Handling time-dependent exposures and confounders when estimating attributable fractions — bridging the gap between multistate and counterfactual modeling

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Abstract

The population-attributable fraction (PAF) expresses the percentage of events that could have been prevented by eradicating a certain exposure in a certain population. It can be strongly time-dependent because either exposure incidence or excess risk may change over time. Competing events may moreover hinder the outcome of interest from being observed. Occurrence of either of these events may, in turn, prevent the exposure of interest. Estimation approaches therefore need to carefully account for the timing of potential events in such highly dynamic settings. The use of multistate models has been widely encouraged to meet this need so as to eliminate preventable yet common types of time-dependent bias, such as immortal time bias. Even so, it has been pointed out that previously proposed multistate modeling approaches for PAF estimation fail to fully eliminate such biases. In addition, assessing whether patients die from rather than with a certain exposure, not only requires adequate modeling of the timing of events, but also of the confounding factors affecting these events and their timing. While proposed multistate modeling approaches for confounding adjustment may be sufficient to accommodate baseline imbalances between infected and uninfected patients, these proposals are not generally equipped to handle time-dependent confounding. For this, a class of generalized methods (abbreviated as $g$-methods), including inverse probability weighting, can be used. Because the connection between multistate models and $g$-methods is not readily apparent, we here provide a detailed mapping between multistate modeling and inverse probability of censoring weighting (IPCW) approaches for estimating PAFs.
In particular, we illustrate that the connection between these two approaches can be made more apparent by means of a weighting-based characterization of multistate modeling approaches. This characterization aids to both pinpoint current shortcomings of these approaches and to enhance intuition into simple modifications to overcome these limitations. Documented R code is made available to foster the uptake of g-methods for PAF estimation.

1 Introduction

The population-attributable fraction (PAF) expresses the percentage of events that could have been prevented by eliminating a certain exposure or risk factor in a certain population, thereby quantifying the contribution of this risk factor to the burden of mortality or morbidity. This quantity involves a comparison of the observable probability of an event (in this world) and the unobservable probability of an event in a hypothetical world where exposure could be eradicated.

A major focus in the field of hospital epidemiology is accurate quantification of the burden of hospital-acquired infections (HAIs) on hospital mortality. Since HAIs are acquired in the course of hospitalization and because the burden may depend on the actual onset and duration, there is special interest in quantifying this burden as a function of time since hospital admission. Accordingly, the time-dependent PAF of hospital mortality due to HAIs can be expressed in terms of cumulative incidences or incidence proportions

\[
PAF(t) = \frac{\Pr(T \leq t, \epsilon = 1) - \Pr(T^0 \leq t, \epsilon^0 = 1)}{\Pr(T \leq t, \epsilon = 1)},
\]

where \(T\) denotes the observed time from hospital admission (i.e. the time origin) to hospital death or discharge, \(\epsilon\) the type of the observed event (\(\epsilon = 1\) indicating hospital death and \(\epsilon = 2\) indicating hospital discharge), and \(T^0\) and \(\epsilon^0\) the hypothetical or counterfactual event time and event type indicator that would (hypothetically) have been observed if — possibly counter to the fact — no infection were acquired.

\(\Pr(T \leq t, \epsilon = 1)\) and \(\Pr(T^0 \leq t, \epsilon^0 = 1)\) respectively denote the observed (factual) and the hypothetical (counterfactual) cumulative incidence of hospital mortality at time \(t\). The observable quantity \(\Pr(T \leq t, \epsilon = 1)\) expresses the cumulative incidence under observed circumstances (i.e. under standard preventive and therapeutic care). Given complete follow-up (until hospital death or discharge), it can be consistently estimated from the observed data without any causal assumptions. Bias-free estimation of the unobservable counterfactual quantity \(\Pr(T^0 \leq t, \epsilon^0 = 1)\) is arguably more challenging, due to its hypothetical nature, and necessitates strong and untestable causal assumptions. Notwithstanding this, consistent estimation of this quantity is required to warrant the intended interpretation of the PAF as a measure of causal attribution (although to some readers this may sound like a tautology).
In this manuscript, we illustrate that proposed approaches for estimating \( \Pr(T^0 \leq t, \epsilon^0 = 1) \) each aim to answer the counterfactual question of how the future of infected patients had unfolded had they not developed an HAI; they do so by letting infected patients transfer their weight in the analysis to uninfected patients. Intuitively, transferring weight from infected to uninfected patients compensates for the depletion of infected patients from the ‘counterfactual risk set’, so as to reconstruct the original study population in a hypothetical world where HAI is eradicated. To avoid bias, these weight transfers should ideally account for subtle aspects related to the timing of observable events. Proposed estimation approaches differ in the way these aspects are taken into account. A weighting based characterization of these approaches therefore sheds light on the biases they may produce and provides a conceptually appealing bridge between multistate and counterfactual modeling approaches.

In the next section, we further formalize and extend notation. In section 3, we more formally define the PAF as an estimand expressed in terms of factual and counterfactual risks. Estimation of the factual risks is discussed and introduced as basis for estimation of the counterfactual risks. In sections 4 and 5, we discuss and compare different proposed approaches for estimating the counterfactual risk \( \Pr(T^0 \leq t, \epsilon^0 = 1) \) using a weighting based characterization of each of these approaches. By means of a toy example, we first illustrate in section 4 how estimation approaches differ in the way their corresponding weights account for the time-dependent nature of exposure and its competing events. We illustrate that multistate modeling approaches can be organized hierarchically in terms of how well they succeed to eliminate different forms of time-dependent bias, and that the preferred multistate modeling approach corresponds to artificially censoring the counterfactual event time at the time of exposure onset. In section 6, we discuss how further accounting for the time-dependent nature of prognostic factors related to the exposure may reduce selection bias due to artificial censoring using inverse probability of censoring weighting (IPCW). In section 7, we present a direct comparison of the discussed estimation approaches in an empirical example using data from the Ghent University Hospital ICUs. Finally, in section 7, we end with a discussion in which we briefly touch upon challenges related to causal interpretation of the PAF in terms of well-defined interventions.

2 Setting and notation

For each patient \( i = 1, ..., n \), we observe the time \( T_i \) from hospital admission to either hospital death or discharge, whichever occurs first, and the event type \( \epsilon_i = j, j \in \{1, 2\} \), with 1 indicating hospital death, the event of interest, and 2 indicating hospital discharge, the competing event (as in the simple competing risk model depicted in Figure 1). In patients who acquire infection, we also observe the time \( C_i \) from hospital admission to infection onset. In patients who get discharged or die at the hospital without having acquired infection, \( C_i \) is set to \( \infty \). To quantify the probability of experiencing an
hospitalization

hospital death
\((\epsilon = 1)\)

hospital discharge
\((\epsilon = 2)\)

Figure 1: A competing risk model in which hospital discharge is treated as a competing event.

exposure- or infection-free event, we also consider \(\hat{T}_i \equiv \min(T_i, C_i)\), the time from hospital admission to either HAI, hospital death or discharge, whichever occurs first, and the event type \(\hat{\epsilon}_i \equiv \delta_i \epsilon_i = j, j \in \{0, 1, 2\}\), with \(\delta_i \equiv 1_{T_i < C_i}\) and \(1_{\cdot}\) the indicator function (as in the competing risk model depicted in Figure 2, with 0 indicating infection onset, 1 infection-free hospital death and 2 infection-free hospital discharge).

Throughout we will consider equally spaced discrete time follow-up intervals indexed by \(k \in \{0, 1, \ldots, K\}\), with interval \(k\) defined by \(t_{k-1}, t_k\), \(t_0 = 0\) indicating the time origin (hospital admission) and \(t_K\) the maximum follow-up time of interest, at or before the maximum possible follow-up time \(t_\tau\) (determined by the administrative end of the study). We define the discrete-time counting processes \(A_k \equiv 1_{\hat{T} \leq t_k, \hat{\epsilon} = 0}\), \(D_k \equiv 1_{T \leq t_k, \epsilon = 2}\) and \(Y_k \equiv 1_{T \leq t_k, \epsilon = 1}\), which denote monotone indicators for infection, hospital discharge and hospital death by time \(t_k\) since hospital admission, respectively (see Bekaert et al. (2010); Young et al. (2020) for similar notation). Because all patients are admitted to the hospital without HAIs, we have \(A_0 = D_0 = Y_0 = 0\). Furthermore, note that \(A_r = 1_{\hat{T} \leq t_r, \hat{\epsilon} = 0} = 1_{\hat{T} \leq T, \hat{\epsilon} = 0} = 1_{\hat{\epsilon} = 0}\). By the end of each interval \(k\), we observe a vector \(L_k\) of time-varying patient-specific covariates (i.e. patient characteristics and prognostic factors). For \(k \geq 1\), this may e.g. include indicators for intercurrent events and time-updated values of either baseline measurements (which form a subset of \(L_0\)) or measurements for which registration only starts at some point after baseline (e.g. measurements that may be contingent on an intercurrent event).

Figure 2: A competing risk model in which HAI is additionally treated as a competing event.
In many applications, including ours, follow-up may not be periodic (e.g. once daily) for HAI onset and hospital death and discharge, but discretization may nonetheless be desirable to some level to warrant appropriate alignment with periodic follow-up measures included in $L_k$. To account for potential ties that may arise from this, within each follow-up interval $k \geq 1$, we assume the temporal ordering $(A_k, D_k, Y_k, L_k)$. As the length of chosen follow-up intervals approximates zero, so does the probability of ties. By consequence, this ordering assumption then becomes practically irrelevant (e.g. Young et al. (2020); Stensrud et al. (2021)). This allows us to define time-dependent indicators for infection-free hospital discharge $\tilde{D}_k \equiv 1_{\tilde{T} \leq t_k, \tilde{\epsilon} = 2} = (1 - A_k)D_k$ and infection-free hospital death $\tilde{Y}_k \equiv 1_{\tilde{T} \leq t_k, \tilde{\epsilon} = 1} = (1 - A_k)Y_k$. For any variable $Z_k$, we define the history of measures from start of follow-up as $Z_k \equiv \{Z_0, \ldots, Z_k\}$ and the future of measures until the end of follow-up of interest as $\tilde{Z}_k \equiv \{Z_k, \ldots, Z_K\}$. As soon as a patient has experienced one of the competing events in any interval $k$, s/he can no longer experience the other event(s). For instance, whenever a patient is discharged from the hospital in interval $k$ ($D_{k−1} = 0, D_k = 1$), all future event indicators $Y_k$ are deterministically zero.

