldsymbol{\theta})\, \pi(\boldsymbol{\theta}), \tag{1}$$

factorizing as the product of the joint conditional distribution of the longitudinal and survival processes $f(\boldsymbol{y}, \boldsymbol{s} \mid \boldsymbol{x}, \boldsymbol{b}, \boldsymbol{\theta})$ where $\boldsymbol{x}$ indicates covariates, the conditional distribution $f(\boldsymbol{b} \mid \boldsymbol{\theta})$ of the random effects given the hyperparameters, and the prior distribution $\pi(\boldsymbol{\theta})$ for the parameters and hyperparameters.

We assume a shared-parameter approach (Hogan & Laird, 1998; Wu & Carroll, 1988) which postulates conditional independence between the longitudinal and survival processes given $\boldsymbol{b}$ and $\boldsymbol{\theta}$. In this way, the distribution in (1) turns out

$$f(\boldsymbol{y}, \boldsymbol{s}, \boldsymbol{b}, \boldsymbol{\theta} \mid \boldsymbol{x}) = f(\boldsymbol{y} \mid \boldsymbol{x}, \boldsymbol{b}, \boldsymbol{\theta})\, f(\boldsymbol{s} \mid \boldsymbol{x}, \boldsymbol{b}, \boldsymbol{\theta})\, f(\boldsymbol{b} \mid \boldsymbol{\theta})\, \pi(\boldsymbol{\theta}). \tag{2}$$

Our joint model contains parameters and hyperparameters, $\boldsymbol{\theta}$, and latent elements $\boldsymbol{b}$. From a Bayesian perspective, $\pi(\boldsymbol{\theta}, \boldsymbol{b} \mid \mathcal{D})$ represents their joint posterior distribution defined through the Bayes theorem and hierarchical modeling (Armero, Forte, Perpiñán, Sanahuja, & Agustí, 2016b)

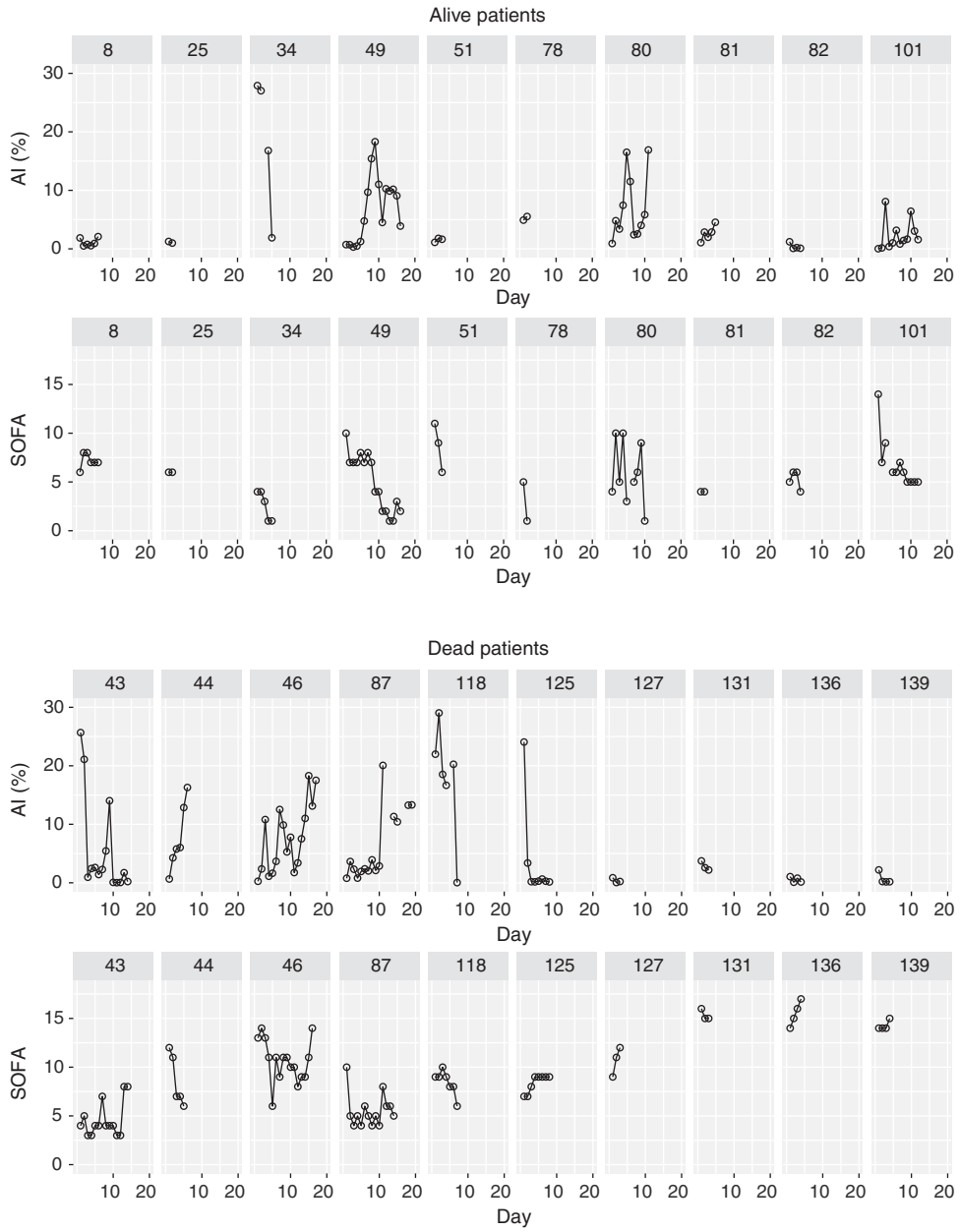

Figure 1 AI and SOFA longitudinal measurements for 20 patients, 10 randomly selected among those discharged alive (top) and 10 randomly selected among those that died at the ICU (bottom).

$$\pi(\boldsymbol{\theta}, \boldsymbol{b} \mid \mathcal{D}) \propto L(\boldsymbol{\theta}, \boldsymbol{b}) f(\boldsymbol{b} \mid \boldsymbol{\theta}) \pi(\boldsymbol{\theta}),$$

where $L(\boldsymbol{\theta}, \boldsymbol{b})$ is the likelihood function of $(\boldsymbol{\theta}, \boldsymbol{b})$ for the observed data $\mathcal{D}$. See Section A.1 in the Appendix for a detailed expression of the likelihood function.

