Reflection on modern methods: competing risks versus multi-state models.

Fran Llopis-Cardona\textsuperscript{1,2*}, Carmen Armero\textsuperscript{3}, and Gabriel Sanfélix-Gimeno\textsuperscript{1,2}

\textsuperscript{1}Health Services Research Unit, Foundation for the Promotion of Health and Biomedical Research of Valencia Region (FISABIO), Valencia, Spain.
\textsuperscript{2}Red de Investigació en Servicios de Salud en Enfermedades Crónicas (REDISSEC), Valencia, Spain.
\textsuperscript{3}Department of Statistics and Operations Research. Universitat de València, Spain.
\*Corresponding author. E-mail: llopis fray@gva.es

Abstract

Survival competing risks models are very useful for studying the incidence of diseases whose occurrence competes with other possible diseases or health conditions. These models perform properly when working with terminal events, such as death, that imply the conclusion of the corresponding study. But they do not allow the treatment of scenarios with non-terminal competing events that may occur sequentially. Multi-state models are complex survival models. They focus on pathways defined by the temporal and sequential occurrence of numerous events of interest and thus they are suitable for connecting competing non-terminal events as well as to manage other survival scenarios with higher complexity. We discuss competing risks within the framework of multi-state models and clarify the usefulness of both models for analysing epidemiological data. We highlight the power of multi-state models through a real-world study of recurrent hip fracture from Bayesian inferential methodology.

Key words: Bayesian inference, cause-specific hazard models, cumulative incidence function, epidemiological data, illness-death models, transition probabilities.

Key messages

- We define the competing risks model as a particularization of the illness-death model, in which no transition from illness to death is allowed.

- Both formulated models provide almost identical estimations of the cumulative incidences for the competing events.

- We propose multi-state models as a preferable tool to estimate those incidences as they also provide evidence regarding transitions between the competing events, in particular from illness to death.
1 Survival and event history analysis

Epidemiology deals with the incidence and evolution of diseases in populations. Although epidemiological studies can be conducted with different objectives and perspectives, time in these projects is an important, and often essential, element. Survival and event history analysis also address time and constitute important methodological tools for the treatment of epidemiological data. They focus on time to the occurrence of one or several events of interest which, in epidemiological research, are usually associated with death, the cure of a disease, a positive and/or negative progression of a disease, the appearance of adverse effects, etc. as well as with the possible trajectories determined by the occurrence of different events in individuals of the target population.

Competing risk and multi-state models are particular survival models developed for the joint statistical treatment of more than one event of interest (Putter et al., 2007). The first one deals with survival times in the presence of competing events where the occurrence of a particular event prevents the occurrence of all remaining events. Competing risks models are very useful in medical and epidemiological research and have been widely used to assess rates and risks (Lou et al., 2009; Andersen et al., 2012; Wei et al., 2018; Schuster et al., 2020).

There are different approaches for studying competing risk models. The two more popular ones are the so-called multivariate time to failure model, which was the first model proposed (Gail, 1975) in the survival literature, and the cause-specific hazards model subsequently introduced by Gaynor (1993). We will focus on the latter because it does not have the problems of lack of identifiability of the former and connects naturally and intuitively with the multi-state framework. They allow to estimate the cumulative incidence of those events, i.e. the proportion of individuals who would fail at any particular time, by means of modelling the hazard rate associated to each event.

Multi-state models are complex models that focus on the complete event history. They are a class of stochastic models that enable individuals to move between different states over time. These states generally represent different conditions of illness and/or health. Relevant survival times are times between states which, from a methodological perspective, can be analyzed by means of stochastic processes and survival procedures (Andersen and Keiding, 2002). Despite their enormous usefulness, multi-state models are not yet very popular in the world of epidemiology (Commenges et al., 1999; Beyersmann et al., 2011; Hill et al., 2021).

Our aim in this paper is to establish connections between competing risks and multi-state models that allow us to clarify the usefulness of both models for analysing data from epidemiological settings as well as to deepen their analogies and differences. In particular, we want to emphasise the potential of multi-state models to study epidemiological processes that require the analysis of different health conditions whose occurrence may be sequential in time and always in environments subject to uncertainty.

