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RESEARCH ARTICLE

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Spline-based accelerated failure time model

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The accelerated failure time (AFT) model has been suggested as an alternative to the Cox proportional hazards model. However, a parametric AFT model requires the specification of an appropriate distribution for the event time, which is often difficult to identify in real-life studies and may limit applications. A semiparametric AFT model was developed by Komárek et al based on smoothed error distribution that does not require such specification. In this article, we develop a spline-based AFT model that also does not require specification of the parametric family of event time distribution. The baseline hazard function is modeled by regression B-splines, allowing for the estimation of a variety of smooth and flexible shapes. In comprehensive simulations, we validate the performance of our approach and compare with the results from parametric AFT models and the approach of Komárek. Both the proposed spline-based AFT model and the approach of Komárek provided unbiased estimates of covariate effects and survival curves for a variety of scenarios in which the event time followed different distributions, including both simple and complex cases. Spline-based estimates of the baseline hazard showed also a satisfactory numerical stability. As expected, the baseline hazard and survival probabilities estimated by the misspecified parametric AFT models deviated from the truth. We illustrated the application of the proposed model in a study of colon cancer.

KEYWORDS
accelerated failure time model, model misspecification, simulations, spline-based method, survival analysis

1 | BACKGROUND

Time-to-event analyses are essential to assess the effects of covariates, exposures, or interventions on clinical outcomes. Such studies often aim to estimate the survival probability over time for subjects with different values of prognostic factors. However, to accurately estimate conditional survival functions, the data analyst has to correctly specify both (i) the baseline hazard and (ii) the way particular covariates affect the hazard.

The Cox proportional hazards (PH) model[1] is the most widely used model for survival analysis, with more than 40 000 citations to date. This model permits assessing covariate effects *without* any assumptions about the distribution of the event time, thus, avoiding the challenges in point (i). However, the PH assumption restricts the estimated HR's to remain constant during the entire follow-up period. If the PH assumption does not hold, the Cox model may lead to misleading conclusions[2] and biased estimates.[3] Indeed, violations of the PH assumption have been frequently reported.[4-6]

The accelerated failure time (AFT) model provides an alternative to the PH model.[7-9] In the AFT model, the covariates act directly on the time scale rather than on the hazard function, so that the time to event is accelerated or decelerated depending on the covariate value.[10,11] Yet, the parametric AFT model requires complete specification of the event time distribution,[12] which may affect the estimates of both survival function and covariate effects.[13,14] Common parametric choices include the log-normal, log-logistic, exponential, and Weibull distributions.[11] In the two latter cases, the AFT and the PH models are both valid.[12,15] However, in many applications, an appropriate event time distribution may be difficult to identify. Whereas one may choose one among a prespecified set of parametric distributions, using for example, the Akaike information criterion (AIC) and/or diagnostic plots,[11,16] such data-dependent choices complicate inference. Furthermore, the true baseline hazard function may not follow conventional parametric distributions, including, for example, nonmonotone, asymmetric shapes reflecting abrupt changes in mortality after cancer diagnosis.[17] To avoid difficulties in specifying the parametric baseline hazard model, different semiparametric AFT models were proposed, including least squares regression,[18-20] rank-based estimators,[21-23] weighted least-absolute-deviations method,[24] and semiparametric median regressions.[25,26] Some of these methods are prone to computational problems, especially with many covariates.[7] Furthermore, the aforementioned methods primarily focus on estimating covariate effects, and only a few of them explicitly derive the estimators of the hazard or survivor function.

We identified a few flexible approaches for modeling hazard functions within the AFT framework. In 1980s Etezadi-Amoli and Ciampi[27,28] proposed a general flexible model for survival analysis, that included both PH and AFT models as special cases. However, complex constrained optimization is required to ensure that the baseline hazard is nonnegative, resulting in numerical problems in the estimation.[28] Moreover, software implementation was not discussed.[27,28] More recently, Komárek et al[29] proposed a semiparametric smoothed error AFT model, which relies on a linear combination of a large number of Gaussian densities with penalization. This approach does not require specifying the event time distribution, while allowing for the estimation of the hazard and survival functions conditional on any covariate pattern.[29] However, to the best of our knowledge, the resulting hazard and survival estimators have not been yet systematically evaluated, through simulations.

In this article, we propose an alternative flexible AFT model, that employs low-dimension unpenalized regression splines to estimate the baseline hazards of arbitrary shapes, covariate effects, and the survival curves, conditional on covariates. Simulation studies are conducted to validate the proposed spline-based model and compare its performance with conventional parametric AFT models and the semiparametric approach by Komárek et al,[29] under different event time distribution. The spline-based AFT model is then applied to reassess mortality in colon cancer.

2 | METHODS

2.1 | General framework of the accelerated failure time model

In the AFT model, the natural logarithm of the event time, $\log T$, is modeled as a linear function of the covariates $X_1, X_2, \ldots, X_J$[10]:

$$\log T = -(\beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_J X_J) + W, \tag{1}$$

where W is a random error term. Parametric AFT models are usually defined by the distribution of the event times, typically assumed to follow Weibull, log-normal, and log-logistic distribution.[10] The specification of the event time distribution inherently determines the error distribution and the hazard function.[10]

The parameters $\boldsymbol{\beta} = (\beta_1, \ldots, \beta_J)$ are the adjusted log time ratios, that are assumed to remain constant across the follow-up time. Exponentiating Equation (1) gives,

$$T = \frac{1}{\exp\left(\sum_{j=1}^{J} \beta_j X_j\right)} T_0, \tag{2}$$

with $T_0 = e^w$ representing the expected survival time of a hypothetical subject with 0 values for all measured covariates.

In the AFT model, the hazard function conditional on covariates equals[10]:

$$\lambda(t|X) = \exp\left(\sum_{j=1}^{J}\beta_j X_j\right)\lambda_0\left(\exp\left(\sum_{j=1}^{J}\beta_j X_j\right)t\right), \tag{3}$$

where $\lambda_0(t)$ is the baseline hazard function, corresponding to $X_1 = X_2 = \ldots, = X_J = 0$. Accordingly, the survival function at time t, conditional on covariates, is given by:

$$S(t|X) = S_0\left(\exp\left(\sum_{j=1}^{J}\beta_j X_j\right)t\right) \tag{4}$$

Equation (4) implies that for one unit increase in the value of X_j the time to event is accelerated or decelerated by a multiplicative factor $\exp(\beta_j)$.[10] Therefore, the covariate effects estimated from AFT models can be interpreted as the expected relative prolongation or shortening of the survival time.

2.2 | Smoothed error AFT model of Komárek et al

Komárek et al[29] developed an elegant semiparametric approach for fitting AFT model (1) without specifying the distributions of event times or errors. They express the density function for the error distribution $f(w|\boldsymbol{c})$ by a mixture of a large number g of the basis Gaussian densities[29]:

$$f(w|\boldsymbol{c}) = \sum_{i=1}^{g} c_i \varphi_{\mu_i,\ \sigma_0^2}(w), \tag{5}$$

where $\varphi_{\mu_i,\ \sigma_0^2}(w)$ is the ith Gaussian density function with mean μ_i and common variance σ_0^2, and $\boldsymbol{c} = (c_1, \ldots, c_g)$ are the mixture coefficients. To avoid the need for constrained optimization, and ensure that w meets the conditions for density, the mixture coefficients are reparametrized: $c_i(\boldsymbol{a}) = \frac{\exp(a_i)}{\sum_{l=1}^{g}\exp(a_l)}$, $i = 1, \ldots, g$ so that $\sum_{i=1}^{g} c_i(\boldsymbol{a}) = 1$ and $c_i(\boldsymbol{a}) > 0$.[29] Values of u_i and σ_0^2 are fixed a priori, but the vector $\boldsymbol{a}$ is estimated jointly with the regression coefficients vector ($\boldsymbol{\beta}$) in (1), using penalized maximum likelihood:

$$\ell_P(\boldsymbol{\theta}; \lambda) = \ell(\boldsymbol{\theta}) - q\{\boldsymbol{a}; \lambda\}, \tag{6}$$

where $\boldsymbol{\theta}$ is the vector of all estimable parameters including $\boldsymbol{a}$, $\boldsymbol{\beta}$ and a scale parameter σ, and $\ell(\boldsymbol{\theta})$ and $\ell_P(\boldsymbol{\theta}; \lambda)$ denote the ordinary and penalized log-likelihood function, respectively. The penalty term $q\{\boldsymbol{a}; \lambda\}$ is applied to the squared difference of the transformed coefficients ($\boldsymbol{a}$) of adjacent Gaussian densities $\varphi_{\mu_i,\ \sigma_0^2}(w)$. The tuning parameter λ, selected by cross-validation, controls the smoothness of the fitted error distribution.[29] Variance of the penalized maximum likelihood estimator is approximated by the pseudo-variance.[29] The Komárek et al's smoothed error AFT model is implemented in the R package "smoothSurv."[30]