Next, we present the different elements of the joint distribution in (2) that define our joint model. Section 3.1 deals with the conditional distribution of the longitudinal process, $f(\boldsymbol{y} \mid \boldsymbol{x}, \boldsymbol{b}, \boldsymbol{\theta})$, and with

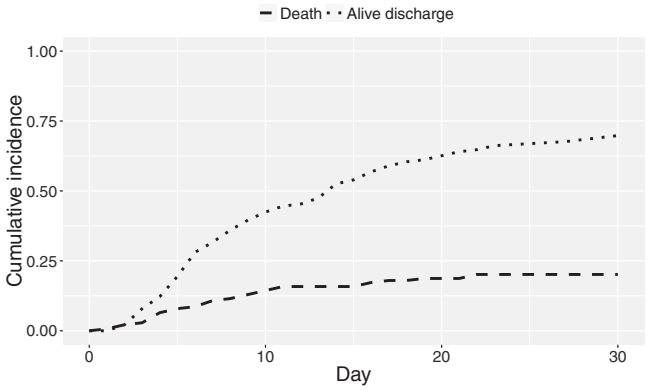

Figure 2 Cumulative incidence function for death in the ICU or alive discharge.

$f(\boldsymbol{b} \mid \boldsymbol{\theta})$, Section 3.2 with the conditional distribution of the survival outcomes, $f(\boldsymbol{s} \mid \boldsymbol{x}, \boldsymbol{b}, \boldsymbol{\theta})$, and Section 3.3 with the prior distribution $\pi(\boldsymbol{\theta})$.

3.1 Longitudinal submodel

The full longitudinal submodel includes $y_{1i}(t)$ and $y_{2i}(t)$ that, respectively, denote the follow-up measurements for the SOFA and AI indices for patient i, $i = 1, \ldots, n$, at time t. Both measurements were obtained at specific time points t_{ij} that can be different for each subject, where $j = 1, \ldots, n_{1i}$ or $j = 1, \ldots, n_{2i}$ indicate the repeated measurement for the i-th patient for the SOFA and AI variables, respectively. Mixed-effects models are used to describe the subject-specific evolution over time of both longitudinal outcomes.

We assumed a normal distribution for the SOFA index and a beta distribution for the AI. In particular, for the SOFA index we get

$$y_{1i}(t) = m_{1i}(t) + \epsilon_{1i}(t), \tag{3}$$

where $m_{1i}(t)$ represents the true SOFA value for patient i at time t, and $\epsilon_{1i}(t)$ the subsequent measurement error. These errors are conditionally i.i.d. as $(\epsilon_{1i}(t) \mid \sigma^2) \sim \mathcal{N}(0, \sigma^2)$. We modeled $m_{1i}(t)$ as a linear combination of a natural cubic splines basis functions $\{N_c(t), c = 1, 2, 3\}$ (Hastie, Tibshirani, & Friedman, 2001) with three knots, an internal knot at day 4 and two boundary knots at days 0 and 30, as follows

$$m_{1i}(t) = (\beta_{11} + b_{1i1})N_1(t) + (\beta_{12} + b_{1i2})N_2(t) + (\beta_{13} + b_{1i3})N_3(t), \tag{4}$$

with regression coefficients associated to each element of the spline basis that include a population effect vector $\boldsymbol{\beta}_1 = (\beta_{11}, \beta_{12}, \beta_{13})'$ and a subject-specific effect vector $\boldsymbol{b}_{1i} = (b_{1i1}, b_{1i2}, b_{1i3})'$. We used splines to model the true SOFA mean for their flexibility and ability to capture multimodal trends.

The AI outcome is a proportion, and consequently, it can be described as a continuous variable with no null density in (0, 1). We modeled AI in terms of a beta distribution with a mean that depends on time on MV and specific individual characteristics. In particular, we considered the following mixed effects beta regression model (Ferrari & Cribari-Neto, 2004)

$$\left\{y_{2i}(t) \mid m_{2i}(t), \phi_{2i}(t)\right\} \sim \text{Beta}\left\{m_{2i}(t), \phi_{2i}(t)\right\},$$

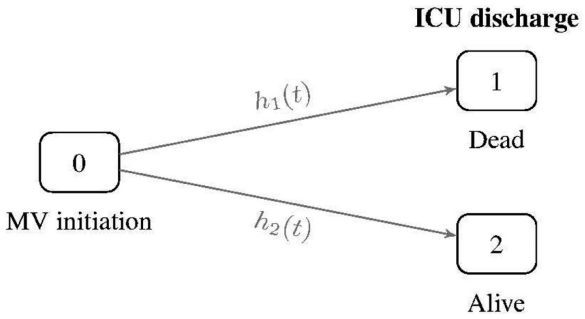

Figure 3 Competing risks schema.

parameterized in terms of the conditional mean of $y_{2i}(t)$, $m_{2i}(t)$, and the parameter $\phi_{2i}(t)$ which can be interpreted as a precision parameter. For simplicity, we assumed $\phi_{2i}(t)$ constant. We used the logit link to model $m_{2i}(t)$ in terms of the linear function

$$\text{logit}\left\{m_{2i}(t)\right\} = (\beta_{21} + b_{2i1}) + (\beta_{22} + b_{2i2})t,$$

with population coefficients $\boldsymbol{\beta}_2 = (\beta_{21}, \beta_{22})'$ and random effects $\boldsymbol{b}_{2i} = (b_{2i1}, b_{2i2})'$ for individual i.

The random effects for the longitudinal SOFA and AI variables corresponding to individual i, $\boldsymbol{b}_{1i}$, and $\boldsymbol{b}_{2i}$, respectively, were assumed to follow a joint multivariate normal distribution

$$\left\{(\boldsymbol{b}_{i1}, \boldsymbol{b}_{i2})' \mid \Sigma\right\} \sim \text{N}\left\{(\boldsymbol{0}, \boldsymbol{0})', \Sigma\right\}, \tag{5}$$

with variance-covariance matrix components $\text{Cov}(\boldsymbol{b}_{i1}) = \Sigma_{b_1}$, $\text{Cov}(\boldsymbol{b}_{i2}) = \Sigma_{b_2}$, and $\text{Cov}(\boldsymbol{b}_{i1}, \boldsymbol{b}_{i2}) = \Sigma_{b_{12}}$. Random effects and error terms were assumed mutually independent.

3.2 Competing risks submodels

We used a cause-specific hazards model for the time-to-event outcomes, death in the ICU ($k = 1$) and alive at ICU discharge ($k = 2$) (see Figure 3). We denote T_{ki} the time from the initiation of MV to the occurrence of event k for patient i; τ_i indicates the censoring time (30 days for all patients); $\delta_i = 0, 1, 2$ is the event indicator where $\delta_i = 0$ represents censoring for both events, $\delta_i = 1$ indicates that patient i is dead at ICU, and $\delta_i = 2$ that patient i is alive at ICU discharge; and $T_i = \min(T_{1i},\ T_{2i},\ \tau_i)$ represents the observed event time for individual i.