Throughout, we assume the observed data for patients $i = 1, \ldots, n$ are independent and identically distributed.

Let $\pi \equiv \pi_K = 0$ denote a HAI-free counterfactual or hypothetical exposure path, and $T_i^{\pi=0}$ the counterfactual event time of patient $i$ under a hypothetical regime where — possibly counter to the fact — patient $i$ remained uninfected while hospitalized. Furthermore, let $\epsilon_i^{\pi=0} = j, j \in \{1, 2\}$, denote the counterfactual event type of patient $i$, where, as before, $j = 1$ in case of hospital death, or $j = 2$ in case of hospital discharge. In the previous section, we have used the shorthand notation $T^0$ and $\epsilon^0$ to indicate $T^{\pi=0}$ and $\epsilon^{\pi=0}$, respectively (Bekaert et al., 2010). Equivalently, we define the counterfactual discrete-time counting processes $D_k^{\pi=0} = 1_{T^{\pi=0} \leq t_k, \epsilon^{\pi=0} = 2}$ and $Y_k^{\pi=0} = 1_{T^{\pi=0} \leq t_k, \epsilon^{\pi=0} = 1}$.

### 3 Factual and counterfactual estimands

The fraction of deceased in-patients that have died with infection by the end of follow-up interval of interest $K$ (or, similarly, by follow-up time of interest $t_K$) is defined as

$$\frac{\Pr(T \leq t_K, \epsilon = 1) - \Pr(\hat{T} \leq t_K, \hat{\epsilon} = 1)}{\Pr(T \leq t_K, \epsilon = 1)} = \frac{\Pr(Y_K = 1) - \Pr(\hat{Y}_K = 1)}{\Pr(Y_K = 1)},$$

which involves a contrast of two observable or factual quantities, the cumulative incidence of hospital death by $t_K$, $\Pr(T \leq t_K, \epsilon = 1)$, and the (cause-specific) cumulative incidence or crude risk of infection-free hospital death by $t_K$, $\Pr(\hat{T} \leq t_K, \hat{\epsilon} = 1)$.

The fraction of deceased in-patients that have died from infection by $t_K$, or the population-attributable fraction (PAF) at time $t_K$, is defined as

$$\frac{\Pr(T \leq t_K, \epsilon = 1) - \Pr(T^{\pi=0} \leq t_K, \epsilon^{\pi=0} = 1)}{\Pr(T \leq t_K, \epsilon = 1)} = \frac{\Pr(Y_K = 1) - \Pr(Y_{K}^{\pi=0} = 1)}{\Pr(Y_K = 1)},$$

(1)
which involves a contrast of a factual and counterfactual quantity: the cumulative incidence of hospital death by $t_K$, $\Pr(T \leq t_K, \epsilon = 1)$, and the cumulative incidence or net risk of hospital death under (hypothetical) elimination of infection by $t_K$, $\Pr(T^{\pi=0} \leq t_K, \epsilon^{\pi=0} = 1)$. Causal contrasts between observed and hypothetical scenarios, such as the numerator of (1), have been termed population intervention effects [Hubbard and Van Der Laan 2008 Westreich 2017].

The factual risks $\Pr(T \leq t_K, \epsilon = 1)$ and $\Pr(\tilde{T} \leq t_K, \tilde{\epsilon} = 1)$ are identifiable from the observed data without causal assumptions, except, perhaps, in the presence of loss to follow-up or administrative censoring. For instance, $\Pr(T \leq t_K, \epsilon = 1) = \Pr(Y_K = 1)$, can be estimated using the Aalen-Johansen estimator

$$\sum_{k=1}^{K} \frac{d_{jk}}{r_k} \prod_{s=1}^{k-1} \left(1 - \frac{d_s}{r_s}\right)$$

with $j$ set to 1 and where $d_{jk} = \sum_{i=1}^{n} 1_{T_i \in (t_{k-1}, t_k], \epsilon_i = j}$ denotes the number of events of type $\epsilon = j$ in interval $k$, $d_k = \sum_{j=1}^{2} d_{jk}$ the number of events of either type (either hospital death or discharge) in interval $k$, and $r_k$ the number of patients at risk at $t_{k-1}$, the start of interval $k$. Because all considered patients are alive and hospitalized at the start of follow-up, we have $d_0 = 0$ and $r_0 = r_1 = n$. In the presence of right censoring at censoring time $U$, the risk set is often chosen to be $r_k = \sum_{i=1}^{n} 1_{\min(T_i, U_i) > t_{k-1}}$, to reflect the usual convention that, in the case of tied event and censoring times in interval $k$, event times are assumed to occur before censoring times, which, in turn, are assumed to occur at $t_k$, the end of interval $k$. For ease of exposition, however, throughout we will assume no right censoring due to administrative end of the study or loss to follow-up, in which case $r_k = \sum_{i=1}^{n} 1_{T_i > t_{k-1}}$ and (2) reduces to the empirical cumulative distribution function of hospital death (see Appendix A.1 for a formal proof)

$$n^{-1} \sum_{k=1}^{K} d_{1k}.$$

Similarly, $\Pr(\tilde{T} \leq t_K, \tilde{\epsilon} = 1) = \Pr(\tilde{Y}_K = 1)$ can be estimated using the following Aalen-Johansen estimator

$$\sum_{k=1}^{K} \frac{\tilde{d}_{jk}}{\tilde{r}_k} \prod_{s=1}^{k-1} \left(1 - \frac{\tilde{d}_s}{\tilde{r}_s}\right)$$

with $j$ set to 1 and where $\tilde{d}_{jk} = \sum_{i=1}^{n} 1_{\tilde{T}_i \in (t_{k-1}, t_k], \tilde{\epsilon}_i = j}$ denotes the number of events of type $\tilde{\epsilon} = j$ in interval $k$ and $\tilde{d}_k = \sum_{j=0}^{2} \tilde{d}_{jk}$ the number of events of any type (HAI onset, HAI-free hospital death or HAI-free discharge) in interval $k$. Again, in the absence of right censoring, $\tilde{r}_k = \sum_{i=1}^{n} 1_{\tilde{T}_i > t_{k-1}}$ denotes the number of patients at risk of any of the three competing events in interval $k$, and (3) reduces to the empirical cumulative distribution function of HAI-free hospital death (see Appendix A.2 for a
formal proof)

\[ n^{-1} \sum_{k=1}^{K} \tilde{d}_{1k}. \] (4)

Equivalent expressions of (2)-(4) in terms of the discrete-time counting processes defined in the previous section, and in terms of discrete-time cause-specific hazards, are given in Appendix A.

Estimation of the counterfactual risk \( \Pr(T^{\pi=0} \leq t_K, \epsilon^{\pi=0} = 1) = \Pr(Y^{\pi=0} = 1) \) is more challenging due to its hypothetical nature. Ideally, we would wish to observe every patient’s death or discharge time if HAIs could somehow have been eradicated. Under the consistency assumption that this counterfactual event time \( T^{\pi=0} \) equals the observed event time \( T \) and that the counterfactual event status \( \epsilon^{\pi=0} \) equals the observed event status \( \epsilon \) in patients who did not acquire infection during their hospitalization (or, similarly, \( D_k = \tilde{D}_k = D_k^{\pi=0} \) and \( Y_k = \tilde{Y}_k = Y_k^{\pi=0} \) in patients for whom \( A_k = 0 \)) and the monotonicity assumption that no exposed patient benefits from being exposed (i.e. no exposed patient would die sooner during hospitalization had s/he not been exposed), a natural lower bound for \( \Pr(T^{\pi=0} \leq t_K, \epsilon^{\pi=0} = 1) \) is the crude risk of HAI-free hospital mortality, \( \Pr(\tilde{T} \leq t_K, \tilde{\epsilon} = 1) \). Equating these two risks is only justified if every patient who dies with infection also dies from infection.

In the next section, we illustrate that proposed approaches for estimating \( \Pr(T^{\pi=0} \leq t_K, \epsilon^{\pi=0} = 1) \) each aim to adjust for the fact that not all patients who die with infection also die from infection by upweighing the increments of (4) but differ in the way their corresponding weights account for subtle but important aspects related to the time-dependent nature of exposure and its competing events.

4 Accounting for time-dependent exposures: different (weighted) means to an (hypothetical) end

Consider the six patients depicted in the toy example in Figure 3 who are followed up for a week, from day 1 (the day of hospital admission) to day 7. Patients A, B and D die while uninfected, whereas patients C and E acquire infection during their hospitalization. For the former three patients, the factual (observed) scenario fully corresponds to the counterfactual scenario (of remaining without infection until death or discharge). This also holds for patient F who gets discharged alive after day 7. The factual scenario of the latter two patients corresponds to their counterfactual scenario only until infection onset. In other words, all patients carry relevant information for estimating the counterfactual infection-free cumulative incidence, because each patient is uninfected for a certain amount of time. Hence, to fully exploit all available information and to avoid bias, it is preferable to artificially censor patients C and E at infection onset rather than to exclude them from further analysis.
| patient | day 1 | day 2 | day 3 | day 4 | day 5 | day 6 | day 7 |
|---------|-------|-------|-------|-------|-------|-------|-------|
| A       |       |       |       |       |       |       | ✗     |
| B       |       |       |       |       |       |       | ✗     |
| C       |       |       |       |       |       |       | ✗     |
| D       |       |       |       |       |       |       | ✗     |
| E       |       |       |       |       |       |       | ✗     |
| F       |       |       |       |       |       |       |       |

- ✗ infected
- ✗ deceased

Figure 3: Toy example trajectories for 6 patients with follow-up of 7 days.