2.3 | Proposed spline-based AFT model

2.3.1 | Modeling baseline log hazard by regression splines

We propose an alternative flexible AFT model[29] which does *not* require penalization. Because the baseline hazard is usually unknown and may be complex, we employ unpenalized low-dimension polynomial regression B-splines that avoid a priori parametric assumptions, and approximate well a wide range of functional shapes,[31,32] including density or (log) hazard functions for event times.[33,34] Therefore, in the proposed flexible AFT model, the log hazard function is modeled as a linear expansion of a basis of $K = p + m + 1$ polynomial regression splines of degree p with m interior knots:

$$\lambda_0\left(\exp\left(\sum_{j=1}^{J}\beta_j X_j\right)t\right) = \exp\left(\sum_{k=1}^{K}\gamma_k S_k(w)\right), \tag{7}$$

where $w = \exp\left(\sum_{j=1}^{J} \beta_j X_j\right) t$, $S_k(\cdot)$ is the kth B-spline in the basis, defined in section A1 of the supporting information, and $\boldsymbol{\gamma} = (\gamma_1, \ldots, \gamma_K)$ are the estimable spline coefficients. Modeling the log hazard ensures that the baseline hazard is always positive, and the log-likelihood function is concave, which ensures convergence to a global maximum (second derivatives are shown in section A2).

Using standard notation $\{t_i, \delta_i, X_{i1}, \ldots, X_{iJ}\}_{i=1}^{n}$ where $t_i = \min(T_i, C_i)$ is the observed time and $\delta_i = I(T_i \leq C_i)$ is the event indicator, the full likelihood is given by:

$$L = \prod_{i=1}^{n} f(t_i)^{\delta_i} S(t_i)^{1-\delta_i} = \prod_{i=1}^{n} \lambda(t_i)^{\delta_i} S(t_i) \tag{8}$$

and the full log-likelihood can be expressed in terms of hazard function as follows:

$$\text{logL} = \sum_{i=1}^{n} \left[\delta_i \log(\lambda(t_i|X_1, \ldots, X_j)) - \int_0^{t_i} \lambda(u|X_1, \ldots, X_j) du \right]. \tag{9}$$

Substituting (3), (7) into (9), we obtain:

$$\text{logL} = \sum_{i=1}^{n} \left[\delta_i \left(\sum_{j=1}^{J} \beta_j X_j + \sum_{k=1}^{K} \gamma_k S_k(w) \right) - \int_0^{t_i} \exp\left(\sum_{j=1}^{J} \beta_j X_j \right) \exp\left(\sum_{k=1}^{K} \gamma_k S_k(w^*) \right) du \right], \tag{10}$$

where $w^* = \exp\left(\sum_{j=1}^{J} \beta_j X_j \right) u$. Estimates of β_j and γ_k are obtained by maximizing the full log-likelihood in (10), and permit estimating the hazard and survival functions, conditional on covariate vectors.

Specifically, conditional survival functions can be computed as:

$$\widehat{S}(t|X_1, \ldots, X_j) = \exp\left\{ - \int_0^{t} \exp\left(\sum_{j=1}^{J} \widehat{\beta}_j \mathrm{X}_j \right) \exp\left(\sum_{k=1}^{K} \widehat{\gamma}_k S_k \left(\exp\left(\sum_{j=1}^{J} \widehat{\beta}_j X_j \right) u \right) \right) du \right\}. \tag{11}$$

2.3.2 | Alternating conditional estimation

Estimating the parameters of the spline-based AFT model is challenging because the covariates affect the hazard in two different ways: (i) by changing the hazard multiplicatively and (ii) by redefining the baseline hazard function in the time scale, as shown in (3). (This complication is avoided in the Cox PH model, where the covariate effects are independent of the baseline hazard).[1] Since the same parameter vector $\boldsymbol{\beta}$ (i) needs to be estimated to assess covariate effects on the survival time but also (ii) must be considered as known when estimating spline coefficients $\boldsymbol{\gamma}$ that define the log baseline hazard, we cannot estimate $\boldsymbol{\beta}$ and $\boldsymbol{\gamma}$ in a single step. Specifically, it is impossible to derive the score function for the joint log-likelihood, due to the difficulty in obtaining the first derivative with respect to $\boldsymbol{\beta}$ in (10), when it is considered as an unknown parameter in the spline-basis function $S_k(\cdot)$ that needs to be calculated using recursive formulas. To address this complexity, we adapt an iterative alternating conditional estimation (ACE) algorithm.[35] Briefly, the parameter space is divided into two subsets: (i) the $\boldsymbol{\beta}$ vector and (ii) the $\boldsymbol{\gamma}$ vector. Each ACE iteration involves two steps, and in each step only one of the two subsets of parameters is estimated (ie, updated) conditional on the most recently estimated values of the other subset, considered at the current step as "known." The iterations stop when the difference between the log-likelihoods from two consecutive iterations is less than 10^{-5}. Section A2 of the supporting information provides details of our ACE algorithm. A dedicated R program is available on GitHub (https://github.com/MenglanPang/Spline-based-AFT-Model).

2.3.3 | Bootstrap confidence intervals

Standard large-sample inference, based on the covariance matrix of all estimated parameters, does not quantify accurately the sampling variance of the ACE-based estimates.[3] Therefore, we rely on bootstrap to estimate both the 95% confidence

intervals (CI) for the covariate effects and the 95% pointwise confidence bands around the survival curves, conditional on covariates. For each of M bootstrap resamples, we use ACE to estimate the spline-based AFT model (7). The 2.5th and 97.5th percentiles of the resulting distribution of M estimates of $\boldsymbol{\beta}$ defines the corresponding 95% CI for the covariate effects. For a given specific covariate pattern, the estimates for both $\boldsymbol{\beta}$ and $\boldsymbol{\gamma}$ are then plugged into Equation (11) to estimate the conditional survival curves $S(t|X_1, \ldots, X_J)$, and 95% pointwise confidence bands are obtained by connecting the 2.5th and 97.5th percentiles of the M corresponding estimates, for each t.

3 | SIMULATION STUDIES

Two simulation studies helped assess the performance of the proposed method under different assumptions about the true hazard. Baseline hazard in simulation B follows a log-normal distribution, but in simulation A represents a mixture of two Weibull distributions, implying a more complex shape than any conventional parametric hazard functions. (Details are described in section A3 of the supporting information).

In both simulations, we generated random samples with N = 500. We generated two independent binary covariates (X_1, X_2) from a Bernoulli distribution with probability 0.5, and two continuous, strongly correlated covariates: $X_3 \sim N(0, 1)$, and $X_4 = X_3^2$. Individual event times were then generated from the following AFT model:

$$\log T = -(\beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4) + W, \tag{12}$$

where $\beta_1 = 1$, $\beta_2 = -1$, $\beta_3 = \beta_4 = 1$.