In agreement with the ICU specialists of the study group, we postulated two joint models, M_1 and M_2. Both models were defined in terms of the two cause-specific hazard functions, which assess for each patient i the hazard of failing due to each event $k = 1, 2$ in the presence of the other competing event (Putter, Fiocco, & Geskus, 2007). In addition, and to evaluate the additional prognostic value of the AI in the presence of SOFA, we also estimated the joint model M_0 which only includes the longitudinal information provided by the SOFA variable. In particular,

$$\begin{aligned}
M_0 : h_{ki}^{(0)}(t) &= h_{k0}^{(0)}(t) \exp\left\{\gamma_k^{(0)} Age + \alpha_{1k}^{(0)} m_{1i}(t)\right\}, \\
M_1 : h_{ki}^{(1)}(t) &= h_{k0}^{(1)}(t) \exp\left\{\gamma_k^{(1)} Age + \alpha_{1k}^{(1)} m_{1i}(t) + \alpha_{2k}^{(1)} m_{2i}(t)\right\}, \\
M_2 : h_{ki}^{(2)}(t) &= h_{k0}^{(2)}(t) \exp\left\{\gamma_k^{(2)} Age + \alpha_{1k}^{(2)} m_{1i}(t) + \alpha_{2k}^{(2)} \int_0^t m_{2i}(s)\mathrm{d}s\right\},\ k = 1, 2.
\end{aligned}$$

For model M_0, $h_{k0}^{(0)}(t)$ are the baseline hazard functions, $\gamma_k^{(0)}$ the age-associated coefficients, and $\alpha_{1k}^{(0)}$ the association parameters that measure the strength of the association between the true value of the longitudinal SOFA and the risk for event k at time point t, $(k = 1, 2)$. Models M_1 and M_2 are similarly defined, except that both also include the longitudinal information of the AI, M_1 in terms of its mean $m_{2i}(t)$ with association parameters $\alpha_{2k}^{(1)}$, and M_2 through the area under the mean of the longitudinal trajectory up to the time point t, $\int_0^t m_{2i}(s)\mathrm{d}s$, with association parameters $\alpha_{2k}^{(2)}$. An interesting issue is the choice of the scale of the AI variable included in the joint model, the subject-specific mean scale $m_{2i}(t)$ or the linear predictor scale $\mathrm{logit}(m_{2i}(t))$ (Andrinopoulou & Rizopoulos, 2016). We opted for $m_{2i}(t)$ because it facilitates interpretation even though more computational effort is required.

Thus, for one unit increase of the true subject-specific SOFA index at a specific time, the hazard ratio (HR) of the k event is $\exp(\alpha_{1k}^{(m)})$, where $m = 0, 1, 2$ indicates model M_0, M_1, and M_2, respectively. For model M_1, a unit increase in the mean of the subject-specific AI indicates the maximum change, from 0 (total absence of asynchronies) to 1 (100% of asynchronic breaths). In this scenario, the HR of the k event would be $\exp(\alpha_{2k}^{(1)})$. A more realistic scenario would be to consider a 0.1 (10%) increase of the subject-specific AI with an associated HR of $\exp(0.1\alpha_{2k}^{(1)})$. For model M_2, $\exp(\alpha_{2k}^{(2)})$ corresponds to the HR of a unit increase in the mean of the area under the longitudinal profile of the AI variable.

In all models, the baseline hazard functions were modeled by means of a B-splines basis that accommodates for possible multimodalities. In particular, we used a B-spline basis function of order 4 with five interior knots (Hastie et al., 2001) located at 5, 10, 15, 20, and 25 days after MV initiation that provides flexibility to the behavior of the baseline hazard functions.

3.3 Prior distribution

Prior independence as a default specification and wide proper prior distributions with the aim of giving all inferential prominence to the data were assumed. Normal distributions were selected for the regression coefficients of the longitudinal outcomes, the parameters of the baseline hazards, the baseline covariates in the survival sub-model, and those that link the longitudinal and time-to-event outcomes. A Uniform distribution $U(0, 10)$ was considered for the standard deviation of the error term of the SOFA variable and for the exponential term of the scale parameter of the AI variable. An inverse Wishart distribution was considered for the random effects variance-covariance matrix.

3.4 Model selection

We used the Watanabe-Akaike information criterion (WAIC) (Watanabe, 2010) and the log pseudo-marginal likelihood (LPML) (Geisser & Eddy, 1979) for model selection. It is considered that WAIC improves the deviance information criterion (DIC) for Bayesian models (Gelman, Hwang, & Vehtari, 2014). WAIC averages over the entire posterior distribution, is not based on plug-in terms, and is very appropriate for models with hierarchical structures, such as joint models. LPML is based on predictive criteria. It combines, in a logarithmic scale, the conditional predictive ordinate value (CPO) associated to the observations of each individual i in the sample and is defined as $\mathrm{LPML}=\sum_{i=1}^{n}\log(\mathrm{CPO}_i)$. Larger LPML values indicate a better fit to the data. CPO for individual i is defined through the cross-validation predictive distributions (CVPD) (Geisser, 1980; Gelfand, 1996).

We approximated the LPML by means of Pareto smoothed importance sampling leave-one-out (PSIS-LOO) (Vehtari, Gelman, & Gabry, 2017). Both approximations use the posterior Markov Chain Monte Carlo (MCMC) sample from the complete posterior distribution $\pi(\boldsymbol{\theta}, \boldsymbol{b}_i \mid \mathcal{D})$. Computation of the PSIS-LOO and WAIC values was done using the `loo` package of `R` (Vehtari, Gelman, & Gabry, 2016) and the Decomposition I of the LPML proposed in Zhang, Chen, Ibrahim, Boye, and Shen (2017) when the primary goal of the study is survival, as in our case. Following Vehtari et al. (2017), WAIC is asymptotically equal to PSIS-LOO, but PSIS-LOO is more robust when working with weak

prior distributions, like ours. In case of inconsistent results for both criteria we decided to select the model based on the PSIS-LOO criterion.

4 Posterior longitudinal and survival inferences

The complexity and flexibility of joint models enables the estimation and prediction of relevant survival and longitudinal outcomes, not only for specific individuals that have participated in the study but also for generic subjects from the same population. The collection of new data, as a consequence of both the follow-up of the individuals who are already in the study or the inclusion of new individuals, makes necessary the update of the posterior distribution of $(\boldsymbol{b}, \boldsymbol{\theta})$ as well as the relevant estimation and outcomes prediction (Armero et al., 2016a). This update process is conceptually easy but computationally intensive because it involves updating the posterior distributions from approximate posterior samples.

We focus here on two different outcomes: (1) posterior profiles of the two longitudinal variables and posterior estimation of the baseline hazard and cumulative incidence functions corresponding to a generic individual from the population; and (2) updated estimates of the cumulative incidence functions for a specific individual in the study with a given longitudinal and survival history.