4.1 Treating exposure onset as a censoring event

Artificially censoring these infected patients aims to emulate a hypothetical world in which they would have further remained without infection beyond their observed infection onset time. In this hypothetical world, counterfactual event times $T^{\pi=0}$ and event type indicators $\epsilon^{\pi=0}$ would be fully observed and the counterfactual infection-free risk of hospital death $\Pr(T^{\pi=0} \leq t_K, \epsilon^{\pi=0} = 1)$ could again be estimated using the Aalen-Johansen estimator

\[
\sum_{k=1}^{K} \frac{\hat{d}_{j_k}^{\pi=0}}{\hat{r}_{k}^{\pi=0}} \prod_{s=1}^{k-1} \left(1 - \frac{\hat{d}_{s}^{\pi=0}}{\hat{r}_{s}^{\pi=0}}\right)
\]

with $j$ set to 1 and where $\hat{d}_{j_k}^{\pi=0} = \sum_{i=1}^{n} 1_{T_i^{\pi=0} \in (t_{k-1}, t_k], \epsilon_i^{\pi=0} = j}$ denotes the counterfactual number of events of type $\epsilon^{\pi=0} = j$ in interval $k$, $\hat{d}_{k}^{\pi=0} = \sum_{j=1}^{2} \hat{d}_{j_k}^{\pi=0}$ the counterfactual number of events of either type (either hospital death or discharge) in interval $k$ and $\hat{r}_{k}^{\pi=0}$ the counterfactual number of patients at risk at time $t_{k-1}$, the start of interval $k$. Expression (5) can alternatively be expressed as a function of counterfactual cause-specific hazard estimates of hospital death and hospital discharge at each interval $k$ (see Appendix A.3).

In Appendix [B.1] we more formally illustrate that when assuming these counterfactual hazards are identical to the observed cause-specific hazards among patients who have remained uninfected up until (and including) interval $k$ the counterfactual infection-free risk of hospital death $\Pr(T^{\pi=0} \leq t_K, \epsilon^{\pi=0} = 1)$ can be estimated using the Aalen-Johansen estimator (2) upon treating exposure onset as a (non-informative) censoring event. This amounts to excluding newly infected patients in interval
Table 1: Overview of accumulated weight over time for each patient in the toy example when exposure onset is treated as a censoring event. Bold and gray typeface indicate a patient has died without infection or has acquired infection the day before, respectively.

| patient | day 1 | day 2 | day 3 | day 4 | day 5 | day 6 | day 7 |
|---------|-------|-------|-------|-------|-------|-------|-------|
| A       | 1     | 1     | 1     | 1     | 1     | 1     | 1     |
| B       | 1     | 1     | 1.25  | 1.25  | 1.875 | 1.875 | 1.875 |
| C       | 1     | 1     | 0     | 0     | 0     | 0     | 0     |
| D       | 1     | 1     | 1.25  |       | 1.25  |       | 1.25  |
| E       | 1     | 1     | 1.25  |       | 1.25  | 0     | 0     |
| F       | 1     | 1     | 1.25  | 1.25  | 1.875 | 1.875 | 1.875 |

conditional odds

\[ \hat{\Pr}(T^{\pi=0} \leq t_K, \epsilon^{\pi=0} = 1) \]

Table 1: OVERVIEW OF ACCUMULATED WEIGHT OVER TIME FOR EACH PATIENT IN THE TOY EXAMPLE WHEN EXPOSURE ONSET IS TREATED AS A CENSORING EVENT. BOLD AND GRAY TYPEFACE INDICATE A PATIENT HAS DIED WITHOUT INFECTION OR HAS ACQUIRED INFECTION THE DAY BEFORE, RESPECTIVELY.

\[ \sum_{k=1}^{K} \frac{d'_{1k}}{r'_{k}} \prod_{s=1}^{k-1} \left(1 - \frac{d'_{s}}{r'_{s}}\right), \]

where, under the assumption that artificial censoring times (infection onset times) occur right before tied event times (infection-free hospital death or discharge times) in interval \( k \), the ‘updated’ risk set for hospital death or discharge at time \( t_{k-1} \) equals the risk set for infection-free hospital death or discharge at time \( t_{k-1} \) after exclusion of newly infected patients \( (r'_{k} = \tilde{r}_{k} - \tilde{d}_{0k}) \) and the number of hospital deaths or discharges in interval \( k \) in this ‘updated’ risk set equals the number of infection-free hospital deaths or discharges in interval \( k \) \( (d'_{k} = \tilde{d}_{k} - \tilde{d}_{0k}) \), such that (6) corresponds to (2) with \( j \) set to 1 and infection onset treated as a non-informative censoring event. Note that this does not hold under the usual assumption that event times occur right before censoring times.

Artificial censoring ensures that as time progresses and as patients get infected, they transfer their weight in the analysis to hospitalized uninfected patients (Table 1). For instance, on day 1 and day 2, corresponding to intervals \( (0, 1] \) and \( (1, 2] \), all patients belong to the risk set \( (r'_{0} = r'_{1} = r'_{2} = 6) \). From day 3, patient A, who died on day 2, and patient C, who gets infected on day 3, are excluded from the risk set \( (r'_{3} = \tilde{r}_{3} - \tilde{d}_{0,3} = 5 - 1 = 4) \). Because patient A died without having acquired infection, she does not transfer weight to the five uninfected patients in the risk set on day 3. In contrast, patient C got infected on day 3 and distributes his weight over the remaining four patients in the risk set.

By the time patient D dies, on day 4, he has an accumulated weight of \( 1+1/4 = 1.25 \). On day 5, patient E acquires infection and, accordingly gets censored and is excluded from the risk set that day \( (r'_{4} = \tilde{r}_{4} - \tilde{d}_{0,4} = 3 - 1 = 2) \). She also distributes her accumulated weight (which includes the weight
she received from patient C) over the remaining two patients in the risk set \((= 1/2 \times (1 + 1/4))\). By now, these remaining patients have accumulated a weight of \(1 + 1/4 + 1/2 \times (1 + 1/4) = 1.875\).

This weight transferal scheme may not be readily apparent from (6), but follows from an alternative formulation of the Aalen-Johansen estimator, in terms of an inverse probability of censoring (IPC) weighted average (see Appendix B.1; for a similar IPC weighted representation of the Kaplan-Meier estimator see: [Robins and Finkelstein, 2000; Satten and Datta, 2001]

\[ n^{-1} \sum_{k=1}^{K} \hat{d}_{1k}^{w_k}, \]  

(7)

where \(\hat{d}_{1k}^{w_k} = \sum_{i=1}^{n} 1_{\tilde{T}_i \in (t_{s-1}, t_s), \tilde{\epsilon}_i = 1} \hat{W}_k^{o}\) is the weighted number of HAI-free hospital deaths in interval \(k\)

\[ \hat{W}_k^{o} = \prod_{s=1}^{k} \frac{1}{1 - \hat{F}(\hat{T} \in (t_{s-1}, t_s), \hat{\epsilon} = 0 | \hat{T} > t_{s-1})} \]  

(8)

\[ = \prod_{s=1}^{k} \frac{1}{\hat{F}(A_s = 0 | Y_{s-1} = D_{s-1} = A_{s-1} = 0)} \]  

\[ = 1 + \sum_{s=1}^{k} \frac{\hat{F}(A_s = 1 | Y_{s-1} = D_{s-1} = A_{s-1} = 0)}{\hat{F}(A_s = 0 | Y_{s-1} = D_{s-1} = A_{s-1} = 0)} \]  

\[ \times \prod_{s'=1}^{s-1} \left\{ 1 + \frac{\hat{F}(A_{s'} = 1 | Y_{s'-1} = D_{s'-1} = A_{s'-1} = 0)}{\hat{F}(A_{s'} = 0 | Y_{s'-1} = D_{s'-1} = A_{s'-1} = 0)} \right\}, \]  

(9)

where the probabilities are non-parametrically estimated. Equivalent expressions of (6) and (7) in terms of the discrete-time counting processes defined in Section 2, and in terms of discrete time cause-specific hazards, are given in Appendix B.1.

Note that (7) is a weighed version of the empirical cumulative distribution of HAI-free hospital death (4) where the weight \(\hat{W}_k^{o}\) apportioned to each HAI-free death in interval \(k\) equals the inverse probability of having remained uninfected while hospitalized by interval \(k\). The product in the denominator of (8) corresponds to the Kaplan-Meier estimator of remaining without infection up to interval \(k\), treating both hospital death and discharge as (non-informative) censoring events. The alternative formulation of \(\hat{W}_k^{o}\) in (9) illustrates that these apportioned weights can be decomposed in a way that formalizes the above transferal scheme (see Appendix C for intermediate steps). That is, over the course of time, each patient accumulates weight that consists of her own unit-weight and weight transferred by patients who got censored during previous time waves, both directly (the first factor in the summation) and indirectly through intermediate transferals (the second factor in the summation). This weight transferal scheme fully respects the timing of events of interest by only prospectively transferring weight from hospitalized infected patients to hospitalized uninfected patients and no sooner than time of infection onset. The weight being directly transferred from one
patient to another at time $t_{k-1}$ can be expressed as the odds of infection in interval $k$ in the risk set at time $t_{k-1}$.

Assuming that the counterfactual infection-free cause-specific hazards of hospital death and discharge among newly infected patients in each interval $k$ equal the observable cause-specific hazards of hospital death and discharge among patients who have remained uninfected, so that

$$E \left[ \frac{d'_{jk}}{r'_k} \right] = E \left[ \frac{d\pi=0_{jk}}{r_{jk}^{\pi=0}} \right], \quad j \in \{1, 2\},$$

is equivalent to assuming HAI onset can be considered a non-informative censoring event of the counterfactual event time $T^{\pi=0}$ or assuming no confounding of the association between HAI, on the one hand, and hospital death or discharge, on the other hand. If this assumption is met, (6) and (7) are consistent estimators of the counterfactual risk $Pr(T^{\pi=0} \leq t_K, \epsilon^{\pi=0} = 1)$. In the next sections, we review two other multistate modeling approaches for estimating $Pr(T^{\pi=0} \leq t_K, \epsilon^{\pi=0} = 1)$, both of which fail to produce consistent estimators, even in the absence of confounding. We illustrate that their bias can be related to their respective weighting schemes.