We assumed a combination of random, uniformly distributed censoring due to losses to follow-up (C_1), and administrative right censoring at $C_2 = 3$ years. C_1 was selected to achieve approximately 25% overall censoring rate in simulation A. The observed time was determined as $\min(T, C_1, C_2)$.

For each simulated scenario, 100 simulated datasets were independently generated and analyzed with each of the following seven alternative models: (i) four conventional parametric AFT models, with different prespecified baseline distribution: Weibull, exponential, log-normal, or log-logistic, (ii) the conventional Cox PH model, (iii) the smoothed error-based AFT model developed by Komárek et al,[29] and (iv) the proposed spline-based AFT model (7). In model (7), unpenalized cubic ($P = 3$) regression B-splines with two ($m = 2$) interior knots, at the terciles of the observed follow-up time, were used to estimate the log baseline hazard. In the smoothed error-based AFT model (iii), we used the default option in the "smoothSurv" package to select the tuning parameter λ from a grid of values, from exp(2) to exp(−9), through cross-validation.[29] In additional analyses, we also forced a priori different values of $\lambda = \{\exp(2), \exp(-4), \exp(-8)\}$, in order to assess how the estimates are affected by increasing penalty.

Section A3 of the supporting information describes criteria used to evaluate and compare the performance of different models.

4 | SIMULATION RESULTS

4.1 | Baseline hazard estimates

Figures 1 and 2 compare the baseline hazard estimates (gray curves) obtained with different estimation models against the true hazard **(**black dashed curve**)** for simulations A and B, respectively. Both the proposed spline-based (Figures 1A and 2A) and the smoothed error Komárek et al (Figures 1B and 2B) estimators are free of bias, as the corresponding mean estimates (white curves) coincide with the true hazard across the follow-up time, with only slight overestimation in the upper tail where events are sparse. However, individual smoothed error estimates (gray curves in Figures 1B and 2B) exhibit large variability, with excessive wiggliness even between $t = 0$ and $t = 2$, when many events occurred. By contrast, spline-based estimates are more stable and accurately reflect the unimodal true shape (Figures 1A and 2A).

As expected, given the complex shape of the true hazard in simulation A, all parametric AFT models yield seriously biased estimates (Figure 1C-F). In simulation B, the correctly specified log-normal AFT model (Figure 2E), unsurprisingly, produces unbiased estimates with very good stability. By contrast, all other parametric AFT models, especially the Weibull and exponential, yield large bias, as they impose constraints inconsistent with the "true" nonmonotone baseline hazard (Figure 2C,D).

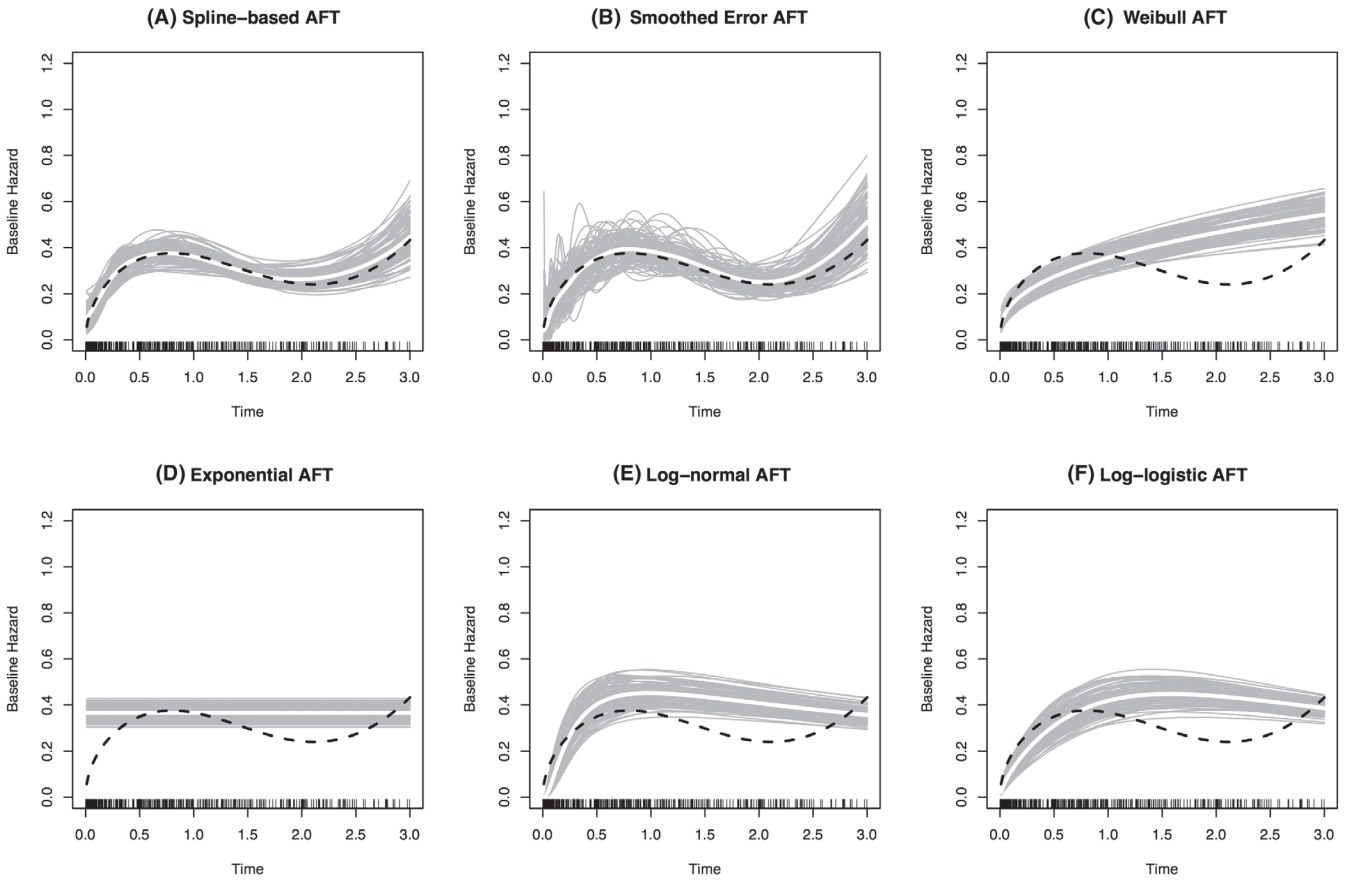

FIGURE 1 Estimated baseline hazard functions using 100 samples in simulation A when the mixture hazard is the true data generating model. The gray curves are the estimated individual baseline hazard functions from 100 samples, and the pointwise mean is shown by the white curve. The black dashed curve represents the true baseline hazard function. The empirical distribution of the observed uncensored event times (75% quantile: 0.88, 90% quantile: 1.58), from one random sample, is shown by rug plot at the bottom of the figures

Figure 3 summarizes the results of additional analyses that help assess how the smoothed error estimates are affected by the user-specified tuning parameter λ in (6). In simulation A, with complex true hazard, a weak penalization ($\lambda = \exp(-8)$), similar to the default option, offers unbiased estimates but induces large variance, whereas a strong penalization ($\lambda = \exp(2)$) yields more stable but seriously biased estimates (Figure 3A-C). For simulation B, with a simple true log-normal baseline hazard function, there is no bias, regardless of λ, but the estimates become increasingly unstable with lower λ (Figure 3E,F). Overall, the results in Figure 3 show that the accuracy of the baseline hazard estimates obtained with the smoothed error AFT model[29] depends on the penalty for lack of smoothness. In both our simulated scenarios, using a moderate penalty of $\exp(-4)$, somewhat stronger than the default option selected by the "smoothSurv" R package, yielded estimates that were almost unbiased (Figures 3B,E) and as numerically stable as the corresponding spline-based estimates (shown in Figures 1A and 2A).