This paper is structured as follows: Section 2 reviews competing risks and multi-state models. In particular, Subsection 2.1 discusses the cause specific-hazard approach to competing risk models, and Subsection 2.2 contains the main elements of multi-state models and describes in detail the so-called illness-death model, a particular type of multi-state models with three states, two of them transient and one terminal. Subsection 2.3 examines the competing risk models in the framework of multi-state models. Section 3 presents a study based on data from the PREV2FO cohort, which comprises patients aged 65 years and older who were discharged after a hospitalization for osteoporotic hip fracture between 2008 and 2015. We use a
competing risks model and a multi-state model to analyse the follow-up of these patients over time with special interest in the occurrence of a subsequent hip fracture or death. Both models were analyzed via Bayesian statistics. This approach allows to obtain posterior distributions of the different quantities of interest such as the cumulative incidence of refracture or death in the competing risks model, or the proportion of people who die or remain alive after a refracture in the case of the multi-state models. The paper ends with some concluding remarks.

2 Competing risks versus illness-death survival models

2.1 Competing risks models

As stated before, competing risks models are survival statistical models which consider many causes of failure. Individuals in the study are followed from a common initial point until the occurrence of the first of the events considered. Such occurrence precludes the observation of the rest of events, acting as a censoring event.

We assume, without loss of generality, a competing risk model with an initial state, 1, and two possible events of interest, 2 and 3 (See Figure 1). Let $T_{ij}$ be the time from the start point (1) to event $j = 2, 3$. Consider $T = \min\{T_{12}, T_{13}\}$ the time to the occurrence of the first event and define the cause-specific hazard function of experiencing the event $j$ in the presence of the competing event as

$$h_{1j}(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T < t + \Delta t, \delta = j \mid T \geq t)}{\Delta t}, \quad t > 0,$$

(1)

where $\delta$ represents the indicator of the cause of the failure in such a way that $\delta = j$ when the observation is failed from cause $j$, and $\delta = 0$ when the observation is censored for events $j = 2, 3$.

![Figure 1: Competing risks model with two possible causes of failure.](image)

The cumulative hazard function for cause $j$ at time $t$ can be defined from (1) as $H_{1j}(t) = \int_0^t h_{1j}(u)du$. The overall survival function $S(t)$ accounts for the probability of not failing from any cause at time $t$ and it is defined as

$$S(t) = P(T > t) = \exp \left\{ - (H_{12}(t) + H_{13}(t)) \right\}.$$

(2)

The cumulative incidence function for cause $j$ at $t$ (also known as crude cumulative incidence function or subdistribution function) describes the probability of failing from cause $j$ before
time $t$ and it is given by

$$F_{1j}(t) = P(T \leq t, \delta = j) = \int_0^t h_{1j}(u) S(u) \, du.$$  

(3)

This probability is not a proper distribution function because $F_{1j}(t)$ does not go to 1 when $t$ goes to $\infty$. In particular, it equals to the probability of failure from cause $j$, $F_{1j}(\infty) = P(\delta = j)$. Cumulative incidence functions are very meaningful, as they can be interpreted as the proportion of individuals who failed by cause $j$ before time $t$. They are the main outcomes of any competing risks analysis.

Cox proportional hazard models (Cox, 1972) introduce covariates on the cause-specific hazard functions. In particular, the cause-specific hazard of cause $j$ at time $t$ for an individual of the target population with covariates $x$ is

$$h_{1j}(t) = h_{0,1j}(t) \exp\{\beta^{(1j)}'x\}, \quad j = 2, 3, \quad t > 0$$  

(4)

where $h_{0,1j}(t)$ is the baseline cause-specific function of failure $j$ and $\beta^{(1j)}$ is the vector of regression coefficients.

### 2.2 Multi-state models

Multi-state models account for different structures depending on the number of states and how they relate to each other (Andersen and Keiding, 2002). We focus on a particular type of multi-state model known as the illness-death or disability model. This is a multi-state model with three states, which generally represent different conditions, usually health, illness and death. A healthy person can go directly to suffering from a certain illness or die without having suffered from that illness. But it is also possible that they die after having suffered from the illness. We are now faced with two competitive events but one of them is of a transitory nature and allows access to the terminal event, death (See Figure 2). This model makes possible to study the risk of death whether the individual has been previously ill or not.