4.1 Generic individual longitudinal and survival profiles

An overview of the evolution of the true SOFA score for a generic individual of the population is based on the marginal expression

$$\{m_{1i}(t) \mid \boldsymbol{\beta}_1, \Sigma_{b1}\} = \int \{m_{1i}(t) \mid \boldsymbol{\beta}_1, \boldsymbol{b}_{1i}\} f(\boldsymbol{b}_{1i} \mid \Sigma_{b1})\, \mathrm{d}(\boldsymbol{b}_{1i}), \tag{6}$$

obtained by integrating out the random effects of the conditional true SOFA in (4). This marginal mean only depends on the common parameters $\boldsymbol{\beta}_1$ and hyperparameters Σ_{b1} and can be interpreted as the true SOFA for a generic individual of the population. Then, we can use the posterior marginal distribution $\pi(\boldsymbol{\beta}_1, \Sigma_{b1} \mid \mathcal{D})$ and compute the posterior distribution, $\pi\left\{(m_{1i}(t) \mid \boldsymbol{\beta}_1, \Sigma_{b1}) \mid \mathcal{D}\right\}$. This posterior distribution provides point estimates of the relevant probabilities such as posterior expectations and credible intervals. The same procedure can be used to obtain the posterior distribution of the AI mean, $\pi\left\{(m_{2i}(t) \mid \boldsymbol{\beta}_2, \Sigma_{b2}) \mid \mathcal{D}\right\}$, and subsequent characteristics of interest.

The baseline hazard functions for the events death and alive at the ICU discharge, $h_{10}^{(m)}(t)$ and $h_{20}^{(m)}(t)$, depend on the coefficients of the B-spline basis functions. We have an approximate posterior marginal distribution of these coefficients and consequently, we can obtain the posterior distribution of both baseline hazard functions.

The conditional cumulative incidence function for the event $k = 1, 2$, for an individual i, is $F_{ki}(t \mid \boldsymbol{x}_i, \boldsymbol{\theta}, \boldsymbol{b}_i) = P(T_i \leq t, \delta_i = k \mid \boldsymbol{x}_i, \boldsymbol{\theta}, \boldsymbol{b}_i)$. In particular, the conditional probability that the individual i experiences the event $k = 1, 2$ is $P(\delta_i = k \mid \boldsymbol{x}_i, \boldsymbol{\theta}, \boldsymbol{b}_i) = F_{ki}(\infty \mid \boldsymbol{x}_i, \boldsymbol{\theta}, \boldsymbol{b}_i)$. The cumulative incidence functions for a generic individual of the population i can be obtained as before by integrating the random effects. Then, one can obtain the posterior distribution of the cumulative incidence function for the event $k = 1, 2$ for a generic individual of the population and the subsequent distribution of the probabilities that she/he dies or is discharged alive from the ICU, $\pi\{P(\delta_i = k \mid \boldsymbol{x}_i, \boldsymbol{\theta}, \boldsymbol{b}_i) \mid \mathcal{D}\}$, $k = 1, 2$, respectively.

4.2 Updated survival estimation for specific individuals

This section refers either to a specific individual in the study sample that has provided new longitudinal measurements, or to a new subject of the population that could be in the study in the future. The

conditional cumulative incidence function of event k for a specific individual i, with baseline covariates $\boldsymbol{x}_i$, random effects $\boldsymbol{b}_i$, longitudinal history $\mathcal{Y}_{in_i}$, and survival time $T_i > t_{in_i}$, is given by the probability

$$P(T_i \leq t, \delta_i = k \mid T_i > t_{in_i}, \mathcal{Y}_{in_i}, \boldsymbol{x}_i, \boldsymbol{\theta}, \boldsymbol{b}_i), \;\; t > t_{in_i}, \tag{7}$$

which is a (nonobservable) quantity of great interest for the study.

Since the survival and longitudinal processes are independent given the random effects and $\boldsymbol{\theta}$, the specific trajectories for the longitudinal variables for individual i are irrelevant in the determination of these probabilities. So, we can rewrite (7) as

$$P(T_i \leq t, \delta_i = k \mid T_i > t_{in_i}, \boldsymbol{x}_i, \boldsymbol{\theta}, \boldsymbol{b}_i) = F_{ki}(t \mid T_i > t_{in_i}, \boldsymbol{x}_i, \boldsymbol{\theta}, \boldsymbol{b}_i), \;\; t > t_{in_i}. \tag{8}$$

Now, our interest becomes F_{ki}, which from a Bayesian perspective can be summarized by means of its posterior distribution. Thus, for any given $t > t_{in_i}$, F_{ki} is defined as a function of the parameters $\boldsymbol{\theta}$ and the random effects $\boldsymbol{b}_i$. Consequently, its posterior distribution can be derived from the posterior distribution $\pi(\boldsymbol{\theta}, \boldsymbol{b}_i \mid T_i > t_{in_i}, \mathcal{Y}_i, \boldsymbol{x}_i, \mathcal{D})$, which includes the sample information, $\mathcal{D}$, and, possibly, extra information for individual i, $(T_i > t_{in_i}, \mathcal{Y}_i, \boldsymbol{x}_i)$, not included in $\mathcal{D}$. In particular, we can obtain the posterior expectation for F_{ki} as

$$\begin{aligned} &\mathrm{E}(F_{ki}(t \mid T_i > t_{in_i}, \boldsymbol{x}_i, \boldsymbol{\theta}, \boldsymbol{b}_i) \mid \mathcal{D}) = \\ &\qquad = \int F_{ki}(t \mid T_i > t_{in_i}, \boldsymbol{x}_i, \boldsymbol{\theta}, \boldsymbol{b}_i)\, \pi(\boldsymbol{\theta}, \boldsymbol{b}_i \mid T_i > t_{in_i}, \mathcal{Y}_i, \boldsymbol{x}_i, \mathcal{D})\, \mathrm{d}(\boldsymbol{\theta}, \boldsymbol{b}_i). \end{aligned} \tag{9}$$

As mentioned previously, the dynamic nature of the data makes it necessary to update the posterior distribution as new information is recorded. The process of updating would need the use of computationally intensive procedures such as sequential Monte Carlo methods. Here, we approximate the posterior expectation of $F_{ki}(t \mid T_i > t_{in_i}, \boldsymbol{x}_i, \boldsymbol{\theta}, \boldsymbol{b}_i)$ following the Monte Carlo simulation scheme proposed by Rizopoulos (2012).

5 Analysis of the ICU data

5.1 Estimation and model selection

The posterior distribution of all unknown quantities in each of the proposed models has been approached by MCMC methods using the `JAGS` software (Plummer, 2003). For each model, we run three MCMC chains for 500,000 iterations plus 150,000 (30%) dedicated to the *burn-in* period. The sample was thinned by only storing approximately one of every 150 iterations to reduce autocorrelation in the saved sample. Convergence of the chains to the subsequent posterior distribution was assessed through the potential scale reduction factor and the effective number of independent simulation draws (Gelman & Rubin, 1992) and (Kass, Carlin, Gelman, & Neal, 1998), respectively.