4.2 | Estimated covariate effects and AIC comparisons

Table 1 compares the accuracy and variability of the estimated covariate effects from the two flexible AFT models. It compares also the AIC from all alternative estimation models, except for the smoothed error model where the effective *degrees of freedom* are not comparable due to penalization.[29]

In simulation A, the estimates of the covariate effects from both smoothed error and spline-based AFT models are free of noticeable biases and yield consistently smaller root mean squared root (rMSE) than all parametric AFT models (shown in Tables A4.1 and A5.1 of the supporting information). As expected, the proposed spline-based AFT model yields much smaller AIC than any of the (misspecified) parametric models (Table 1).

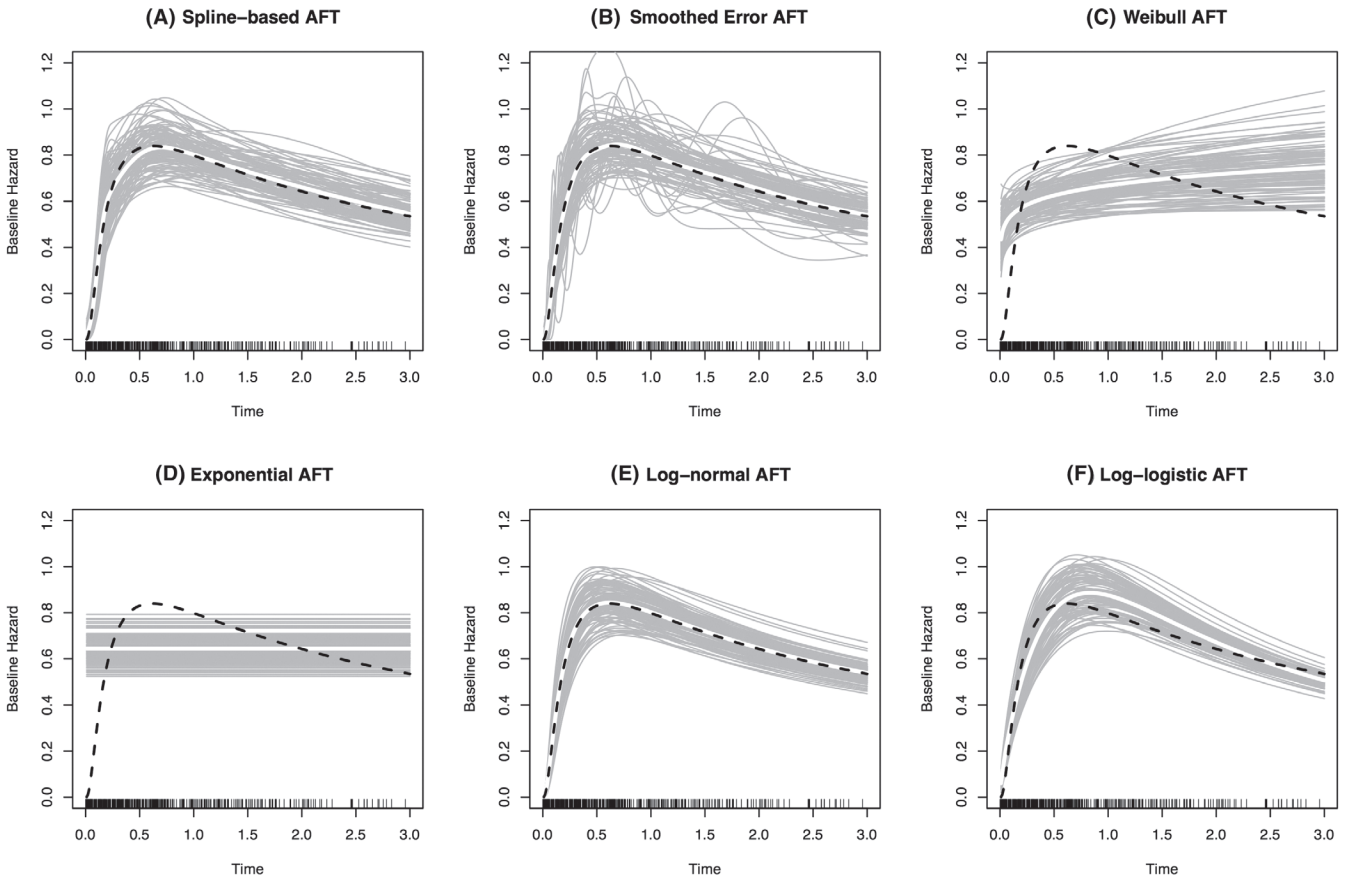

FIGURE 2 Estimated baseline hazard functions using 100 samples in simulation B when the log-normal distribution is the true data generating model. The gray curves are the estimated individual baseline hazard functions from 100 samples, and the pointwise mean is shown by the white curve. The black dashed curve represents the true baseline hazard function. The empirical distribution of the observed uncensored event times, from one random sample (75% quantile: 1.31, 90% quantile: 2.08), is shown by rug plot at the bottom of the figures

In simulation B, the correctly specified log-normal model, as expected, provides unbiased estimates with the smallest rMSE, and the best AIC (Table 1). Still, both the proposed spline-based and Komárek et al's smoothed error AFT models yield similarly small bias and rMSE and, for spline model, AIC close to the log-normal model. By contrast, misspecified Weibull and exponential models yield somewhat biased covariate effects and the worst AIC's.

4.3 | Survival curve estimates

Figures 4 and 5 compare survival curves, estimated with alternative models for an arbitrary covariate pattern, in simulations A and B, respectively. The smoothed error and the spline-based AFT models (Figures 4A,B and 5A,B) survival estimates are unbiased across the follow-up, reflecting accurate estimation of both the covariate effects (Table 1) and the baseline hazard (Figures 1 and 2). By contrast, most survival curves estimates based on parametric AFT models and PH model (Figures 4C-G and 5C,D,G) are seriously biased, except for the log-normal AFT model (Figure 5E) in simulation B where it corresponds to the data-generating model. PH model-based estimates are biased because the underlying assumption is not satisfied. The log-logistic AFT model performs reasonably well in simulation B (Figure 5F) because it accommodates the nonmonotonic hazard (Figure 2F). However, the estimated survival probabilities are biased at later times (Table 2).

Table 2 shows the relative bias and empirical standard deviations of the 100 estimates of the probability of survival, for three equidistant time points. Consistent with Figures 4 and 5, both the smoothed error and the spline-based AFT models perform consistently well. By contrast, the PH model and all parametric AFT models, except for the log-normal model in simulation B, yield biased survival estimates for at least some time points. Finally, the variance of the corresponding $S(t)$