![Figure 2: Illness-death model with an initial state (1), a transient state for illness (2), and an absorbing state such as death (3).](image)

The methodological framework of multi-state models in survival analysis is initially analogous to that of competing risks. In the case of the cause-specific hazards approach we focus on the hazard function for the survival times from state 1 to 2, $T_{12}$, from 1 to 3, $T_{13}$, and from 2 to
As follows:
\[
h_{1j}(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T_{1j} < t + \Delta t \mid T_{1j} \geq t), \quad j = 2, 3}
\]
\[
h_{23}(t - t_{12} \mid T_{12} = t_{12}) = \lim_{\Delta t \to 0} \frac{P(t - t_{12} \leq T_{23} < t - t_{12} + \Delta t \mid T_{23} \geq t - t_{12}, T_{12} = t_{12})}{\Delta t}
\]

In many real problems (e.g. those associated with relapses of cancer diseases) the behaviour of \(T_{23}\) often depends on the characteristics of transition 1 to 2. This situation is reflected in the hazard in (5) which depends on the time when “illness occur” \((T_{12} = t_{12})\), as it represents the hazard of dying after illness.

Multi-state models are also a particular class of stochastic processes so their analysis is enriched with the procedures associated with this type of models. In this regard, transition probabilities are conditional probabilities \(p_{ij}(s, t)\) defined as the probability of being at the state \(j\) at time \(t\) given that the individual was in state \(i\) at \(s\). In the case of illness-death models, the relevant transition probabilities are \(p_{11}(s, t)\), \(p_{22}(s, t \mid t_{12})\), which assess the permanence in states 1 and 2, respectively, \(p_{12}(s, t)\) and \(p_{13}(s, t)\) which quantify the transition to the illness and the death state from the initial state, respectively and, \(p_{23}(s, t \mid t_{12})\) for the transition from the illness state to death. Probabilities \(p_{22}(s, t \mid t_{12})\) and \(p_{23}(s, t \mid t_{12})\) account for the transition time \(t_{12}\) from the healthy to the illness state. Note that \(p_{33}(s, t \mid t_{12}) = 1\) as death is a terminal state.

In practice, transition probabilities are calculated through transition intensities. The specific linkage between transition probabilities and hazard functions is as follows (Armero et al., 2016):

\[
p_{11}(s, t) = \exp \left\{ - \int_{s}^{t} (h_{12}(u) + h_{13}(u)) \, du \right\}
\]
\[
p_{22}(s, t \mid t_{12}) = \exp \left\{ - \int_{s}^{t} h_{23}(u - t_{12}) \, du \right\}
\]
\[
p_{12}(s, t) = \int_{s}^{t} p_{11}(s, u) h_{12}(u) p_{22}(u, t \mid u) \, du
\]
\[
p_{13}(s, t) = 1 - p_{11}(s, t) - p_{12}(s, t)
\]
\[
p_{23}(s, t \mid t_{12}) = 1 - p_{22}(s, t)
\]
\[
p_{33}(s, t) = 1
\]

It is important to mention that \(p_{11}(s, t)\), the probability associated with the permanence at the initial state (1) during the time interval \([s, t]\), is also well defined for a competing risks model, with the same interpretation.

### 2.3 Competing risks model as a multi-state model

A competing risk model can be considered as a multi-state model with two types of events: an initial state and two states for the competing causes of failure which can be terminal and without connection among them. The only transitions between states with probability not zero are the two that start from the initial state to each of the other two states. Transition probabilities between the states can also be expressed in terms of the subsequent transition intensities as follows (Andersen and Keiding, 2010):

5
\[ p_{11}(s, t) = \exp \left\{ - \int_s^t (h_{12}(u) + h_{13}(u)) du \right\} \]

\[ p_{1j}(s, t) = \int_s^t \exp \left\{ - \int_s^u (h_{12}(x) + h_{13}(x)) dx \right\} h_{1j}(u) du, j = 2, 3 \]

\[ p_{22}(s, t) = p_{33}(s, t) = 1. \]

(7)

It is worth mentioning that the overall survival function \( S(t) \) defined in (2) within the competing risk scenario is the transition probability that assesses the permanence of the process in the initial state at time \( t \), \( S(t) = p_{11}(0, t) \). Moreover, the cumulative incidence function for cause 2 and for cause 3, \( F_{12}(t) \) and \( F_{13}(t) \), in the competing risk framework are the transition probabilities \( p_{12}(0, t) \) and \( p_{13}(0, t) \), respectively.