In Table 1, models M_0, M_1, and M_2 are compared using the PSIS-LOO and WAIC criteria, where in both of them the smaller the better. According to the PSIS-LOO, models M_0 and M_1 have the same predictive ability, slightly superior than model M_2. The WAIC indicates that M_1 is better, although the difference in the performance of the three models is not very relevant. Model M_1 seems better than M_2 and slightly better than M_0. Given that the goal of the study, from a clinical point of view, was assessing the contribution of the AI in the presence of the SOFA score, we finally selected model M_1.

Table 2 summarizes the approximate MCMC random sample from the marginal posterior distribution of the most relevant parameters and hyperparameters of model M_1. The analogous information for models M_0 and M_2 is shown in Tables A.1 and A.2.

Table 1 PSIS-LOO and WAIC criteria for models M_0, M_1, and M_2.

Model	PSIS-LOO	WAIC
M_0	995.2	994.5
M_1	995.2	993.3
M_2	997.7	996.3

Table 2 Posterior summaries of the more relevant parameters and hyperparameters of model M_1.

	Mean	SD	2.5%	97.5%	$P(\cdot > 0 \mid \mathcal{D})$
Longitudinal process for SOFA					
β_{11}	8.203	0.302	7.607	8.795	1.000
β_{12}	−8.716	0.495	−9.685	−7.764	0.000
β_{13}	−1.306	0.486	−2.231	−0.340	0.004
σ	1.675	0.042	1.594	1.759	–
Longitudinal process for AI					
β_{21}	−3.509	0.098	−3.704	−3.320	0.000
β_{22}	0.058	0.024	0.011	0.105	0.991
ϕ	32.058	1.695	28.860	35.414	–
Survival process (Death)					
α_{AI}	−2.650	3.080	−9.631	2.393	0.205
α_{SOFA}	0.223	0.051	0.123	0.324	1.000
γ_{Age}	−0.017	0.009	−0.034	0.001	0.038
Survival process (Alive)					
α_{AI}	2.142	1.221	−0.100	4.700	0.968
α_{SOFA}	−0.158	0.050	−0.262	−0.065	0.000
γ_{Age}	−0.003	0.006	−0.015	0.009	0.322

Longitudinal information of the asynchronies index in terms of the true mean.

The last column of the table contains the probability that the corresponding parameter is positive. A probability equal to 0.5 indicates that a positive value of the parameter is equally likely than a negative one, hence indicating little relevance of the corresponding variable (given the remaining covariates). This is not the case for most of the parameters of our model with posterior probabilities that show a clear *preference* for being above or under zero.

Figure 4 shows the posterior distribution of the association parameters between the longitudinal and the survival processes.

Results in Table 2 and Figure 4 clearly indicate that the SOFA score is strongly related to vital status at ICU discharge. The posterior distribution of the association parameter for the events *death* and *alive discharge* lies at opposite sides of zero. The distributions do not overlap, indicating strong association of the SOFA score with respect to vital status. Considering the posterior MCMC sample and taking the exponential transformation of the α parameters, the mean HRs for both events can be estimated. These HRs indicate that for a specific time t a unit increase in the SOFA score corresponds to a mean 1.25-fold increase in the risk of *death* and a mean 0.85-fold risk of *alive discharge*.

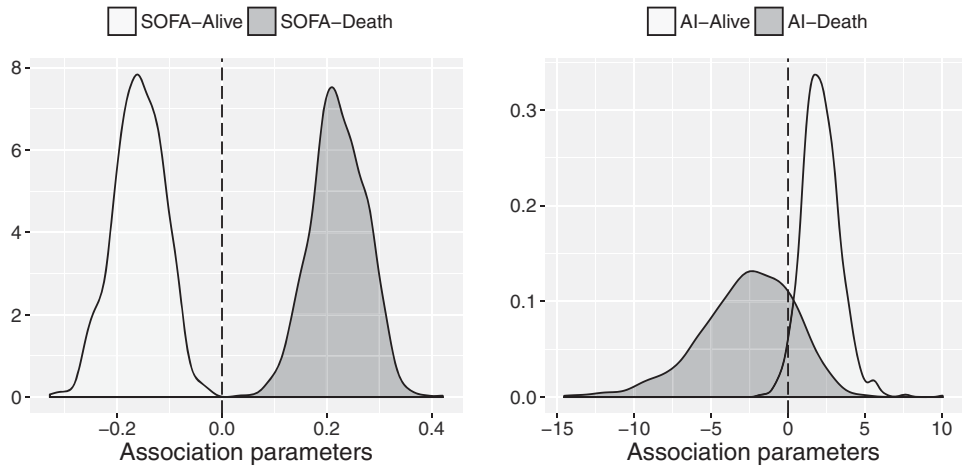

Figure 4 Posterior distribution for the association parameters in model M_1.

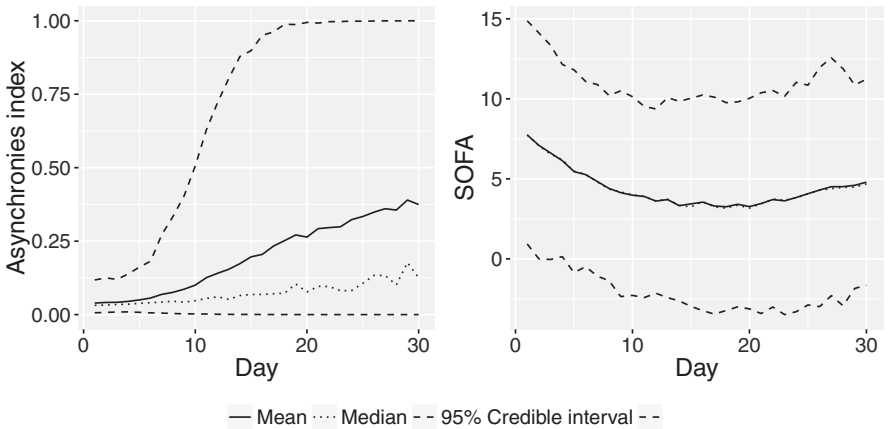

Figure 5 Posterior mean, median, and 95% credible interval for the temporal AI (on the left) and SOFA (on the right) profiles corresponding to a generic individual from the population.

In contrast to the SOFA score, the true AI at time t does not seem to be associated with vital status as clearly, when overall severity is taken into account. For the event *alive discharge*, the posterior distribution of α_{AI} has a positive support indicating that PVAs are a sign of good prognosis. For the event *death in the ICU,* a wide posterior distribution of the α_{AI} parameter and the estimated $P(\alpha_{AI} > 0 \mid \mathcal{D}) = 0.205$ indicate that PVAs at time t do not provide a more accurate indication of death prognosis than the SOFA score alone.