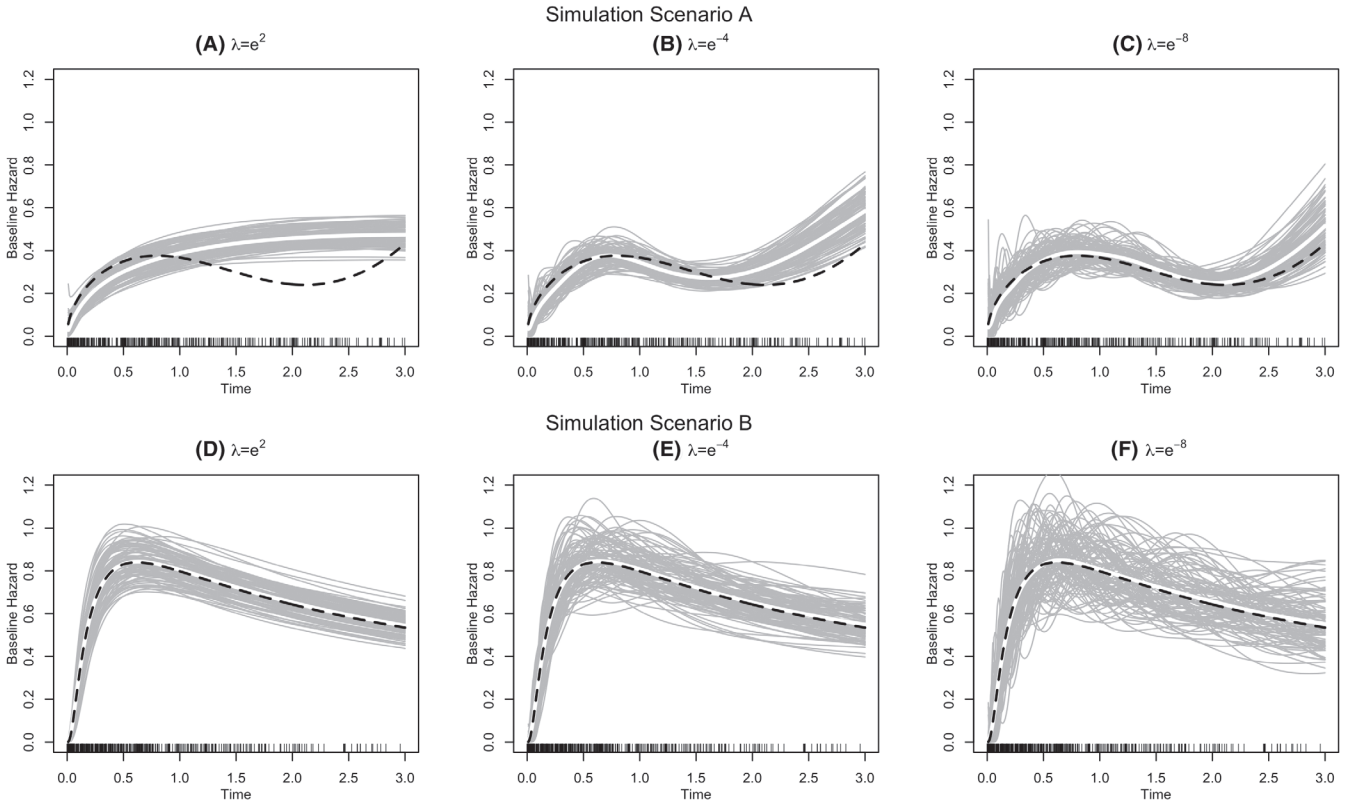

FIGURE 3 Estimated baseline hazard functions using 100 samples in simulation A and B using different values for the tuning parameter λ. The gray curves are the estimated individual baseline hazard functions from 100 samples, and the pointwise mean is shown by the white curve. The black dashed curve represents the true baseline hazard function

estimates is similar for all models (Table 2). Similar results were obtained for other covariate vectors (sections A4 and A5 of the supporting information).

Similar results were obtained when event times were generated from exponential, Weibull, log-logistic, and gamma (results not shown).

5 | APPLICATION: SURVIVAL IN COLON CANCER

5.1 | Methods

To illustrate a real-life application of the proposed model, we reanalyzed data from a trial of adjuvant chemotherapy in colon cancer. Data are publicly available in the *survival* R package[36], and described by Moertel et al.[37,38] Patients recently diagnosed with stage III colon cancer, in 1984-1987, were enrolled soon after their surgeries, and randomized to: (i) observation only, (ii) levamisole alone, or (iii) levamisole plus fluorouracil (levamisole+5FU). The outcome was time to death of any cause.[37,38] Baseline covariates included: age, gender, treatment, time since surgery, and several cancer pathological variables: obstruction, perforation, adhesion to nearby organs, histologic differentiation, depth of invasion, and the number of lymph nodes involved. Table A6.1 in the supporting information summarizes covariate distributions. During the median follow-up of 5.4 years, 430 (48%) of the 888 participants died.

All models discussed in Section 3 were used to assess the associations of the baseline covariates with all-cause mortality. Unpenalized cubic B-splines, with two interior knots at the terciles of the observed follow-up distribution (3.1 and 6.1 years), were used to implement the proposed spline-based AFT model. The penalization parameter in the smoothed error model was determined by cross-validation.[29] Age was transformed into z-scores, so that the baseline hazard corresponded to the mean age.

TABLE 1 Results of the estimated covariates from alternative methods in simulation A and B

		Covariates	Relative bias[a] (%)	SD	rMSE	AIC
Simulation A	Spline-based AFT	X_1	−1.1	0.05	0.05	**290.25**
		X_2	−0.1	0.04	0.04	
		X_3	0.2	0.02	0.02	
		X_4	0.1	0.02	0.02	
	Smoothed Error AFT	X_1	−0.4	0.04	0.04	299.08[a]
		X_2	0.3	0.04	0.04	
		X_3	0.5	0.02	0.02	
		X_4	0.2	0.01	0.01	
		AIC				
		Weibull	Exponential	Log-logistic	Log-normal	
		375.14	424.62	449.52	461.18	
Simulation B	Spline-based AFT	X_1	−0.9	0.10	0.10	142.17
		X_2	−1.8	0.12	0.12	
		X_3	0.2	0.05	0.05	
		X_4	0.5	0.04	0.04	
	Smoothed Error AFT	X_1	−0.8	0.11	0.11	137.68[ba]
		X_2	−1.0	0.11	0.11	
		X_3	0.3	0.05	0.05	
		X_4	0.3	0.03	0.03	
	Log-normal	X_1	−0.9	0.09	0.09	**137.89**
		X_2	−0.6	0.10	0.10	
		X_3	0.1	0.04	0.04	
		X_4	0.2	0.03	0.03	
		AIC				
		Weibull	Exponential	Log-logistic		
		193.38	198.47	143.95		

[a] Relative bias is defined as $\frac{\hat{\beta}_j - \beta_j}{\beta_j} \times 100\%$.

[b] Not comparable to other methods.

5.2 | Results

The baseline hazards, corresponding to mean age and 0 values of all binary covariates, estimated by different AFT models, are compared in Figure 6. The estimates from the parametric AFT models are monotonic, reflecting the underlying distributional assumptions, whereas both more flexible AFT models suggest nonmonotone hazards. However, the estimate from the smoothed error AFT model using the default option for the penalty (dashed black curve) seems excessively wiggly, consistent with the simulation results (Figures 1 and 2). (With increasing penalty, the smoothed error estimates are more similar to the spline-based estimates (Figure A6.1 in the supporting information), but the model fit is worse (AIC are shown in Table A6.2). By contrast, the proposed spline-based AFT model (solid black curve) yields a much smoother estimate with hazard increasing before 3 years, reaching a plateau from 3 to 4 years and slightly declining thereafter. The spline-based AFT model fits the data better than all parametric AFT models (Table 3), even if the log-normal AFT model has only slightly higher AIC.