### 4.2 Treating exposure as an exclusion criterion

A naive approach for estimating $Pr(T^{\pi=0} \leq t_K, \epsilon^{\pi=0} = 1)$ is to completely ignore HAI onset by only considering patients who never got infected during hospitalization. This approach implicitly relies on the assumption that the counterfactual risk equals the factual risk in patients who did not acquire infection during hospitalization

$$Pr(T^{\pi=0} \leq t_K, \epsilon^{\pi=0} = 1) = Pr(T \leq t_K, \epsilon = 1 | \tilde{\epsilon} \neq 0) = Pr(\tilde{T} \leq t_K, \tilde{\epsilon} = 1 | \tilde{\epsilon} \neq 0).$$

In the absence of censoring due to loss to follow-up or administrative end of the study, this corresponds to a naive way of rescaling the empirical cumulative distribution of HAI-free hospital death by a constant (time-fixed) factor (see Appendix B.2)

$$n^{-1} \sum_{k=1}^{K} \hat{d}^\pi_{1k},$$

with $\hat{d}^\pi_{1k} \equiv \sum_{i=1}^{n} 1_{\tilde{T}_i \in (t_{k-1}, t_k], \tilde{\epsilon}_i = 1} \hat{W}^*$ the weighted number of HAI-free hospital deaths in interval $k$ and

$$\hat{W}^* \equiv \frac{1}{1 - P_n(\tilde{\epsilon} = 0)} = \frac{1}{P_n(A_r = 1)} = 1 + \frac{P_n(A_r = 1)}{P_n(A_r = 0)},$$

\footnote{Although, to our knowledge, the specific approach discussed in this section (which considers a time-to-event outcome subject to a competing event) has never been advocated as such, it is similar in spirit to application of traditional (e.g. regression- or matching-based) estimation methods for the PAF in cross-sectional or time-fixed settings in a setting with a time-dependent exposure, in that it compares outcomes between ever and never exposed patients. For a recent example, see Suzuki et al. (2019) or references in von Cube et al. (2020b).}
Table 2: Overview of accumulated weight over time for each patient in the toy example when exposure onset is treated as an exclusion criterion. Bold and gray typeface indicate a patient has died without infection or has acquired infection the day before, respectively.

where \( P_n(X = x) \equiv \frac{1}{n} \sum_{i=1}^{n} 1_{X_i = x} \) denotes the empirical probability. An equivalent expression of (10) and of the corresponding Aalen-Johansen estimator in terms of the discrete-time counting processes defined in Section 2, and in terms of discrete-time cause-specific hazards, is given in Appendix B.2.

Only considering uninfected patients corresponds to weighing each uninfected patient’s contribution by a fixed amount \( \hat{W}^* \) equal to the inverse probability of remaining uninfected until the end of hospitalization. In other words, the weight transferred from infected patients to each uninfected patient equals the odds of acquiring infection at any point during hospitalization and hence does not depend on the time of HAI onset. This weight is transferred uniformly at the start of follow-up.

Let’s return to our toy example. Two out of 6 patients (patients C and E) acquire an HAI during their hospitalization. Hence, the marginal odds of HAI is 2/4, which is the weight transferred at day 0 from patients who eventually acquire HAI (possibly after day 0) to patients who remain uninfected during hospitalization (Table 2). This approach systematically fails to account for HAI onset time by treating patients’ future infection status (at hospital death or discharge) as if it were already known at hospital admission and using it as an exclusion criterion, thereby violating the key principle of not conditioning on the future. Failing to appropriately apportion infection-free time to infected patients (by erroneously coding patient time as infected time) is equivalent to censoring infected patients at hospital admission instead of at their HAI onset. This artificially and inadvertently makes infected patients immortal until infection onset and produces so-called immortal time bias (Suissa 2003; Van Walraven et al., 2004). This bias is also reflected in the corresponding weight transferal scheme, where weights incorporate information that is not yet available at the time they are transferred and therefore fail to adequately account for the relative timing of events. Because the apportioned
weights compensate for the depletion of all future infected patients from the risk set, they tend to overcompensate. Accordingly, early HAI-free deaths get disproportionally large weights, resulting in systematic overestimation of \( \Pr(T^\mathcal{A} = 0 \leq t_K, e^\mathcal{A} = 1) \), especially early on during follow-up. In certain cases, estimates of this counterfactual risk may even exceed the factual cumulative incidence \( \Pr(T \leq t_K, e = 1) \) translating into negative PAF estimates that may possibly lead to erroneous interpretations in terms of a seemingly protective effect of early onset HAIIs. Certain longevity studies have been criticized on similar grounds because for the same reason, in contrast to reported findings, becoming a jazz musician or winning an Oscar doesn’t necessarily make you live longer (Rothman 1992; Sylvestre et al. 2006).

Considering HAI-free time of infected patients (or, equivalently, leaving infected patients uncensored as long as they are uninfected) is therefore imperative to ensure that weights adequately quantify the likelihood of each deceased uninfected patient to have remained without infection until her individual time of death (rather than at the maximal follow-up time). This, in turn, avoids overcompensation for depletion of infected patients from the risk set and properly weighs the increments of the empirical cumulative distribution function of infection-free hospital death and eliminates immortal time bias.

4.3 Treating exposure onset as a time-dependent exclusion criterion

One of the dominant estimation approaches based on multistate modeling (Schumacher et al. 2007) does take HAI-free time of infected patients into account in estimation of the counterfactual risk. It does so by treating HAI onset as a competing event (rather than as an exclusion criterion at baseline) and excluding all patients who have experienced this competing event by landmark of interest \( t_K \) from the analysis for the purpose of estimating the counterfactual risk by \( t_K \). In the absence of censoring due to loss to follow-up or administrative end of the study, this corresponds to rescaling the empirical cumulative distribution of HAI-free hospital death at each landmark \( t_K \) by the inverse probability of having remained without infection until (and including) \( t_K \) (see Appendix B.3)

\[
n^{-1} \sum_{k=1}^{K} \hat{d}_{1k}^{\mathcal{W}_K}
\]

with \( \hat{d}_{1k}^{\mathcal{W}_K} = \sum_{i=1}^{n} 1_{t_{i} \in (t_{k-1}, t_{k}], \mathcal{e}_{i} = 1} \hat{W}_K^{\dagger} \) the weighted number of HAI-free hospital deaths in interval \( k \) and

\[
\hat{W}_K^{\dagger} = \frac{1}{1 - P_n(T \leq t_K, e = 0)} = \frac{1}{P_n(A_K = 0)} = 1 + \frac{P_n(A_K = 1)}{P_n(A_K = 0)}.
\]

An equivalent expression of (11) and of the corresponding Aalen-Johansen estimator in terms of the discrete-time counting processes defined in Section 2 and in terms of discrete-time cause-specific hazards, is given in Appendix B.3.
| patient | day 1 | day 2 | day 3 | day 4 | day 5 | day 6 | day 7 |
|---------|------|------|------|------|------|------|------|
| A       | 1    | 1    | 1.2  | 1.2  | 1.5  | 1.5  | 1.5  |
| B       | 1    | 1    | 1.2  | 1.2  | 1.5  | 1.5  | 1.5  |
| C       | 1    | 1    | 0    | 0    | 0    | 0    | 0    |
| D       | 1    | 1    | 1.2  | 1.2  | 1.5  | 1.5  | 1.5  |
| E       | 1    | 1    | 1.2  | 1.2  | 0    | 0    | 0    |
| F       | 1    | 1    | 1.2  | 1.2  | 1.5  | 1.5  | 1.5  |

| marginal odds | 0/6 | 0/6 | 1/5 | 1/5 | 2/4 | 2/4 | 2/4 |
| Pr(T_{pi=0} ≤ t_K, ε_{pi=0} = 1) | 0   | 1/6 | 1.2/6 | 2.4/6 | 3/6 | 3/6 | 4.5/6 |

Table 3: Overview of accumulated weight over time for each patient in the toy example when exposure onset is treated as a time-dependent exclusion criterion. Bold and gray typeface indicate a patient has died without infection or has acquired infection the day before, respectively.

This resulting weighting scheme accommodates the progressive selection of uninfected patients over time by rescaling these patients’ contributions to compensate for the depletion of infected patients from the risk set of infection-free hospital death. It does so by assigning time-dependent (instead of time-fixed) weights that are smaller for earlier landmarks and thereby reduces the time-dependent bias that plagues the naive estimation approach discussed in the previous section. More specifically, as soon as patients acquire infection, they are excluded from the risk set and transfer their weight to patients who have until that time remained uninfected. The total amount of weight transferred to each uninfected patient by t_K corresponds to the marginal odds of HAI by t_K.

However, infected patients also distribute their weight to uninfected patients who have already died or have been discharged, i.e. patients who are no longer at risk of HAI. This can be seen upon noting that \( \tilde{W}_K^j \) is not a function of k but of K, the landmark at which the empirical cumulative distribution function is evaluated. Because of this inappropriate selection of time-dependent weights, this approach hence fails to entirely eliminate the time-dependent bias it is intended to eliminate.

Let’s reconsider our toy example. According to this approach, weights get transferred at each HAI onset time (Table 3). For instance, when patient C acquires infection on day 3, she distributes her weight among all patients who have so far remained without HAI, irrespective of whether they have already died or been discharged. That is, each of these patients increases his/her weight with the odds of having acquired infection by that day (=1/5). In contrast to the naive approach discussed earlier, weight is also transferred to patient E, who is uninfected on day 3 but develops infection two days later. On day 4, patient E similarly distributes her weight to all patients who have remained without infection (each receives a weight of 1/4), along with the weight she has (in the meantime) received from
patient C (each indirectly receives a weight of \((1/4) \times (1/5)\) from patient C via patient E). As a result, each patient that has remained without infection by day 4, accumulates weight received from both patient C and patient E, corresponding to a total transferred weight of \(1/5 + 1/4 + (1/4) \times (1/5) = 1/2\), which equals the odds of having acquired infection by day 4.

