

Supplementary file 1

Mixture split-population (MSP) models

Let W be the indicator denoting a subject is non-susceptible ($W = 0$) or susceptible ($W = 1$) to the desired event and T is a nonnegative random variable indicating the survival time. The MSP model is given by

$$S(t|\mathbf{x}, \mathbf{y}) = 1 - \pi(\mathbf{x}) + \pi(\mathbf{x}) \times S_{W=1}(t|\mathbf{y}) \quad (\text{I})$$

where $S(t|\mathbf{x}, \mathbf{y})$ is the unconditional survival time function for the entire population, $\pi(\mathbf{x})$ is the probability of being long-term survivors given a covariate vector \mathbf{y} , and $S_{W=1}(t|\mathbf{y})$ is the survival time function for short-term survivors given a covariate vector \mathbf{y} .²⁸⁻³⁰ Note that $S(t|\mathbf{x}, \mathbf{y}) \cong 1 - \pi(\mathbf{x})$, i.e. the long-term OS rate, as t approaches infinity. As seen in the formula (I), the MSP models consist of two components: incidence component ($\pi(\mathbf{x})$) and latency component ($S_{W=1}(t|\mathbf{y})$). An advantage of the MSP models is that the proportion of long-term survivors and the survival distribution of the short-term survivors are modeled separately.²⁹ Different link functions can be utilized to the incidence component such as logit, complementary log-log, and probit link functions. In this study, the logit link function is

$$\text{logit}(\pi(\mathbf{x})) = \beta_0 + \sum_{j=1}^p \beta_j x_j \Leftrightarrow \pi(\mathbf{x}) = \frac{e^{\beta_0 + \sum_{j=1}^p \beta_j x_j}}{1 + e^{\beta_0 + \sum_{j=1}^p \beta_j x_j}} \quad (\text{II})$$

where β_j s are unknown parameters, is applied to model the effects of \mathbf{x} .^{29,30,34}

In the parametric acceleration failure time MSP (AFTMSP) models, the survival function for short-term survivors, $S_{W=1}(t|\mathbf{y})$, takes the form of parametric distribution like exponential, Weibull, lognormal, loglogistic, EGG etc.³⁵ By using the AFTMSP with logit link function, the impact of the different covariates on the survival of susceptible and non-susceptible individuals can be interpreted via the ETR and odds ratio (OR) statistics, respectively. The long-term OS rate can be estimated based on the results from the incidence component. Using formula (II), we can obtain the following formula for the long-term OS rate:

$$\text{Long-term OS rate} = 1 - \pi(\mathbf{x}) = 1 - \frac{e^{\beta_0 + \sum_{j=1}^p \beta_j x_j}}{1 + e^{\beta_0 + \sum_{j=1}^p \beta_j x_j}} \quad (\text{III})$$

The model parameters are estimated by maximizing the observed log-likelihood function directly and the standard error estimates are obtained from minus the second derivatives of the log-likelihood function.^{28,34,35}