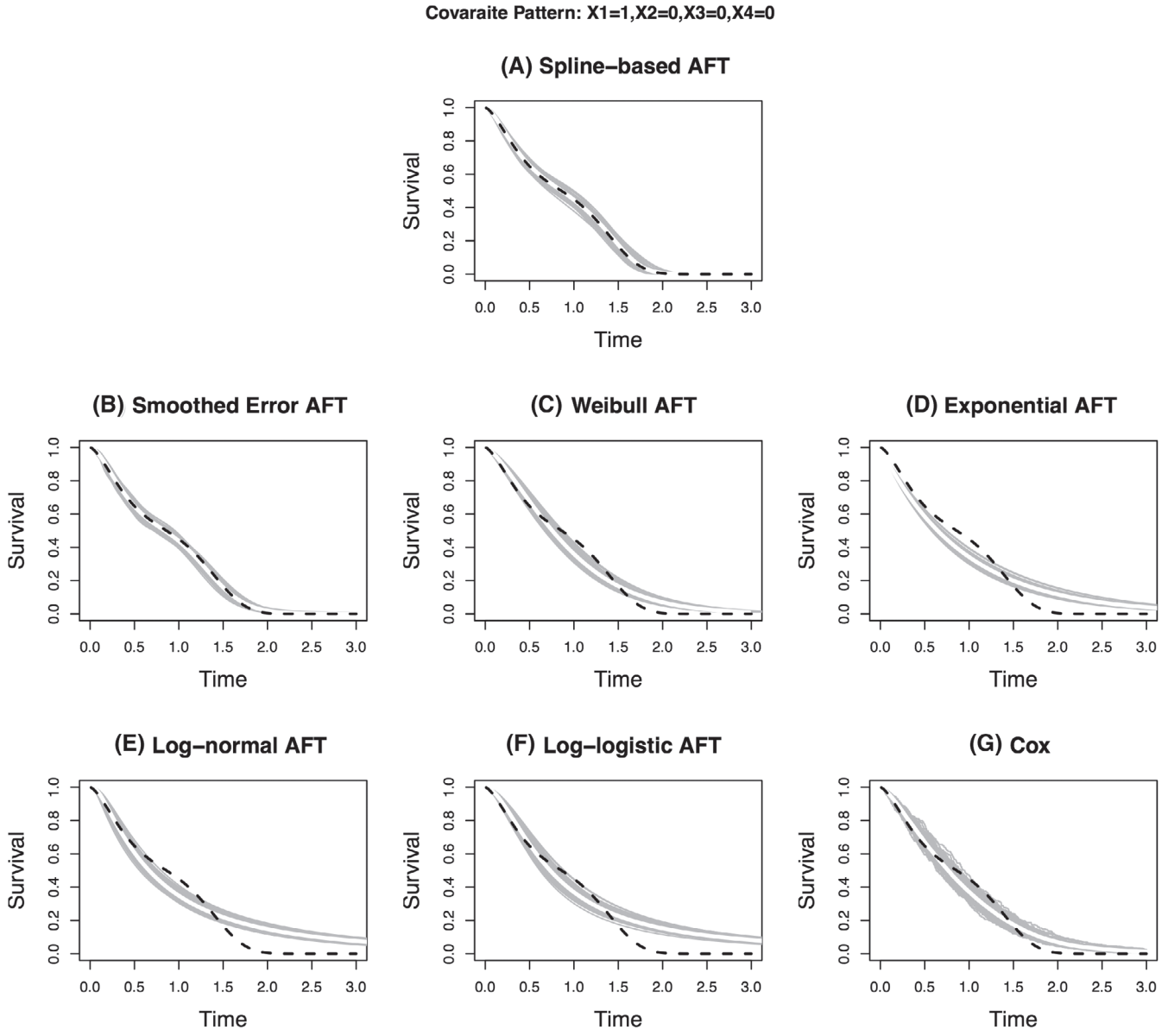

FIGURE 4 Comparison of the survival curve estimates, associated with a specific covariate vector, obtained with alternative estimation models (seven panels) in simulation A when the mixture hazard is the true data generating model. The white curve is the pointwise mean of the estimated individual survival curves from 100 simulated samples (gray curves). The true survival function is represented by the black dashed curve

In the Cox model, the global test rejects the PH assumption ($P < .001$), which seems violated for obstruction, poor tumor differentiation, and node4, according to Schoenfeld residuals plot and test (data not shown). On the other hand, the QQ plot (Figure A6.2 in the supporting information) does not reveal strong violation of the constant time-ratio assumption underlying the AFT models. Furthermore, the Cox-Snell residuals[39] in Figure A6.3 suggest that the proposed spline-based AFT and the Komárek's smoothed error AFT model fit the data well, as the residual cumulative hazards follow the diagonal, in contrast to important deviations seen in the upper tail for all parametric AFT models and the Cox PH model.

Figure 7 shows that alternative AFT models produced generally similar covariate effects (time ratios). (Cox PH model-based hazard ratios are shown in Figure A6.4 in the supporting information). Based on (i) Cox-Snell residuals in Figure A6.3 and AIC comparisons (Table 3), below we focus on the results of our proposed spline-based AFT model (the first model in the left panel of Figure 7). Levamisole alone and observation only groups have similar survival, but

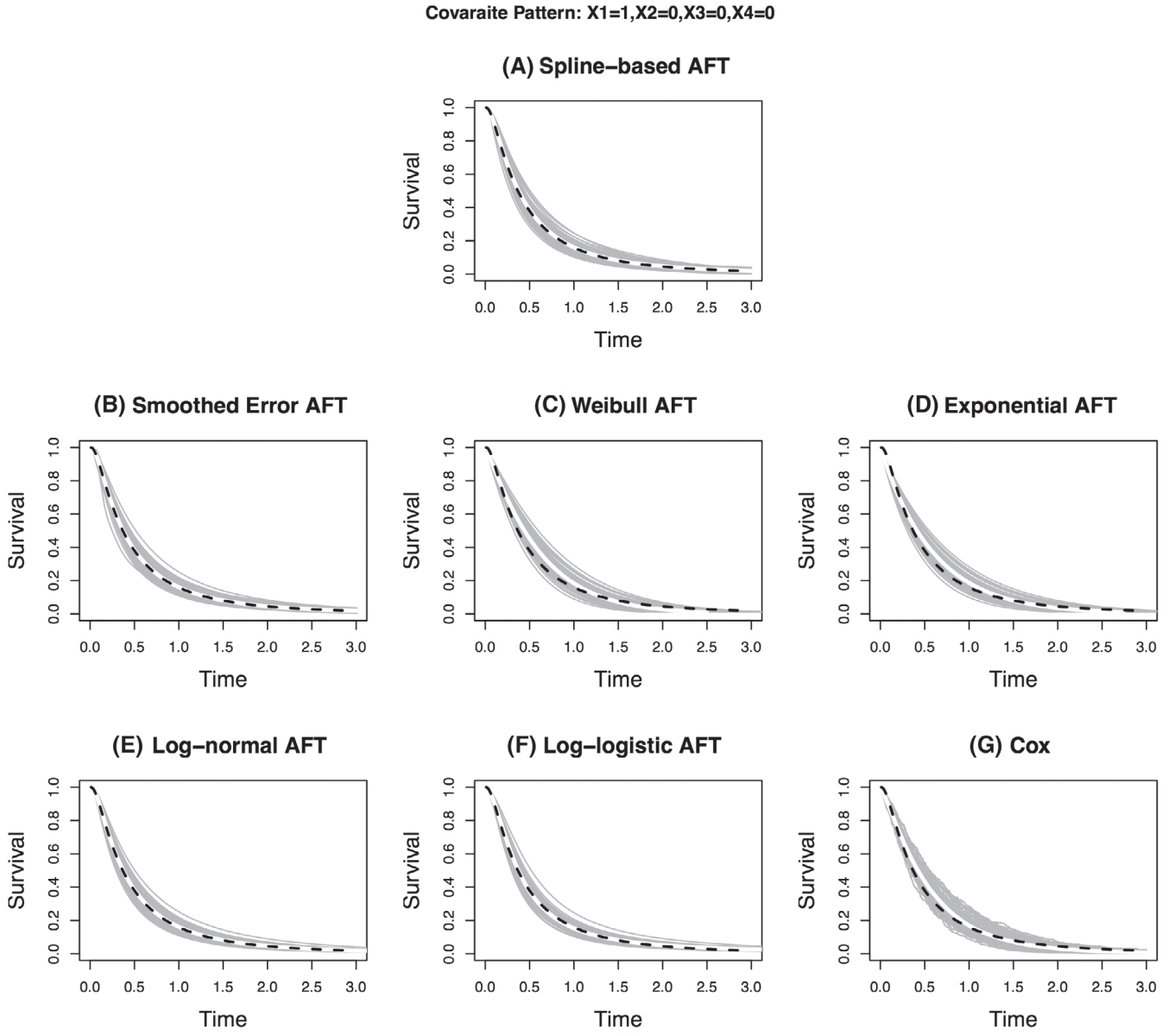

FIGURE 5 Comparison of the survival curve estimates, associated with a specific covariate vector, obtained with alternative estimation models (seven panels) in simulation B when the log-normal distribution is the true data generating model. The white curve is the pointwise mean of the estimated individual survival curves from 100 simulated samples (gray curves). The true survival function is represented by the black dashed curve

treatment with both levamisole and fluorouracil extends median survival time by about 51.5%. Consistent with literature, obstruction, invasion to serosa and contiguous structures, and increased number of lymph nodes involved are associated with higher mortality.[37,38] However, our spline-based AFT model suggests also that initiating the treatment within 1 to 3 weeks after the surgery may be associated with 30% longer survival time, although the confidence interval is wide (Figure 7). This finding, not reported in the previous analyses of the same data,[37,38] suggests that starting treatment early may maximize the therapeutic benefits.