Importantly, patient A now receives a smaller weight when she dies than patients B and D at their respective death times. This is because patients B and D have accumulated more weight (from patient C, and from patients C and E, respectively) by their time of death than patient A by the time she died. However, after their death, patient A and patient D receive additional weight, such that it eventually matches the weight accumulated by patient B. Even though patients who die early have accumulated less weight by their time of death than patients who die at later time points, they eventually accumulate the same weight by a fixed landmark \(t_K\). As with the naive approach, their accumulated weight by \(t_K\) is identical to that of patients who die later in time, even though it should be smaller (and fixed from the time of their death onward) so as to reflect their shorter time at risk for HAI and, accordingly, the smaller degree of depletion of infected patients by their time of death (that needs to be compensated for). Due to this weighting scheme, it seems as if patients who died (or got discharged) without infection are implicitly (re)considered to still be at risk of infection-free hospital death because, even after their time of death (or discharge), they continue to accumulate weight via newly infected patients. This finding is not readily apparent when adopting multistate model notation, but can intuitively be appreciated by resorting to a weighting-based characterization of the corresponding multistate model based estimator. Moreover, this implies that an event that has already occurred gets reweighed based on information (on future infections) that is not available at the time of that event, again violating the key principle of not conditioning on the future. As a result of this persistent failure to fully respect the temporal order of events, bias inadvertently gets re-introduced. However, this residual form of time-dependent bias is rather subtle (especially when the incidence of infection is low).

4.4 Censoring a competing event (hypothetically) eliminates that event

An astute reader may have noticed that, in the introduction, HAI onset \((\tilde{\epsilon} = 0)\) was introduced as a competing event for HAI-free hospital death \((\tilde{\epsilon} = 1)\) and HAI-free hospital discharge \((\tilde{\epsilon} = 2)\). In section 4.1, HAI onset was instead treated a censoring event. Finally, in section 4.3, it is again treated as a competing event. This may have caused some confusion.

To avoid confusion, we would like to clarify that in all these sections, HAI onset can be considered as a competing event for HAI-free death or discharge. What matters is how this competing event is treated in the analysis. As recently pointed out by Young et al. (2020), the choice whether or
not to censor a competing event depends on whether one targets a counterfactual quantity with or without hypothetical elimination of that event (also see Keiding et al., 2001; von Cube et al., 2019, 2020a). The aim of eliminating the competing event was explicit in section 4.1 but was left rather implicit in section 4.3. Censoring a competing event at its corresponding event time re-weighs the events of interest in a way that fully respects the temporal ordering of all considered event types. IPC weighting is also implicitly achieved by multistate modeling based approaches that impose constraints on the intensities or hazards between health states to emulate a hypothetical world where entry into states corresponding to that competing event is somehow prevented (Arjas and Eerola, 1993; Keiding et al., 2001). More specifically, it corresponds to calculating the risk of HAI-free hospital mortality by setting to zero the intensity for the transition from the state ‘hospitalized without infection’ to ‘HAI’ in the progressive disability model (depicted in Figure 6 in Appendix B.3), as proposed by Schumacher et al. (2007) (also see von Cube et al., 2019, 2020a). This is identical to setting the time-dependent hazards of infection in the multistate model depicted in Figure 2 to zero. Intuitively, artificially setting these hazards to zero corresponds to artificially censoring infected patients, such that, as patients get infected, their weight in the analysis is transferred to patients who may still enter one of the other (infection-free) health states, i.e. those at risk of HAI-free hospital death or discharge, but not to those who have already entered one of these health states (see Appendix B.1).

This stands in contrast with the multistate modeling based approach proposed by Schumacher et al. (2007), discussed in section 4.3 where weight also (tacitly) gets transferred to patients who have already died or been discharged. Nonetheless, the implicit rationale behind this approach is also hypothetical elimination of the competing event, at least when one wishes to endow the estimated PAF a causal interpretation. While this is also achieved by re-weighing the contribution of HAI-free hospital deaths to the cumulative incidence curve, weighing is done in a way that does not fully correspond to treating the competing event HAI onset as a censoring event. As a result, the applied weights deviate from the corresponding IPC weights and fail to respect the temporal ordering of all considered event types. In Appendix B.4.4 we illustrate that a re-weighted version of Schumacher et al. (2007)’s estimator is equivalent to the IPC weighted estimator.

In the previous sections we have illustrated that, even in the absence of confounding, bias may occur in the estimation of time-dependent counterfactual quantities such as \( \Pr(T_{\bar{a}_0} \leq t_K, \epsilon_{\bar{a}_0} = 1) \) when failing to adequately account for the temporal ordering of events. However, while time-dependent bias can be eliminated by treating HAI onset (the time-dependent exposure of interest) as a censoring event, the resulting estimator only enables bias-free estimation in the absence of confounding of the association between HAI onset, on the one hand, and hospital mortality and discharge, on the other hand. In other words, the Aalen-Johansen estimator that treats HAI as a censoring event (discussed
in section 4.1 is consistent only under the assumption of non-informative or independent (artificial) censoring. Under this assumption, progressive depletion of infected patients from the risk set over time, does not introduce bias due to differential selection of uninfected hospitalized patients. However, in most (if not all) applications, this assumption is unrealistic. In the next section, we discuss how the Aalen-Johansen estimator can be modified to accommodate settings in which censoring at each time can be assumed independent conditional on a set of baseline and time-varying prognostic factors or confounders measured up to that time.

5 Accounting for time-dependent confounding: tackling informative censoring of a hypothetical endpoint

The progressive selection of a risk set of uninfected patients poses additional challenges regarding confounding adjustment or, equivalently, modeling the censoring mechanism when treating HAI onset as a censoring event. Bias-free estimation necessitates confounding adjustment for indicators of disease severity, e.g. by standardization of estimates obtained from stratified multistate models (Walter, 1976; Whittemore, 1982; Benichou, 2001). As such, estimation approaches based on multistate modeling enable to reduce selection bias due to imbalances in the distribution of baseline confounders between censored and uncensored patients at hospital admission. However, because HAIs are rarely acquired upon hospital admission, but are inherently time-dependent, confounding of their effects on hospital death and discharge inevitably is also time-dependent. Equivalently, progressive selection of HAI-free patients in the risk set over time is driven by a censoring or selection mechanism that is likely to also depend on prognostic factors that evolve over time.

For instance, prior to acquiring infection, patients may deteriorate further and may therefore be at increased risk of infection, even if, at admission, their prognosis is similar to that of patients who eventually do not acquire infection. Consequently, confounding adjustment should not only be made at baseline (e.g. for severity of illness indicators recorded at time of admission), but also for the evolution of such indicators over time. Even though current approaches for estimating the PAF based on multistate models may account for the time-dependent nature of acquiring HAI, they do not readily permit to account for the time-dependent nature of prognostic factors that drive the progressive selection of uninfected patients over time, except upon adequate reweighting (see Appendix B.4.4 for more details). They are therefore bound to provide biased estimates of the fraction of hospital mortality that can be attributed to HAIs.

Generalized methods, abbreviated g-methods (Robins and Hernan, 2008; Hernán and Robins, 2020) enable to additionally tackle the time-dependent nature of confounding or, equivalently, selection of HAI-free patients. This class of methods, in particular inverse probability (IP) weighting, can be
characterized as a natural generalization of the censoring approach discussed in section 4.1. That is, the Aalen-Johansen estimator in expression (6) can be further refined so as to also consider the impact of relevant time-dependent confounders on the censoring process. As such, IPCW estimation can be tailored to not only eliminate time-dependent bias, but also to reduce bias due to the differential selection of uninfected patients as characterized by baseline and time-dependent prognostic factors \cite{RobinsFinkelstein2000, Sattenetal2001}. This can be achieved upon re-weighing the Aalen-Johansen estimator (6) as follows

\[
\sum_{k=1}^{K} \frac{d_{ik}^{\text{w}_ke}}{r_{ik}^{\text{w}_ke}} \prod_{s=1}^{k-1} \left(1 - \frac{d_{is}^{\text{w}_se}}{r_{is}^{\text{w}_se}} \right),
\]

where \(d_{jk}^{\text{w}_ke} \equiv \sum_{i=1}^{n} 1_{t_i \in (t_{k-1}, t_k], \tilde{c}_i = c} \hat{W}_{ik}^{\prime} \) denotes the weighted number of events of type \(\epsilon = j\) in interval \(k\) and \(r_{ik}^{\text{w}_ke} \equiv \sum_{i=1}^{n} 1_{t_i > t_{k-1}} \hat{W}_{ik}^{\prime}\) the weighted number of patients at risk of any of the events in the competing risk model depicted in Figure 2 (after exclusion of newly infected patients) at \(t_{k-1}\), 

\[
\hat{W}_{ik} = (1 - A_{ik}) \hat{W}_{ik}
\]

and

\[
\hat{W}_{ik} = \prod_{s=1}^{k} \frac{1}{1 - \Pr(T \in (t_{s-1}, t_s], \tilde{c} = 0 | T \geq t_{s-1}, \mathcal{L}_{i,s-1})} - 1 \Pr(A_{is} = 0 | \mathcal{L}_{i,s-1}, A_{i,s-1} = D_{i,s-1} = Y_{i,s-1} = 0) \\
= 1 + \sum_{s=1}^{k} \frac{\Pr(A_{is} = 0 | \mathcal{L}_{i,s-1}, A_{i,s-1} = D_{i,s-1} = Y_{i,s-1} = 0)}{\Pr(A_{is} = 0 | \mathcal{L}_{i,s-1}, A_{i,s-1} = D_{i,s-1} = Y_{i,s-1} = 0)} \\
\times \prod_{s'=1}^{s-1} \left\{1 + \frac{\Pr(A_{i,s'} = 0 | \mathcal{L}_{i,s'-1}, A_{i,s'-1} = D_{i,s'-1} = Y_{i,s'-1} = 0)}{\Pr(A_{i,s'} = 0 | \mathcal{L}_{i,s'-1}, A_{i,s'-1} = D_{i,s'-1} = Y_{i,s'-1} = 0)} \right\}
\]

(13)

with the vector \(\mathcal{L}_{ik}\) denoting the history up to \(t_k\) of baseline and time-dependent prognostic factors of both future HAI onset and hospital death or discharge in patient \(i\), assumed to be sufficient for confounding adjustment.