3 The PREV2FO study: Incidence of refracture and death after an osteoporotic hip fracture.

3.1 Problem, objective and data

Hip fracture is a main complication of osteoporosis in elder populations. Beyond its economic cost for health care systems and society, it results in significant reductions in quality of life, disability, morbidity and mortality (Lips et al., 2005, Hopkins et al., 2016, Hernlund et al., 2013). Patients after a hip fracture are at much higher risk of a subsequent hip fracture (Johnell et al. 2004, Ryg et al. 2009) as well as death, and excess of mortality is even higher after a second hip fracture (Abrahamsen et al., 2009, Sobolev et al., 2015).

For the case study we used the PREV2FO cohort, a population-based cohort of all patients aged 65 years and older, discharged alive after hospitalization for osteoporotic hip fracture from January 1, 2008, to December 31, 2015. Patients were followed from the date of discharge (time zero) to December 31, 2016 (end of study) or death. The study was conducted in the region of Valencia in Spain (around 5 million inhabitants, representing 10% of the whole country population) providing free, universal health care services (besides drug cost-sharing) to 97% of the region’s population. Data were obtained from the Valencia Health System Integrated Database (VID). The VID is the result of the linkage, by means of a single personal identification number, of a set of publicly owned population-wide health care, clinical, and administrative electronic databases in the region of Valencia, Spain, which has provided comprehensive information since 2008 (Garcia et al. IJE., 2020).

From 34491 patients discharged alive after hip fracture, 25807 (74.8%) were women and 8684 (25.2%) men. Regarding age, 12.4% of patients were under 75 years old, 43.6% were between 75 and 85 years old, 40.6% were between 85 and 94 years old, and 3.4% were over 95 years old. The mean age at the first fracture was 83.4 years (IQR: 79.0-88.3). Patients were followed a median time of 5.0 years (IQR: 3.0-7.0 years).

The estimation of the incidence of recurrent hip fractures and death after an osteoporotic hip fracture, one of the main objectives of the study, could be approached by means of a competing risk model when the refracture condition is considered as a terminal event which competes with the risk of death or as an illness-death multi-state model in the case that the refracture condition can be considered as a transitory state towards death. Figure 3 shows both approaches.
We started by working with a competing risk model with two possible causes of failure, recurrent fracture \((R)\) and death \((D)\) from the initial state discharge after fracture \((F)\) and as relevant survival times the time from discharge after fracture to refracture, \(T_{FR}\), and time from discharge after fracture to death, \(T_{FD}\). Later on we discussed an illness-death model with the same three states as in the competing model but allowing the access to death from the refracture state and the subsequent time from refracture to death, \(T_{RD}\) (See Figure 3). The latter model has a structure much closer to the reality of the problem than the one proposed by the competing risks framework. The number of patients in each transition \((F \rightarrow R, F \rightarrow D,\) and \(R \rightarrow D)\) for women and men is shown in Figure 5 of supplementary material.

### 3.2 Bayesian modeling

Cox proportional hazards models are very popular regression models (Cox, 1972). They express the hazard function of the survival time of interest in terms of a baseline hazard function, which determines the temporal shape of the hazard, and an exponential term which includes the relevant covariates. Cox proportional hazards models with Weibull baseline hazard functions, and gender and age at discharge as covariates have been used to model the random behaviour of times \(T_{FR}\) and \(T_{FD}\) in the competitive risk model and of times \(T_{FR}, T_{FD},\) and \(T_{RD}\) in the multi-state model in terms of the hazard functions as follows:

#### Competing risks model:

\[
\begin{align*}
    h_{FR}(t) &= h_{0,FR}(t) \exp\{\beta_1^{(FR)} I_{Woman} + \beta_2^{(FR)} Age\}, \\
    h_{FD}(t) &= h_{0,FD}(t) \exp\{\beta_1^{(FD)} I_{Woman} + \beta_2^{(FD)} Age\},
\end{align*}
\]

where \(I_{Woman}\) is an indicator variable that takes the value 1 when the individual is considered as a woman and zero if he is registered as a man. \(h_{0,FR}(t)\) and \(h_{0,FD}(t)\) is the baseline hazard function for \(T_{FR}\) and \(T_{FD}\), respectively, which we define below as

\[
\begin{align*}
    h_{0,FR}(t) &= \alpha^{(FR)} \lambda^{(FR)} t^{\alpha^{(FR)}-1}, \\
    h_{0,FD}(t) &= \alpha^{(FD)} \lambda^{(FD)} t^{\alpha^{(FD)}-1},
\end{align*}
\]

being \(\beta_1^{(FR)}, \beta_2^{(FR)} (\beta_1^{(FD)}, \beta_2^{(FD)})\) the regression coefficients associated to sex and age, respectively, for time \(T_{FR} (T_{FD})\).
ILLNESS-DEATH MODEL:

The definition of the hazard functions for the survival times in the illness-death model were analogous to the ones for the competing risk model. The common transitions, i.e., from state $F$ to $R$ and from $F$ to $D$, were modelled identically. However, transition from refracture to death required to be modelled with consideration to the time when patients refractured as follows

$$h_{RD}(t - t_{FR} | T_{FR} = t_{FR}) = h_{0,RD}(t - t_{FR} | T_{FR} = t_{FR}) \exp\{\beta_1^{(RD)} I_{W\text{oman}} + \beta_2^{(RD)} \text{Age}\}, \quad (9)$$

for $0 < t_{FR} < t$, where $h_{0,FD}(t | T_{FR} = t_{FR})$ is the baseline hazard function and $\beta_1^{(RD)}$, $\beta_2^{(RD)}$ are the regression coefficients associated to sex and age, respectively. The baseline hazard function was defined as

$$h_{0,RD}(t - t_{FR} | T_{FR} = t_{FR}) = \alpha^{(RD)} \lambda^{(RD)}(t - t_{FR})^{\alpha^{(RD)} - 1}. \quad (10)$$

Note that although we modelled the common transitions in the competing risk model and the illness-death model identically, they are different models. Despite the fact that the common parameters have the same names, they are not equal because of their distinct provenance.

We used a Bayesian approach to estimate the parameters of both models. We have followed the usual steps of the Bayesian inferential process: specification of a prior distribution for the parameters of the model, construction of the likelihood function, and computation of the posterior distribution via Bayes’ theorem.

The prior distribution is elicited assuming a prior independence and non-informative scenario. Wide normal prior distributions were selected for the regression coefficients, $\beta$, and Gamma distributions for the shape and scale parameters $\alpha$ and $\lambda$ (See Alvares et al., (2021) for a wide tutorial on Bayesian survival models). Posterior distributions were approximated via Markov Chain Monte Carlo methods (MCMC) as well as through the integrated nested Laplace approximation (INLA). The former are simulation procedures very used in Bayesian statistics for dealing with non-analytical posterior distributions (Chen, Shao, and Ibrahim, 2000). The latter method computes approximations of the posterior marginals for the parameters and hyperparameters in latent Gaussian models, a subset of models which includes generalized regression models, smoothing splines models, spatial and survival models, among others (Rue, Martino and Chopin, 2009). In particular, age as a covariate is included in the model as mean-centered in order to improve the convergence of the subsequent computational Markov chain Monte Carlo methods used.

3.3 Results

Posterior distribution

The approximate posterior distribution of the competing risk and of the illness-death model parameters have been summarized in Table 1 via their posterior mean and standard deviation. No differences have been observed between the results of the competing risk and the illness-death model for the two common transitions, from fracture to refracture and from fracture to death. However, the illness-death model provides additional information regarding the transition from refracture to death.
### Table 1: Summary of the posterior distribution of the parameters for the competing risks model and of the illness-death model.

| Transition | Parameter | Competing risks model | Illness-death model |
|------------|-----------|-----------------------|---------------------|
| From $F$ to $R$ | $\alpha^{(FR)}$ | 0.9197 ± 0.0156 | 0.9198 ± 0.0157 |
| | $\lambda^{(FR)}$ | 0.0279 ± 0.0013 | 0.0279 ± 0.0013 |
| | $\beta_1^{(FR)}$ | 0.0254 ± 0.0496 | 0.0262 ± 0.0486 |
| | $\beta_2^{(FR)}$ | 0.0244 ± 0.0030 | 0.0244 ± 0.0030 |
| From $F$ to $D$ | $\alpha^{(FD)}$ | 0.7759 ± 0.0051 | 0.7759 ± 0.0051 |
| | $\lambda^{(FD)}$ | 0.3310 ± 0.0051 | 0.3311 ± 0.0050 |
| | $\beta_1^{(FD)}$ | -0.5088 ± 0.0169 | -0.5092 ± 0.0166 |
| | $\beta_2^{(FD)}$ | 0.0705 ± 0.0012 | 0.0705 ± 0.0012 |
| From $R$ to $D$ | $\alpha^{(RD)}$ | 0.6234 ± 0.0154 | 0.6234 ± 0.0154 |
| | $\lambda^{(RD)}$ | 0.5769 ± 0.0329 | 0.5769 ± 0.0329 |
| | $\beta_1^{(RD)}$ | -0.6127 ± 0.0655 | -0.6127 ± 0.0655 |
| | $\beta_2^{(RD)}$ | 0.0498 ± 0.0046 | 0.0498 ± 0.0046 |