The estimated 5 years survival rates, at mean age and reference values of all binary variables, are 82%, 84%, and 90%, respectively, for the observation only, Levamisole and Levamisole+5FU groups. The corresponding survival curve estimates are shown in section A6 of the supporting information.

TABLE 2 Relative bias and SE of the estimated survival probabilities from all the alternative model for different time points in simulation A and B (the results for later time points, e.g., $t = 2, 2.5$, are not provided for simulation A, given that the corresponding true survival probabilities are nearly zero)

		Spline-based AFT		Smoothed error AFT		Weibull AFT		Exponential AFT		Log-normal AFT		Log-logistic AFT		Cox	
	True survival	Relative bias[a] (%)	SD	Relative bias[a] (%)	SD	Relative bias[a] (%)	SD	Relative bias[a] (%)	SD	Relative bias[a] (%)	SD	Relative bias[a] (%)	SD	Relative bias[a] (%)	SD
Simulation A															
$t = 0.5$	0.65	0.70	0.02	−0.23	0.02	4.28	0.03	**−9.84**	0.02	**−6.48**	0.03	1.23	0.03	3.59	0.03
$t = 1$	0.45	−0.77	0.02	−2.58	0.02	**−19.84**	0.03	**−24.03**	0.02	**−22.47**	0.02	**−17.8**	0.03	**−17.19**	0.03
$t = 1.5$	0.17	5.38	0.03	−4.78	0.02	0.03	0.02	**19.29**	0.02	**30.97**	0.02	**35.55**	0.02	4.50	0.03
Simulation B															
$t = 0.5$	0.38	1.96	0.04	1.03	0.04	**18.31**	0.04	**13.13**	0.04	0.70	0.04	−1.46	0.04	**14.29**	0.05
$t = 1$	0.16	1.23	0.03	1.13	0.03	**15.08**	0.04	**17.20**	0.04	1.35	0.03	−3.90	0.02	**6.82**	0.04
$t = 1.5$	0.08	2.08	0.02	1.19	0.02	**−9.80**	0.02	1.64	0.02	1.99	0.02	2.38	0.01	**−11.21**	0.03
$t = 2$	0.05	4.78	0.01	1.44	0.01	**−37.62**	0.01	**−20.81**	0.01	2.65	0.01	**13.63**	0.01	**−31.62**	0.01
$t = 2.5$	0.03	2.20	0.01	1.92	0.01	**−60.08**	0.01	**−42.48**	0.01	3.31	0.01	**28.31**	0.01	**−48.47**	0.01

[a] Relative bias is defined as $\frac{\hat{S}(t|X)-S(t|X)}{S(t|X)} \times 100\%$.

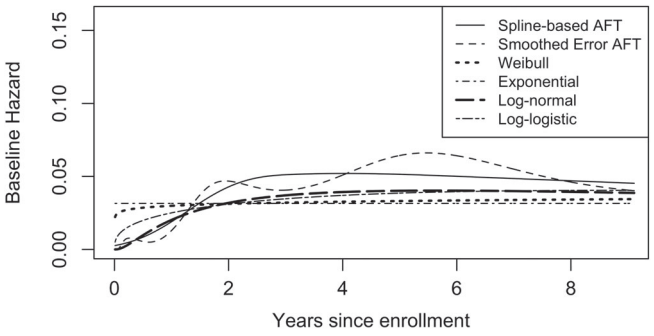

FIGURE 6 The baseline hazards of all-cause mortality in the stage III colon cancer, estimated from different modeling approaches

TABLE 3 Model fit of alternative analysis methods in the colon cancer study

	Spline-based AFT	Smoothed error AFT[a]	Weibull	Exponential	Lognormal	Loglogistic
Log likelihood	−1292.19	−1280.18	−1325.12	−1326.18	−1296.28	−1304.09
Degrees of freedom	20	24.69[a]	16	15	16	16
AIC	2624.38	2609.74[a]	2682.25	2682.36	2624.57	2640.19

[a] Not comparable to other methods; number of parameters is 54.

6 | DISCUSSION

We proposed a flexible spline-based AFT model, that avoids a priori parametric assumptions about the event time distribution. Comprehensive simulations, under different assumptions about the shape of the baseline hazard, indicated that the proposed model yields unbiased estimates of baseline hazard, covariate effects and survival functions, conditional on covariates. Simulations allowed us also to compare the performance of our model with both the conventional parametric AFT models and the semiparametric approach developed by Komárek et al.[29]

An accurate assessment of both (i) relative risks, associated with patient characteristics and treatments, and (ii) absolute risks, that is, the probability of survival for patients with different characteristics, are essential for disease prognosis and treatment decisions. One reason why, in clinical and epidemiological applications, AFT models are used considerably less frequently than the Cox PH model, may be related to the difficulties in specifying the distribution of the event times. Indeed, our simulation results confirm that misspecification of this distribution in the AFT analyses may produce biased estimates of both the baseline hazard and survival curves, conditional on covariates. In some AFT-based analyses, this issue was addressed by using regression diagnostics based on comparing the AIC's of alternative parametric models and/or residual plots.[40-43] However, in complex real-life studies, the baseline hazard may *not* follow any of the common parametric distributions, implying that more flexible AFT models may be necessary to avoid biased estimates and inaccurate conclusions.

In the last three decades, several flexible extensions of the Cox PH model were proposed to allow assumption-free modeling of both relative risks[44-46] and absolute risks.[3,47] By contrast, we found only a few flexible extensions of the AFT model. Whereas some authors used splines to model nonlinear effects of continuous covariates on log event time,[48-50] or to relax the variance homogeneity assumption,[51] they did *not* describe flexible modeling of the baseline hazard. Indeed, to our knowledge, Komárek et al's smoothed error semiparametric model[29] may be the only frequentist AFT model, that can be easily implemented to estimate the baseline hazard without parametric assumptions. The spline-based AFT model we propose offers a flexible alternative to their elegant model. In our simulations, both the smoothed error[29] and our spline-based AFT models yielded unbiased estimates of the baseline hazard *regardless* of whether (i) it was more complex than allowed by the conventional parametric models or (ii) followed a conventional parametric distribution. Our simulation results suggest also that the choice of the penalty parameter may affect the accuracy of the smoothed error model estimates. Specifically, in some of our simulations and real-life analyses using the default option for the penalty, implemented by the "smoothSurv" package, increased the variance of the baseline hazard estimates. By contrast, a slightly more strict penalty of exp(−4) offered the estimates that were practically unbiased and as numerically stable as our spline-based estimates.