Under non-parametric estimation of the IPC weights \(\hat{W}_{ik}\) (13), this weighted Aalen-Johansen estimator (12) can again be shown to be algebraically equivalent to a weighted version of the empirical cumulative distribution of HAI-free hospital death (4) (see Appendix B.4),

\[
n^{-1} \sum_{k=1}^{K} \hat{d}_{ik}^{\text{w}_ke},
\]

(14)

where \(\hat{d}_{ik}^{\text{w}_ke} \equiv \sum_{i=1}^{n} 1_{t_i \in (t_{k-1}, t_k], \tilde{c}_i = c} \hat{W}_{ik} = \hat{d}_{jk}^{\text{w}_ke}\). However, even under correct specification of the IPC weights, due to sampling variability (14) may produce estimates \(> 1\). To accommodate for this, sample bounded IPC weighted estimators (Tan 2010) can be used, such as the one proposed in Bekaert et al. (2010) (see Appendix B.4.4).
These estimators again aim to construct a pseudo-population that matches the original population, but in which HAIs are eradicated. It assigns weights to patient time contributions that do not only depend on time, but also on individual prognostic factors over time. By incorporating information on time-dependent prognostic factors for both HAI onset and hospital death and discharge in the weights this estimator relaxes the strong assumption of non-informative censoring by HAI onset and replaces it with the weaker assumption of conditionally independent censoring. In Appendix B.4.4 we illustrate that this is equivalent to assuming that, for every interval \( k \), within strata defined by a set of (time-dependent) confounders \( T_k \), the observable cause-specific hazards of hospital death and discharge among patients who have remained uninfected equals the counterfactual cause-specific hazards, so that, under known IPC weights, we have

\[
E\left[ \frac{d_{jk}^{w,k}}{y_{jk}^{w,k}} \right] = E\left[ \frac{d_{jk}^{a=0}}{y_{jk}^{a=0}} \right], j \in \{1, 2\}.
\]

More specifically, because the relation between timing of infection and covariate history is explicitly accounted for in the weights, censored (infected) patients prospectively transfer their weight to uncensored (uninfected) patients with the same covariate history. In doing so, potential imbalances between infected and uninfected patients with respect to relevant prognostic factors can be restored at each single time point and confounding bias can be eliminated, at least insofar as the selected set of time-dependent covariates is sufficient to adjust for confounding of the effect of infection on hospital death and hospital discharge or insofar as censoring is rendered independent or explainable conditional on \( T \) (see Appendix B.4.1-B.4.3 for more details on identification assumptions and results and Appendix B.4.4 for more details on the connection with other proposed estimators).

6 Empirical data example

In this section we illustrate the differences between the four estimation approaches discussed in the two previous sections using an empirical example. In particular, we highlight that different sources of bias can be attributed to weight transfer schemes that do not adequately account for the temporal ordering of events or time-dependent prognostic factors of those events. As the main focus of this paper (and of the empirical example) concerns point estimation and bias, we do not report any confidence intervals. However, for each of the estimation approaches these can generally be obtained using the non-parametric bootstrap. R code to replicate these analyses is available from [https://github.com/jmpsteen/time-dep-paf](https://github.com/jmpsteen/time-dep-paf).

The population attributable fraction of ICU death due to HAIs was estimated in a cohort of 1,478 patients hospitalized at the Ghent University Hospital medical and surgical intensive care units for at least 48 hours between 2013 and 2017. Patients were included in the cohort if they had received me-
Table 4: Overview of required data for application of each of the four discussed estimation approaches which, respectively, treat HAI onset as an exclusion criterion (section 4.2), a time-dependent exclusion criterion (section 4.3), a non-informative censoring event (section 4.1), and an informative censoring event (section 5).

| Required data depending on whether estimation approach treats HAI onset as… | exclusion criterion | competing event | non-informative censoring | informative censoring |
|---|---|---|---|---|
| time of ICU death/discharge | × | × | × | × |
| HAI status at death/discharge | × | × | × | × |
| time of HAI onset | × | × | × | |
| baseline and time-dependent confounders | | | | × |

Mechanical ventilation and had remained without (suspected) infection within the first 48 hours following admission. Pseudonymized records were extracted from the Intensive Care Information System (ICIS) database (GE Healthcare Centricity Critical Care). Unique admission identifiers allowed to link these records to corresponding records from the infection surveillance system (Computer-based Surveillance and Alerting of nosocomial infections, Antimicrobial Resistance and Antibiotic consumption in the ICU; COSARA) database (Steurbaut et al., 2012; De Bus et al., 2014, 2018) that included detailed information on HAI diagnosis, presumed onset and antibiotic therapy. This cohort forms a subgroup of a larger cohort that has been described in more detail in a clinical paper focusing on estimation of the population attributable fraction of ICU death due to ventilator-associated pneumonia (Steen et al., 2021). The Ghent University Hospital Ethics Committee approved this study (registration number B670201732106) and waived informed consent since all analyses were performed retrospectively on pseudonymized records.

For illustrative purposes and to demonstrate clear differences between estimation methods, we here focus on estimation of the population attributable fraction of ICU death within the first 30 days since admission due to ICU-acquired bacterial infections (including abdominal, catheter-related, respiratory, and urinary tract infections acquired at least 48 hours following ICU admission) developed during this 30-day time window in this patient cohort. Note that these analyses are merely intended as an illustration of the discussed estimation approaches. Results should therefore not be interpreted as conclusive evidence as insufficient attention was paid to correct HAI classification or careful confounder selection based on expert opinion or available substantive knowledge.

As listed in Table 4, due to different levels of complexity, the different estimation approaches also differ in terms of required data, either in terms of granularity or type of data. The naive estimation
approach treats HAI onset as an exclusion criterion and therefore does not require any data on HAI onset time. In addition, when accounting for timing of HAI onset but not for differential selection of uninfected patients (the second and third estimation approaches listed in Table 4), estimation can, in principle, be done based on aggregated data (i.e. so-called life tables which list the number of events of each type $\tilde{\epsilon}$ at each discrete time point) and hence no individual patient data is required. To tackle selection bias due to informative censoring (the fourth approach listed in Table 4), however, individual patient characteristics and prognostic factors need to be taken into account in the IPC weights. To estimate these weights, a Cox model was fitted for the cause-specific discrete time hazard of developing an ICU-acquired bacterial infection conditional on gender, admission category (medical versus surgical ICU), admission year, age at admission, updated Charlson comorbidity index (restricted cubic spline with 2 knots) and the Sequential Organ Failure Assessment (SOFA) score, both at admission (restricted cubic spline with 4 knots) and two days prior to potential development of infection (to acknowledge that this severity-of-illness score may be a surrogate marker for an incubating infection) (restricted cubic spline with 4 knots).

Figure 4 displays the unadjusted state occupation probabilities corresponding to the competing risk models depicted in Figures 1 and 2, as estimated by the Aalen-Johansen estimators in expressions (2) and (3), respectively. By day 30, 26.1% of the considered patients had acquired a bacterial infection at the ICU, 81.0% had been discharged from the ICU (63.9% without infection), 14.5% had died at the ICU (9.3% without infection), and 4.5% was still hospitalized (0.7% without infection). The contrast between the observed cumulative incidence of ICU death $\hat{\Pr}(\tilde{T} \leq t_K, \tilde{\epsilon} = 1)$ and the observed cumulative incidence of HAI-free ICU death $\hat{\Pr}(T \leq t_K, \tilde{\epsilon} = 1)$ expresses the proportion of patients who have died with an ICU-acquired bacterial infection (the contrast between the dark red curve and the dark red shaded area in Figure 4 as also depicted in panel A of Figure 5). By day 30, this is about $14.5 - 9.3 = 5.2\%$ of patients. In other words, about $(14.5 - 9.3)/14.5 \approx 36\%$ of patients who have died at the ICU by day 30, have died with an ICU-acquired bacterial infection.

Because not all patients who die with infection die from infection, and since infections are consi-
dered harmful (rather than beneficial) for all patients, $\Pr(\tilde{T} \leq t_K, \tilde{\epsilon} = 1)$ can be considered as a lower bound for the counterfactual HAI-free cumulative incidence $\Pr(T^{\pi=0} \leq t_K, \pi=0 = 1)$ (i.e. assuming all patients dying with infection also die from infection), while $\Pr(T \leq t_K, \epsilon = 1)$ can be considered as an upper bound (i.e. assuming no patient dying with infection dies from infection). The gray shaded area in panel B of Figure 5 displays the corresponding lower and upper bounds for the PAF.

To acknowledge that some patients who have died at the ICU with infection within 30 days from admission may not have died had they not acquired infection within that time window, different approaches for estimating $\Pr(T^{\pi=0} \leq t_K, \pi=0 = 1)$ borrow missing information on counterfactual
event times in infected patients from patients who did not (yet) acquire infection. For each of the four considered estimation approaches, this is achieved by upweighing ICU deaths in the latter group in the analysis. However, each approach applies a different weighting scheme, as displayed in Figure 5.

When treating HAI onset as an exclusion criterion (panel C of Figure 5), exclusion of infected patients is compensated for by uniformly weighing each HAI-free ICU death by the inverse (marginal) probability of remaining without ICU-acquired bacterial infection until ICU death or discharge (about 74%), which corresponds to a factor $\approx 1.35$. According to this approach it was estimated that, had all patients remained without infection (at least until day 30), 12.6% would have died at the ICU by day 30, corresponding to an estimated excess mortality due to infection of $14.5 - 12.6 = 1.9\%$ or an estimated PAF of $(14.5 - 12.6)/14.5 = 13.1\%$ (panel B of Figure 5). In contrast, during roughly the...
first two weeks of hospitalization, this approach estimates that certain deaths may have been prevented (or delayed) by infection, as reflected by negative estimated PAFs (panels B–C of Figure 5). This can be explained by the fact that, as every HAI-free ICU death is weighed by the same factor (that can only be determined by the last HAI onset time), early ICU deaths get weighed disproportionally compared to later ICU deaths, resulting in immortal time bias.