5.2 SOFA, AI, and survival profiles for a generic individual

Figure 5 presents the posterior means, medians, and 95% credible intervals of the trajectories over time for the AI (left) and SOFA score (right), for a generic individual of the population. The mean and median AI trajectories are increasing over time which can be due, in part, to the logistic link used for the longitudinal process. The width of the AI credible intervals indicates a high uncertainty in the

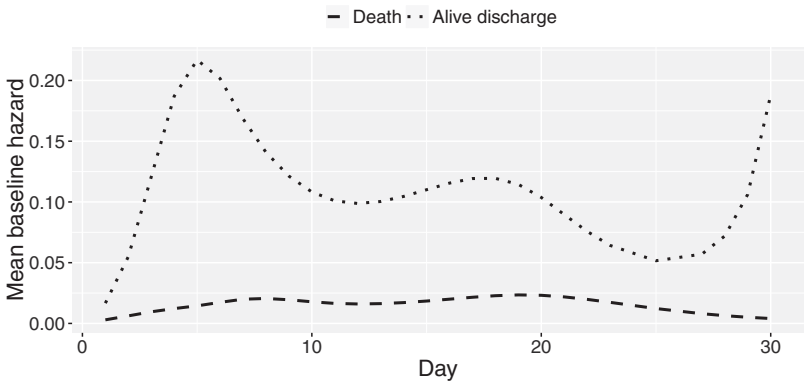

Figure 6 Mean posterior distribution for the baseline hazard functions of death at the ICU and alive discharge.

expected trajectory of the AI over time, and the difference between the mean and median trajectories reflects strong asymmetry. The SOFA-estimated trajectories show a decreasing trend of the SOFA score until day 15 and a slight increase thereafter. This is probably a reflect of increasing average severity over time of patients that remain in the ICU. There is also a high degree of uncertainty in the SOFA trajectories which now are distributed symmetrically in consistency with the Gaussian assumption.

Figure 6 shows the posterior mean of the baseline hazard functions for the two events death and alive discharge. The highest hazard of death seems to happen around days 7 and 20 on MV whereas the hazard of alive discharge increases sharply until day 5 and then decreases and slightly peaks again between days 15 and 20 on MV.

As an overall survival indicator we have estimated the mean posterior probability that a generic individual aged 63 years (sample median) will eventually die in the ICU or be discharged alive as 0.187 and 0.710, respectively.

5.3 Updated survival estimations for specific individuals

Using model M_1, Figure 7 shows, for two patients in the study, how the posterior expectation of the conditional cumulative incidences of death in the ICU or alive discharge are updated after each extra longitudinal measurements, for the AI and SOFA variables, have been recorded. Patient 4 (top) had a decreasing trend in the SOFA score and a changing trend in the AI, during the first four days. Their conditional cumulative incidence of death (solid line) was low and did not change much over time, whereas the conditional cumulative incidence of alive discharge (dashed line) was high and increased over time. Patient 4 was discharged alive at day 4. In contrast, patient 136 (bottom), started with a higher SOFA value, had an increasing trend in the SOFA score and a decreasing trend in the AI, during the first four days. Their conditional cumulative incidence of death (solid line) was higher at the beginning, compared with patient 4, and slightly increased over time, whereas the conditional cumulative incidence of alive discharge (dashed line) was lower, compared with patient 4, and slightly decreased over time. Patient 136 died at day 4.

6 Discussion

Updating risk prediction for patients admitted to ICUs is a necessary step toward personalized medicine in critical care. Standard survival methods, that is, the Kaplan-Meier and the Cox model are widely used to assess the effect of interventions or to obtain predictive scores. However, these methods

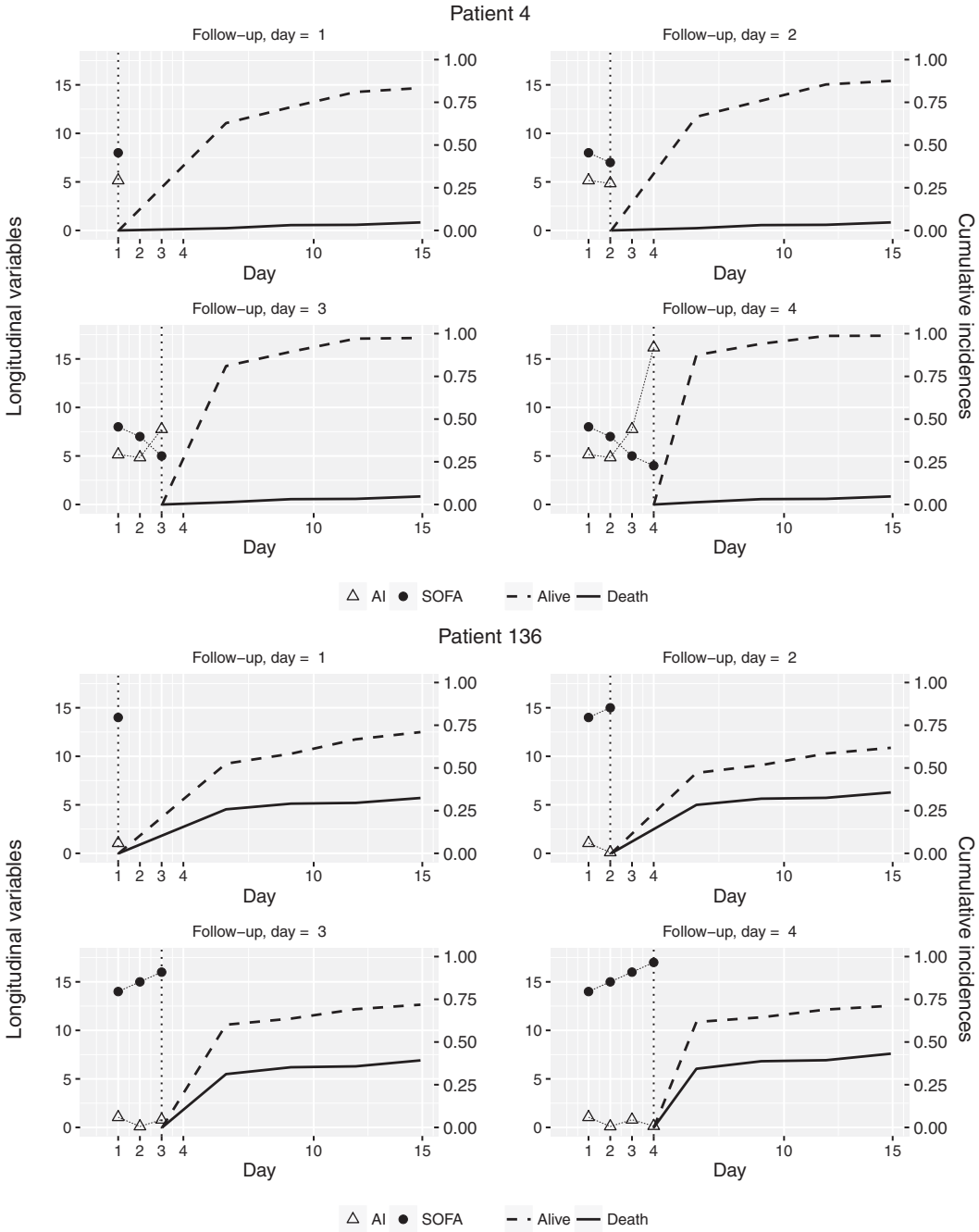

Figure 7 Individual estimations of the dynamic cumulative incidences for two patients in the study, Patient 4 was discharged alive (top) and Patient 136 died in the ICU (bottom). AI: asynchronies index, SOFA: sequential organ failure system. The vertical dotted lines represent the time point of the last AI and SOFA measurements.

assume that censoring is noninformative, which means that patients discharged alive from the ICU at time t are representative of all other individuals who have survived up to time t but who are still in the ICU. This assumption, in most situations is not correct, being dropout a consequence of a deterioration or an improvement in the patient's condition. In this setting, more complex models need to be considered (Resche-Rigon, Azoulay, & Chevret, 2006).