### Refracture and death

The cumulative incidence function for refracture (death) assesses the probability that a person refractures (dies) before a certain time. These probabilities depend on the parameters of the model and consequently their posterior distribution is determined by the posterior distribution computed previously. Competing risk and illness-death models provide almost identical results for the incidence of refracture and death without refracture (See Table 2, posterior mean of the one-year cumulative incidence of refracture and death from any cause by sex and age). However, the illness-death model provides additional information regarding the probability of transition from refracture to death (or the cumulative incidence of death after refracture).

Overall, refracture probability increases with age and women have also higher incidence (one-year incidences of 1.96% at 70 and 2.80% at 90 years old for women, whilst 1.86% and 2.46% for men). Regarding death without refracture, incidence increases with age and has been estimated higher for men (one-year incidences of 7.36% at 70 and 26.73% at 90 years old among women, versus 11.94% and 40.34% for men).

### Death after refracture

The illness-death model provides relevant information about the transition from refracture to death that the competing risks model cannot address. Figure 4 shows the posterior mean of the cumulative incidence of refracture and the posterior mean of the transition probability from the initial state of fracture to the refracture state. Both outcomes are defined in relation to a specific time $t$. The upper curve corresponds to the total accumulation of refractures (cumulative incidence) occurred before time $t$ and the lower curve refers to the probability that a patient is in the state of refracture at time $t$, and therefore alive. Thus, it should be understood that at time $t$ the dark shaded area shows living patients who have refractured and the light shaded area shows refractured patients who have died.
In broad terms, death after refracture shows a similar pattern to death without refracture, i.e. incidence increases with age and is higher for men (one-year incidences of 14.77% at 70 and 35.14% at 90 years old for women, whereas 25.56% and 55.03% for men).

### 4 Concluding remarks

Several authors have addressed the relation between competing risks and multi-state models, with consensus on identifying the first as a particularization of the second (Andersen, 2002; Putter, 2007). Moreover, some authors performed comparisons between both model estimations (Leffondré, 2013). However, there is no literature available comparing both estimations from a Bayesian perspective. In this paper, we showed that not only can the competing risks model be considered as a particular case of an illness-death model, but also they provide identical information of the common transitions under some given conditions. It is a matter of prior independence of the parameters and separability of the likelihood. Regarding likelihood from both models, it presents a separated structure, with separated products for each transition. It results in a sort of “independent” transitions, what makes the inclusion of a new transition after refracture not to change the estimations of the other transitions. Had transitions had shared parameters, estimations might have differed. Correlated random effects would be also supposed to violate the separability, resulting in different estimations from a competing risks and an illness-death model. Finally, non-informative and independent priors were assumed for
Figure 4: Posterior mean of the cumulative incidence of refracture (upper curve) and of the transition probability from initial state to refracture state (lower curve). Light area in both figures represents the proportion of dead patients who had previously suffered a refracture while the dark area represents the proportion of refractured people still alive.

the parameters. Prior correlation between parameters might translate into posterior correlation and thus posterior distributions would be sensitive to the addition of new transitions.

An important consideration should be made about the estimation of the incidence of death among the population. Although the incidence of refracture can be estimated equally from both of our models, it is not the case with the incidence of death. The proposed competing risks model only accounts for death without refracture, as the observation of death is censored for those refractured patients. However, when including death after refracture through the illness-death model, the total incidence of death becomes a natural outcome. In particular, it is defined as the transition probability from the initial state at the beginning of the follow-up time to death state. This advantage, always under the aforementioned assumptions and considerations, makes the illness-death model a preferable tool/method to assess cumulative incidences when studying more than one event or when death is an unavoidable event to consider (e.g. elder population).

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**Ethics**

The study was approved by the Ethics Committee for Clinical Research of the General Directorate of Public Health and the Centre for Public Health Research (session on October 26, 2012). All protocols were performed in accord with Spanish laws on data protection for health research (Act 3/2018 transposing the 2015 European Data Protection Regulation).

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Supplementary

Figure 5: Number of patients in each transition by sex.