When treating HAI onset as a time-dependent exclusion criterion (panel D of Figure 5), progressive depletion of infected patients from the risk set over time is compensated for by weighing each HAI-free ICU death by day $K$ by the inverse (marginal) probability of remaining without ICU-acquired bacterial infection until day $K$, a factor that increases over time. According to this approach it was estimated that, had all patients remained without infection (at least until day 30), 12.6% would have died at the ICU by day 30, corresponding to an estimated excess mortality due to infection of $14.5 - 12.6 = 1.9\%$ or an estimated PAF of $(14.5 - 12.6)/14.5 = 13.1\%$. Even though this approach ensures that smaller weights are apportioned at earlier landmarks, thereby mitigating immortal time bias, its resulting time-dependent PAF estimates may still misleadingly raise the impression that infection may be beneficial during the first 10 days after admission (panel B of Figure 5). This is because all ICU deaths by day $K$ are uniformly weighed by a factor that is determined that day. Hence, at each landmark time $t_K$ all deaths before $t_K$ are weighed by a factor that incorporates information that will only become available at $t_K$. This approach essentially perpetuates the problem of the first approach, but in a nested (and therefore more subtle) fashion. Instead of uniformly weighing each single death across future landmark times, this approach uniformly weighs all deaths that have occurred by $t_K$ at each landmark time $t_K$. This leads to deaths getting reweighed at each future landmark with incident infections. At landmarks with no future infections estimates of this approach coincide with those of the first approach, which explains why these two approaches converge toward the end follow-up (panel B of Figure 5).

When treating HAI onset as a non-informative censoring event (panel E of Figure 5), progressive depletion of infected patients from the risk set over time is compensated for by recursively weighing each patient at risk at day $K$ on each of the previous days by the inverse complement of the cause-specific hazard of HAI. This corresponds to weighing each HAI-free ICU death on day $K$ by the inverse probability of remaining without ICU-acquired bacterial infection by day $K$ while still being hospitalized the prior day. According to this approach it was estimated that, had all patients remained without infection (at least until day 30), 13.2% would have died at the ICU by day 30, corresponding to an estimated excess mortality due to infection of $14.5 - 13.2\% = 1.3\%$ or an estimated PAF of $(14.5 - 13.2\%)/14.5 = 9.0\%$. In contrast to the previous two approaches, this approach does not upweigh deceased HAI-free patients based on information that is not yet available at their respective
Figure 5: Observed cumulative incidence of ICU death $\hat{\Pr}(T \leq t_K, \epsilon = 1)$ within the first 30 days following ICU admission (solid black line in panels A,C-F), counterfactual HAI-free cumulative incidence of ICU death $\hat{\Pr}(T^0 \leq t_K, \epsilon^0 = 1)$ as estimated by the four different estimation approaches (solid colored lines in panels C-F), and corresponding estimated population-attributable fractions (PAFs) (panel B; with lower and upper bounds for the PAF under consistency and monotonicity depicted by the gray shaded area). Each of the four estimation approaches have a distinct way of upweighing the increments of the cumulative incidence of HAI-free ICU death $\hat{\Pr}(\tilde{T} \leq t_K, \tilde{\epsilon} = 1)$, as graphically represented by different color shades, with darker shades reflecting larger weights. As a visual reference, $\hat{\Pr}(\tilde{T}_{24} \leq t_K, \tilde{\epsilon} = 1)$ is depicted with unit weights in light gray (panel A).
death times, and therefore fully respects the temporal ordering of event times.

When treating HAI onset as an informative censoring event (panel F of Figure 5), progressive depletion of infected patients from the risk set over time is compensated for in a similar fashion, while additionally accounting for differential selection of uninfected patients over time to avoid selection bias. This approach weighs each HAI-free ICU death on day $K$ by the inverse probability of remaining without ICU-acquired bacterial infection by day $K$ while still being hospitalized the prior day among patients with the same covariate history. According to this approach it was estimated that, had all patients remained without infection (at least until day 30), 14.3% would have died at the ICU by day 30, corresponding to an estimated excess deaths due to infection of $14.5 - 14.3\% = 0.2\%$ or an estimated PAF of $(14.5 - 14.3)/14.5 = 0.14\%$.

7 Discussion

Several different approaches have been proposed in the epidemiologic literature for estimating the population-attributable fraction (PAF) in the presence of time-dependent exposures and competing events. Recent work by von Cube et al. (2019, 2020a) has compared these approaches and has shed light on conceptual confusion concerning targeted estimands of these respective approaches. Their work indicated that differences between approaches can be related to whether or not the corresponding target estimand is meant to be interpreted causally or not, leading these authors to suggest a distinction between the directly ‘observable’ PAF estimand and the causal or ‘counterfactual’ PAF estimand. It may be argued, however, that, due to clear reference to the term attribution, the PAF was meant to be interpreted causally from its outset, or that at least, such interpretation is usually (although perhaps implicitly) evoked by most of the scientific community. The estimand targeted by treatment of HAI onset as a time-dependent exclusion criterion (the ‘observable’ PAF), can be interpreted as the reduction in hospital mortality by day $K$ among patients who had not acquired an infection by that day relative to that in the original population (see Appendix B.4.4). While, arguably, this estimand lacks a causal interpretation, it remains unclear whether this ‘factually observed burden’ of exposure has any relevance or implications for clinical practice.

This work builds upon and extends these recent important contributions by von Cube and colleagues. We highlight that, considering the main goal of estimating the PAF as defined as a causal, counterfactual quantity, proposed estimation approaches can be ordered along a certain hierarchy. By proposing a weighting-based characterization of estimation approaches that aids to better pinpoint different sources of bias within a unified framework, we highlight that each approach implies a refinement with respect to the approach right below it in the hierarchy. Importantly, this characterization may foster deeper and more intuitive understanding both of differences between multistate model
based approaches (in terms of how well they respect certain key principles of causal inference) and of the connection between these approaches and g-methods for causal inference, in particular inverse probability of censoring (IPC) weighting.

In this paper, we mainly target estimation of the counterfactually defined PAF in retrospective studies. Recently, there have been increasing calls to cast observational studies for comparative effectiveness research into a more formal causal framework that revolves around explicit ‘target trial emulation’ (Hernán and Robins, 2016; Hernán et al., 2016; Sterne et al., 2016; Didelez, 2016; Labrecque and Swanson, 2017; Prosperi et al., 2020). This approach encourages researchers to first define the causal question of interest in terms of a hypothetical (possibly pragmatic) randomized controlled trial and to then either conduct that RCT or to emulate its results from observational data, using its protocol as a guidance to avoid common pitfalls. When trying to endow the PAF with an explicitly interventional interpretation, as often done implicitly by interpreting the PAF as the proportion of preventable death cases, a randomized prevention trial may naturally come to mind. More specifically, under certain assumptions, the PAF can be interpreted as the relative risk reduction in a randomized experiment that compares standard of care with a fully effective prevention strategy, i.e. one that eradicates the exposure of interest. As such, the estimation approaches under comparison can alternatively be organized hierarchically with respect to how well they may emulate this hypothetical target trial.

While we have briefly touched upon assumptions for point identification of the PAF (although see Appendix B.4.1-B.4.3 for a more formal and detailed discussion), in particular independent censoring by exposure onset conditional on a sufficient set of baseline and time-varying confounders, an explicit description of the hypothetical target prevention trial (or any attempt thereof) forces researchers to pay additional attention to other identifying assumptions, in particular the consistency assumption (Rubin, 1980, 1986; Robins, 1986; Cole and Frangakis, 2009). This assumption links the observable data characterized by observed exposures (e.g. under standard of care) to the counterfactual or interventional world, characterized by intervened upon exposures (e.g. under fully effective prevention). For this assumption to be met, uninfected patients’ observed outcomes need to be the same as their (counterfactual) outcomes that would have been observed if they had received the preventive intervention that eradicates infection. To endow PAF estimates in our example with a clear interventional interpretation, in terms of preventable ICU deaths, we would need to be more specific as to how ICU deaths would be prevented: by means of a preventive intervention, or a bundle of interventions (a so-called compound treatment (Hernán and VanderWeele, 2011)), that successfully eradicates HAIs without affecting ICU mortality or discharge other than through elimination of HAIs. In most studies that aim to estimate PAFs, however, such hypothetical preventive intervention bundles are left im-
licit and are therefore ill-defined. This is mostly because fully effective prevention of the exposure is usually impossible given current means and measures and is therefore inherently hypothetical.

This vague and hypothetical nature of interventions doesn’t necessarily need to be a major obstacle, as long as one is willing to assume such intervention exists, or may at some point exist. Even if none will ever exist, the result is arguably useful as an upper bound to the impact that imperfect prevention bundles might achieve at the ICU population level. However, without making this (possibly) complex hypothetical intervention more explicit, a few central questions tend to get obscured, even though they seem crucial for certain analytical choices along the way (Hernán, 2005; Hernán and Taubman, 2008; Hernán and VanderWeele, 2011). For instance, does it include all current preventive measures? If so, how does the choice whether or not to adjust for them, change our interpretation? Another important issue is that, if we don’t know which exact measures are included in this prevention bundle, how are we supposed to identify a minimal adjustment set to ensure exchangeability? Finally, apart from the above issues, a fully effective bundle may not be realistic, because not all HAIs may be (easily) preventable. From a decision-making perspective, it may be more sensible to shift focus to so-called ‘generalized impact fractions’ which contrast clinically feasible interventions with varying degrees of prevention effectiveness (Morgenstern and Bursic, 1982).

In conclusion, assessing whether patients die from rather than with a certain time-dependent exposure not only requires adequate modeling of the timing of events, as has been emphasized in the past (e.g. Schumacher et al., 2013), but also adequate adjustment for the confounding factors affecting these events and their timing. A weighting based characterization of proposed approaches for estimating the PAF (i) enables more intuitive understanding of these respective approaches, their differences and their connections and (ii) clearly links potential sources of bias to violations of certain key principles of causal inference inherent to some of these approaches.

8 Software

Documented R code for each of the discussed estimation approaches is available from https://github.com/jmpsteen/time-dep-paf.