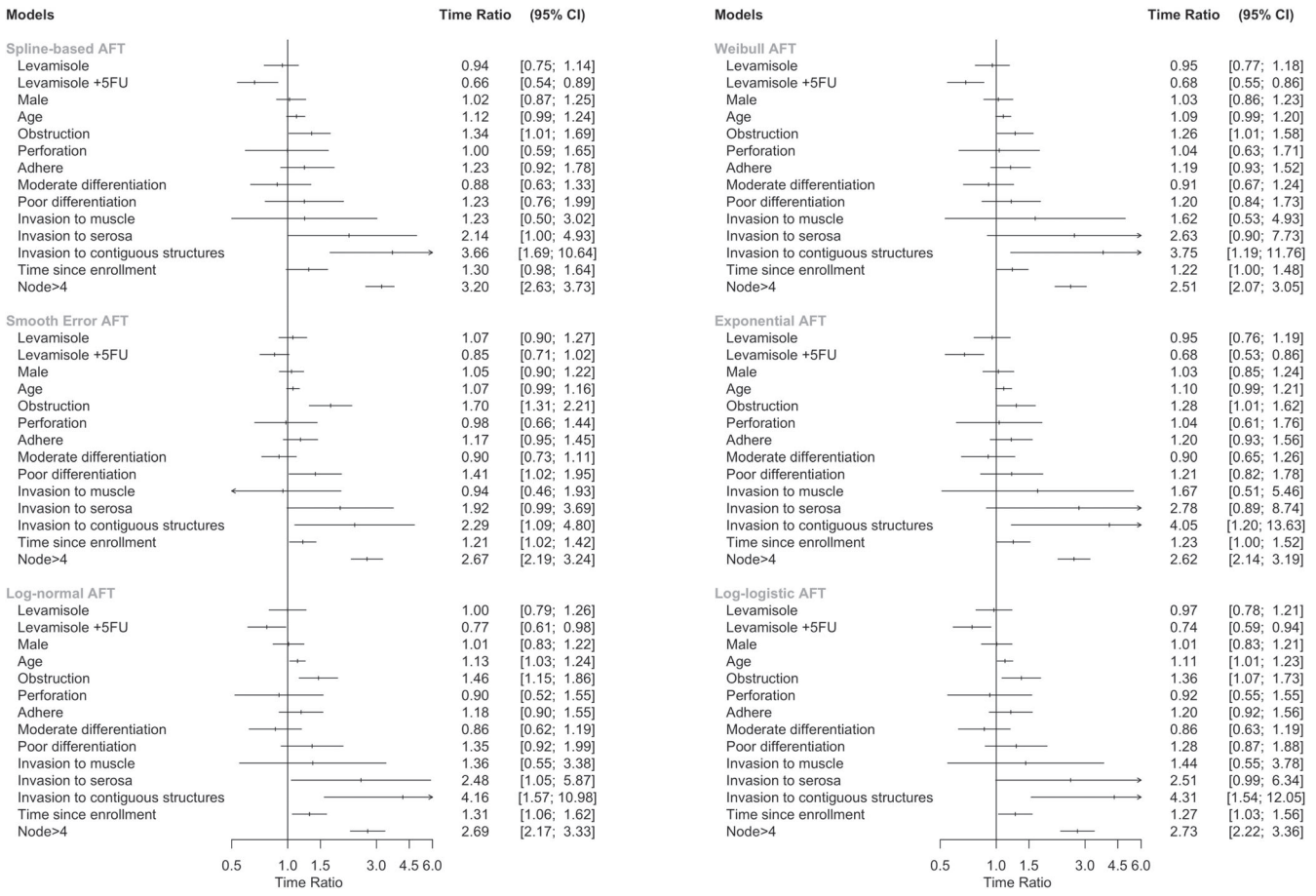

FIGURE 7 Estimated covariate effects in time ratio from alternative AFT model in the colon cancer study

We recognize that a fair comparison of these two flexible AFT models is complicated by their different approaches to control the smoothness of the estimates. The penalization parameter that controls the smoothness of the Komárek et al's estimates is chosen through cross-validation, that is, based on data-dependent critetia.[29] However, the user may select a different value of the penalization parameter.[30] By contrast, the number of knots ($m = 2$) and degree ($P = 3$) of the splines in our proposed model are specified a priori, based on previous experience with regression spline modeling of survival data, that favors relatively parsimonious models.[3,17] Thus, to further ensure a fair comparison of the two methods, in simulations we refitted the smoothed error model with arbitrary variations of the penalization parameter. The results suggest that whereas a strong penalization improves estimation of relatively simple hazards, it produces excessively smooth and, thus, seriously biased estimates if the true hazard is complex. On the other hand, a weak penalization increases instability of the estimates. Still, as suggested by our simulation results summarized in Figure 3, a careful choice of the penalty may offer an optimal variance/bias trade-off. Thus, in applications where it is unclear how complex the underlying hazard function may be, we recommend sensitivity analyses with a few alternative penalty values. However, further research is necessary to develop reliable empirical criteria for the choice of the optimal penalty term for a given application. In the meantime, the researchers may start with the default option and then visually assess the resulting estimate. If it appears too wiggly relative to expectations based on substantive knowledge, then using a more strict, higher penalty may be recommended. Moreover, further comparisons of the two flexible AFT models, using both simulated and real-life data, will be necessary, to more systematically assess their relative advantages and weaknesses.

We applied the proposed spline-based AFT model to reassess survival in stage III colon cancer. The PH assumption was violated for three covariates and rejected by the omnibus test. On the other hand, diagnostics plots did *not* suggest important deviations from the AFT assumption. Our proposed spline-based AFT model fit these data better than most of the conventional unpenalized AFT parametric models, most of were too constrained to recover the nonmonotone baseline hazard. Although the log-normal AFT model fit these data almost equally well, the advantage of our flexible

spline-based model was that it avoided the need to "guess" the shape of the baseline hazard. Moreover, our nonmonotone spline estimate was quite smooth and "regular," in contrast to a wiggly estimate yielded by the Komárek et al's smoothed error model.

Some limitations of the proposed model, and our simulations, should be recognized. First, the hyperparameters: the degree of the splines, as well as the number and the location of interior knots, are chosen a priori. Further research may assess the potential benefits of considering alternative hyperparameter values and selecting their values a posteriori, based on goodness of fit or cross-validation, similar to the approach of Komárek et al.[29] Second, because we rely on a two-step alternating conditional estimation (ACE) of (i) the regression coefficients and (ii) the spline coefficients that define the baseline hazard, the covariance matrix of all estimable parameters cannot be approximated using standard large-sample inference. Thus, a nonparametric bootstrap is necessary to correctly quantify the sampling variance of the ACE-based estimates and obtain accurate 95% CI's.[3,35] Third, given the computational effort required to fit our spline-based model in multivariable analyses, our simulations were limited to a few scenarios, with an arbitrary combination of sample size, censoring levels, covariate effects, but with different event time distributions. We were encouraged to observe that the proposed method performed well across all scenarios considered. Nonetheless, further evaluations, under a wider range of assumptions and parameter values, will be necessary to assess the robustness of our results and conclusions. Finally, our model relies on the constant time ratio assumption, essential for the AFT modeling, which is as arbitrary as the constant hazard ratio assumption imposed by the PH model. Because the AFT assumption was used to generate data in our simulations, the PH assumption was usually violated, except for exponential or Weibull distributions of event times. Accordingly, our simulations do *not* permit a fair comparison of the AFT vs PH models. In real-life applications, researchers should attempt to compare whether the AFT or the PH model seems more appropriate for a given dataset, as illustrated in our colon cancer analysis, where regression diagnostics suggested a better fit of the two flexible AFT models. Yet, the issue will be more complex if different covariates affect the survival according to either the PH or the AFT assumption. Arguably, when the AFT constant time ratio assumption holds for most covariates but a few other behave consistently with the PH assumption, flexible time-dependent extensions of the Cox model could accommodate the resulting nonproportional hazards.[3,45,52-54] However, this would require estimating more parameters, and more complex interpretation, than the AFT model. By contrast, to the best of our knowledge, no currently available AFT model can accommodate time-dependent time ratios. To address this challenge, in future work, we plan to develop an even more flexible version of the AFT model that will allow for time-dependent covariate effects, in order to relax the constant time ratio assumption. Furthermore, more formal tests of the constant time ratio assumption, underlying the AFT model, should be developed and validated.

In summary, we believe that our findings demonstrate both the good performance of our flexible AFT model with spline-based estimation of the baseline hazard and its potential benefits in real-life time-to-event analyses. Therefore, we suggest our model may be considered, together with alternative models, such as the smoothed error method of Komárek et al,[29] in future applications, especially when the PH assumption may be questionable and the event time distribution is difficult to specify. We also hope our work will stimulate both wider use of the AFT modeling and further methodological developments.

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The data that support the findings of this study are openly available in survival R package at https://cran.r-project.org/web/packages/survival/survival.pdf, reference number [36].

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SUPPORTING INFORMATION

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