Joint models of longitudinal and survival data seem to be the most adequate approach to assess the effect of interventions or potential risk factors in patients admitted to ICUs, and to dynamically update patients' prognosis. Although the joint modeling of longitudinal and survival data has recently received much attention in medical research (Andrinopoulou et al., 2015a; Armero et al., 2016b; Ibrahim, Chu, & Chen, 2010; Proust-Lima, Dartigues, & Jacqmin-Gadda, 2016), to our knowledge, it has been scarcely applied in the ICU setting (Deslandes & Chevret, 2010; Liu, Wolfe, & Kalbfleisch, 2007). With the aim of assessing a treatment effect, Deslandes and Chevret (2010) proposed a joint random effects model for the longitudinal mean SOFA score and a proportional subdistribution hazards submodel for the competing risks *death* or *alive discharge*. In the present work, we have intended to illustrate how joint models can help to obtain a more accurate indication of prognosis, for patients in critical care, using a cause-specific hazards submodel.

Our selected joint model links the subject-specific profiles of two longitudinal variables with the competing risks outcomes to assess if, in mechanically ventilated patients, the addition of PVAs to a generic severity measure improves outcome prediction. This joint model is applicable to a variety of biomedical studies that investigate two longitudinal outcomes and competing risks data. Our results indicate that the estimated subject-specific trajectories of overall severity, measured with the SOFA index, highly discriminate dead or alive patients at the ICU discharge. The 25% increase estimate in the risk of death per unit increase in the SOFA score is concordant with estimates obtained in some clinical studies. Marra, Edmond, Wenzel, and Bearman (2007) estimated an odds ratio for death of 1.4 per 1-point increment in the SOFA score at infection onset in patients with a hospital-acquired infection. Geerse, Span, Pinto-Sietsma, and van Mook (2011) studied the prognosis of patients with hematological malignancies admitted to the ICU. They also obtained an odds ratio of 1.4 per 1-point increment in the SOFA score at day 1 and 1.44 for each additional point in the highest SOFA score in the first week. Lopes-Ferreira, Peres-Bota, Bross, Mélot, and Vincent (2001) studied the usefulness of repeated measurements of the SOFA score for prediction of mortality in the ICU. They concluded that the mean and the highest SOFA scores through the ICU stay were good prognostic indicators, independently of the initial SOFA value. It is worth mentioning that these studies did not account for the nonignorable dropout mechanism when obtaining the summary measures, that is, mean or highest value, or SOFA trend (decreasing, no change, increasing).

The results of our model with respect to PVAs are unexpected and difficult to interpret. Blanch et al. (2015) found that PVAs occurred throughout the entire period of MV and might be associated with adverse outcome or just be a marker of patient severity. Our hypothesis was that PVAs increase the risk of death and, according to our model, higher AIs are associated with a higher probability of *alive discharge*. Schuit et al. (2013) illustrate causes and solutions for unexpected findings in clinical prediction research. They described the six following causes, that we discuss below: chance, misclassification, selection, confounding, intervention effects, and heterogeneity.

Chance may have played a role in our results because the probability of observing an unexpected finding of a predictor-outcome relation strongly depends on sample size and our study sample is small. A bigger sample size would facilitate obtaining more precise estimates, robuster results, and a better view of the role of PVAs. *Misclassification* due to measurement error is accounted for using joint models but we may have modeled incorrectly the predictor-outcome relation (e.g., logit link instead of probit or log-log) or the distribution and trajectory over time of the longitudinal variables or the adequate summary measure of PVAs. The use of a logistic transformation for the AI could also have been a wise choice. Working with normal scenarios facilitates statistical inference despite the loss of interpretability in terms of the original scale. The observed trajectories for the AI showed great variability, especially in shape, suggesting the convenience of using a more flexible assumption than normality. A beta

regression model (Cribari-Neto & Zeilis, 2010) was used because of its flexibility to accommodate natural heteroskedasticity and the asymmetry of the regression models in the unit interval. In particular, the beta densities cover a variety of asymmetric shapes such as inverted J, J, and U. Although the use of splines in the SOFA trajectory and the baseline hazard functions increases modeling flexibility, it gives less precise estimates than other simpler approaches. We assume a normal distribution for the SOFA score, a variable that can not take negative values. A distributional form allowing only positive values or some mathematical transformation would be preferable. However, in our study the SOFA profile for a generic individual of the population under the normal distribution provides a reasonable approach and facilitates the interpretation. With respect to the adequate summary measure, Vaporidi et al. (2017) found that clusters of asynchronies occurring between prolonged uneventful periods during MV are associated with longer duration of MV and higher hospital mortality. According to them, clusters predict outcomes better than the proportion of PVAs during the MV period, highlighting the need for continuous monitoring.

Some *selection bias* could also be present. Even though the study patients were prospectively included while on MV, they had to be admitted to one of the rooms equipped with specific software. Our study is observational, therefore some degree of *confounding* may be present because a variable has been omitted that is related to both the predictor and the outcome. There is some evidence that sedation has an important role in PVAs (Epstein, 2011). One of the indications for sedation is to facilitate patient-ventilator interaction (Murias, Lucangelo, and Blanch, 2016). Sedation decreases inspiratory muscle effort and lowers maximal inspiratory flow, so the patient may appear calmer; nevertheless, asynchronies may persist and there is a high probability that they are under diagnosed (de Wit, Pedram, Best, & Epstein, 2009; Vaschetto et al., 2014). However, the use or increase of sedation to improve patient-ventilator interaction is under debate. Chanques et al. (2013) found that adapting the ventilator to patient breathing effort was much more effective in reducing PVAs than adjusting the sedation dose. These results highlight the importance of an accurate clinical examination in deeply sedated patients or in patients with poor patient-ventilator interaction, to prevent the adverse clinical consequences associated with excessive sedation and asynchronies (Mauri et al., 2016). For this study, we did not have enough longitudinal information on asynchronies presentation and patients sedation status, an interesting extension would be to model and incorporate this information.

According to Schuit et al. (2013) *intervention effects* may occur when predictor values may guide the decision to start a medical intervention. If this intervention is effective the probability of the outcome may decrease and the relation predictor-outcome may be attenuated or even reversed. Finally, *heterogeneity*, also known as effect modification or interaction may have produced the observed results. For instance, if the effect of the AI differs across subgroups of patients or the relations predictor-outcome across subgroups are opposite, the direction of the observed relation depends on the proportional contributions of the subgroups. Even though we are taking severity into account, the limited number of events in our data did not allow assessing effect modification of the AI across subgroups of patients.

In conclusion, joint modeling allows to account for longitudinal markers during the ICU stay to obtain updated predictive distributions of potential clinical outcomes or longitudinal measurements based on data accumulated to date. We highlight having extracted relevant information from the ICU dataset, and having made a contribution with regard to the use of mixed effects beta regression in joint modeling. Our joint model supports the importance of PVAs and, at the same time, suggests that more research on the role of PVAs is necessary. A bigger study with a more detailed analysis of PVAs together with the state of wakefulness or sedation is necessary to shed light on their role on patients' outcomes.

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Conflict of interest

LB is inventor of a US patent owned by Corporació Sanitària Parc Taulí: Method and system for managing related patient parameters provided by a monitoring device, US Patent No. 12/538,940. LB owns stock options in BetterCare S.L., a research and development start-up of Corporació Sanitària Parc Taulí (Spain).

Appendix

A.1 Likelihood function

The likelihood function of the parameters and random effects of the model for the observed data is the product of the likelihood corresponding to each individual of the sample

$$L(\boldsymbol{\theta}, \boldsymbol{b}) = \prod_{i=1}^{n} L_i(\boldsymbol{\theta}, b_i). \tag{A.1}$$

The contribution to the likelihood of individual i with longitudinal measurements $\boldsymbol{y}_{i1} = (y_{ij1}, j = 1, \ldots, n_i)'$, $\boldsymbol{y}_{i2} = (y_{ij2}, j = 1, \ldots, n_i)'$, and survival information (T_i, δ_i) is defined as

$$\begin{aligned} L_i(\boldsymbol{\theta}, b_i) &= f\{\boldsymbol{y}_{i1}, \boldsymbol{y}_{i2}, (T_i, \delta_i) \mid \boldsymbol{\theta}, b_i\} = \\ &= f(\boldsymbol{y}_{i1} \mid \boldsymbol{\theta}_{y1}, b_i)\, f(\boldsymbol{y}_{i2} \mid \boldsymbol{\theta}_{y2}, b_i)\, f\{(T_i, \delta_i) \mid \boldsymbol{\theta}_s, b_i\} \end{aligned} \tag{A.2}$$

with

$$f(\boldsymbol{y}_{i1} \mid \boldsymbol{\theta}_{y1}, b_i) = \prod_{j=1}^{n_i} \mathrm{N}\left(y_{ij1} \mid m_{1i}, \sigma_1^2\right) = \left(2\pi\sigma_1^2\right)^{-n_i/2} \exp\left\{-\frac{1}{2\sigma_1^2} \mid\mid \boldsymbol{y}_{1i} - \boldsymbol{m}_{1i} \mid\mid^2\right\},$$

$$\begin{aligned} f(\boldsymbol{y}_{i2} \mid \boldsymbol{\theta}_{y2}, b_i) &= \prod_{j=1}^{n_i} \mathrm{Beta}(y_{ij2} \mid m_{2i}, \phi_{2i}) = \\ &= \prod_{j=1}^{n_i} \frac{\Gamma(\phi_{ij2})}{\Gamma(m_{ij2}\,\phi_{ij2})\,\Gamma(\phi_{ij2}(1 - m_{ij2}))}\, y_{ij2}^{m_{ij2}\,\phi_{ij2}-1}\, (1 - y_{ij2})^{\{\phi_{ij2}(1-m_{ij2})-1\}}, \end{aligned}$$

$$f\{(T_i, \delta_i) \mid \boldsymbol{\theta}_s, b_i\} = \prod_{k=1}^{2} \{h_{ik}(T_i)\}^{I(\delta_i = k)} \exp\left\{-\sum\nolimits_{k=1}^{2} \int_0^{T_i} h_{ik}(s)\, \mathrm{d}s\right\},$$

where $\boldsymbol{m}_{1i} = \{m_{1i}(t_{ij}),\ j = 1, \ldots, n_i\}'$, $\boldsymbol{m}_{2i} = \{m_{2i}(t_{ij}),\ j = 1, \ldots, n_i\}'$, and $|| \boldsymbol{a} ||^2 = \sum a_i^2$ represents the Euclidean distance associated to vector $\boldsymbol{a} = (a_i,\ i = 1, \ldots, n)'$.

A.2 Joint models $\mathbf{M_0}$ and $\mathbf{M_2}$

Table A.1 Posterior summaries of the more relevant parameters and hyperparameters of model M_0.

	Mean	SD	2.5%	97.5%	$P(\cdot > 0 \mid \mathcal{D})$
Longitudinal process for SOFA					
β_{11}	8.199	0.297	7.616	8.782	1.000
β_{12}	−8.700	0.492	−9.661	−7.740	0.000
β_{13}	−1.288	0.482	−2.236	−0.351	0.002
σ	1.673	0.042	1.594	1.758	–
Survival process (Death)					
α_{SOFA}	0.224	0.051	0.123	0.321	1.000
γ_{Age}	−0.017	0.009	−0.035	0.001	0.033
Survival process (Alive)					
α_{SOFA}	−0.143	0.049	−0.243	−0.053	0.002
γ_{Age}	−0.003	0.006	−0.015	0.009	0.290

Table A.2 Posterior summaries of the more relevant parameters and hyperparameters of model M_2.

	Mean	SD	2.5%	97.5%	$P(\cdot > 0 \mid \mathcal{D})$
Longitudinal process for SOFA					
β_{11}	8.198	0.303	7.604	8.795	1.000
β_{12}	−8.708	0.489	−9.676	−7.747	0.000
β_{13}	−1.283	0.490	−2.251	−0.324	0.003
σ	1.676	0.042	1.595	1.760	–
Longitudinal process for cumulative AI					
β_{21}	−3.498	0.097	−3.691	−3.311	0.000
β_{22}	0.052	0.023	0.007	0.097	0.987
ϕ	32.081	1.704	28.845	35.519	–
Survival process (Death)					
$\alpha_{cum(AI)}$	−0.482	0.512	−1.698	0.264	0.161
α_{SOFA}	0.223	0.051	0.121	0.324	1.000
γ_{Age}	−0.016	0.009	−0.034	0.003	0.047
Survival process (Alive)					
$\alpha_{cum(AI)}$	0.188	0.139	−0.085	0.464	0.917
α_{SOFA}	−0.149	0.049	−0.248	−0.058	0.000
γ_{Age}	−0.004	0.006	−0.015	0.008	0.274

Longitudinal information of the asynchronies index in terms of the area under the true mean.

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