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A Simplified expressions of the Aalen-Johansen estimator in the absence of right censoring

A.1 Cumulative incidence of hospital death \( \Pr(T \leq t_K, \epsilon = 1) \equiv \Pr(Y_K = 1) \)

Throughout, let \( P_n(X = x) \equiv n^{-1} \sum_{i=1}^{n} 1_{X_i=x} \) and \( E_n(X) \equiv n^{-1} \sum_{i=1}^{n} X_i \) denote the empirical probability and empirical expectation, respectively, with \( 1_{(\cdot)} \) the indicator function. Furthermore, let \( P_n(X = x|Z = z) \equiv \frac{P_n(X = x, Z = z)}{P_n(Z = z)} \) and \( E_n(X|Z = z) \equiv \frac{\sum_{i=1}^{n} 1_{Z_i = z} X_i}{\sum_{i=1}^{n} 1_{Z_i = z}} \). Following the definitions from Section 2 in the main text, under the assumed temporal ordering \( (D_k, Y_k) \), we have

\[
1_{T \in (t_{k-1}, t_k], \epsilon = 1} = Y_k(1 - D_k)(1 - Y_{k-1}) \\
1_{T \in (t_{k-1}, t_k], \epsilon = 2} = D_k(1 - Y_{k-1})(1 - D_{k-1}) \\
1_{T > t_{k-1}} = (1 - Y_{k-1})(1 - D_{k-1}) \\
1_{T \in (t_k, t_{k+1}]} = 1_{T > t_k} - 1_{T > t_{k-1}} = (1 - Y_{k-1})(1 - D_{k-1}) - (1 - Y_k)(1 - D_k),
\]

such that

\[
d_{1k} \equiv \sum_{i=1}^{n} 1_{T_i \in (t_{k-1}, t_k], \epsilon_i = 1} = nE_n[Y_k(1 - D_k)(1 - Y_{k-1})] \\
d_{2k} \equiv \sum_{i=1}^{n} 1_{T_i \in (t_{k-1}, t_k], \epsilon_i = 2} = nE_n[D_k(1 - Y_{k-1})(1 - D_{k-1})] \\
d_k \equiv \sum_{i=1}^{n} 1_{T_i \in (t_{k-1}, t_k]} = nE_n[(1 - Y_{k-1})(1 - D_{k-1}) - (1 - Y_k)(1 - D_k)] \\
r_k \equiv \sum_{i=1}^{n} 1_{T_i > t_{k-1}} = nE_n[(1 - Y_{k-1})(1 - D_{k-1})].
\]

Define discrete-time cause-specific hazards \( \lambda_k^1 \) and \( \lambda_k^2 \) as

\[
\lambda_k^1 \equiv \Pr(Y_k = 1|D_k = Y_{k-1} = 0) = \frac{E[Y_k(1 - D_k)(1 - Y_{k-1})]}{E[(1 - D_k)(1 - Y_{k-1})]} \\
\lambda_k^2 \equiv \Pr(D_k = 1|Y_{k-1} = D_{k-1} = 0) = \frac{E[D_k(1 - Y_{k-1})(1 - D_{k-1})]}{E[(1 - Y_{k-1})(1 - D_{k-1})]},
\]

and their respective estimators

\[
\hat{\lambda}_k^1 \equiv \frac{E_n[Y_k(1 - D_k)(1 - Y_{k-1})]}{E_n[(1 - D_k)(1 - Y_{k-1})]} \\
\hat{\lambda}_k^2 \equiv \frac{E_n[D_k(1 - Y_{k-1})(1 - D_{k-1})]}{E_n[(1 - Y_{k-1})(1 - D_{k-1})]}
\]

We then have

\[
\frac{d_{1k}}{r_k} = \frac{E_n[Y_k(1 - D_k)(1 - Y_{k-1})]}{E_n[(1 - Y_{k-1})(1 - D_{k-1})]} = \frac{E_n[Y_k(1 - D_k)(1 - Y_{k-1})]}{E_n[(1 - D_k)(1 - Y_{k-1})]} \cdot \frac{E_n[(1 - D_k)(1 - Y_{k-1})]}{E_n[(1 - Y_{k-1})(1 - D_{k-1})]}
\]
where the second equality holds because for each mortality:

\[ \hat{\lambda}_k^2, \]

so that, in the absence of censoring due to loss to follow-up or administrative end of study, the Aalen-Johansen estimator (2) with \( j \) set to 1 reduces to the empirical distribution function of hospital mortality:

\[
\sum_{k=1}^{K} d_{1k} \prod_{s=1}^{k-1} \left( 1 - \frac{d_{sk}}{r_s} \right) = \sum_{k=1}^{K} \frac{E_n[Y_k(1-D_k)(1-Y_{k-1})]}{E_n[(1-Y_{k-1})(1-D_{k-1})]} \prod_{s=1}^{k-1} \frac{E_n[(1-Y_s)(1-D_s)]}{E_n[(1-Y_{s-1})(1-D_{s-1})]} \tag{15}
\]

\[
= \sum_{k=1}^{K} E_n[Y_k(1-D_k)(1-Y_{k-1})] \tag{16}
\]

\[
= n^{-1} \sum_{k=1}^{K} \sum_{i=1}^{n} 1_{T_i \in (t_{k-1}, t_k], \epsilon_i = 1}
\]

\[
= n^{-1} \sum_{k=1}^{K} d_{1k},
\]

where the second equality holds because for each \( k \leq 0 \) we have \( Y_k = D_k = 0 \).

Note that the Aalen-Johansen estimator (2) with \( j \) set to 1 can be expressed as the following function of the non-parametrically estimated discrete-time cause-specific hazards \( \hat{\lambda}_k^1 \) and \( \hat{\lambda}_k^2 \)

\[
\sum_{k=1}^{K} d_{1k} \prod_{s=1}^{k-1} \left( 1 - \frac{d_{sk}}{r_s} \right) = \sum_{k=1}^{K} \hat{\lambda}_k^1 (1 - \hat{\lambda}_k^2) \prod_{s=1}^{k-1} (1 - \hat{\lambda}_s^1) (1 - \hat{\lambda}_s^2).
\]

In the absence of tied competing event times, we have \( \hat{\lambda}_k^1 \hat{\lambda}_k^2 = 0 \), for every \( k \), so that

\[
\frac{d_{1k}}{r_k} = \hat{\lambda}_k^1,
\]

\[
\frac{d_{2k}}{r_k} = \hat{\lambda}_k^2,
\]

\[
\frac{d_{dk}}{r_k} = \hat{\lambda}_k^1 + \hat{\lambda}_k^2.
\]

The Aalen-Johansen estimator can then simply be expressed as

\[
\sum_{k=1}^{K} \hat{\lambda}_k^1 \prod_{s=1}^{k-1} \left( 1 - \hat{\lambda}_s^1 - \hat{\lambda}_s^2 \right).
\]

The above illustrates that the fractions \( d_{1k}/r_k \) and \( d_{2k}/r_k \) can only be interpreted as cause-specific hazard estimates in the absence of tied competing event times.
A.2  Cumulative incidence of infection-free hospital death  \( \Pr(\tilde{T} \leq t_K, \tilde{\epsilon} = 1) \equiv \Pr(\tilde{Y}_K = 1) \)

Following the definitions from Section 2 in the main text, under the assumed temporal ordering \((A_k, \tilde{D}_k, \tilde{Y}_k)\), we have

\[
1_{\tilde{T} \in (t_{k-1}, t_k), \tilde{\epsilon} = 0} = A_k(1 - A_{k-1})(1 - \tilde{Y}_{k-1})(1 - \tilde{D}_{k-1})
\]

\[
= A_k(1 - A_{k-1})(1 - Y_{k-1}(1 - A_{k-1}))(1 - D_{k-1}(1 - A_{k-1}))
\]

\[
= \begin{cases} 
A_k(1 - Y_{k-1})(1 - D_{k-1}), & \text{if } A_{k-1} = 0 \\
0, & \text{if } A_{k-1} = 1 
\end{cases}
\]

\[
= A_k(1 - A_{k-1})(1 - Y_{k-1})(1 - D_{k-1}),
\]

\[
1_{\tilde{T} \in (t_{k-1}, t_k), \tilde{\epsilon} = 1} = \tilde{Y}_k(1 - \tilde{Y}_{k-1})(1 - \tilde{D}_k)(1 - A_k)
\]

\[
= Y_k(1 - A_k)(1 - Y_{k-1}(1 - A_{k-1}))(1 - D_k(1 - A_k))(1 - A_k)
\]

\[
= \begin{cases} 
Y_k(1 - Y_{k-1})(1 - D_k), & \text{if } A_k = 0 \\
0, & \text{if } A_k = 1 
\end{cases}
\]

\[
= Y_k(1 - Y_{k-1})(1 - D_k)(1 - A_k),
\]

\[
1_{\tilde{T} \in (t_{k-1}, t_k), \tilde{\epsilon} = 2} = \tilde{D}_k(1 - \tilde{D}_{k-1})(1 - A_k)(1 - \tilde{Y}_{k-1})
\]

\[
= D_k(1 - A_k)(1 - D_{k-1}(1 - A_{k-1}))(1 - A_k)(1 - Y_{k-1}(1 - A_{k-1}))
\]

\[
= \begin{cases} 
D_k(1 - D_{k-1})(1 - Y_{k-1}), & \text{if } A_k = 0 \\
0, & \text{if } A_k = 1 
\end{cases}
\]

\[
= D_k(1 - D_{k-1})(1 - A_k)(1 - Y_{k-1}),
\]

\[
1_{\tilde{T} > t_{k-1}} = (1 - Y_{k-1})(1 - D_{k-1})(1 - A_{k-1})
\]

\[
1_{\tilde{T} > t_{k-1}} - 1_{\tilde{T} > t_k} = (1 - Y_{k-1})(1 - D_{k-1})(1 - A_{k-1}) - (1 - Y_k)(1 - D_k)(1 - A_k),
\]

such that

\[
d_{0k} = \sum_{i=1}^{n} 1_{\tilde{T}_i \in (t_{k-1}, t_k), \tilde{\epsilon}_i = 0} = nE_n[A_k(1 - Y_{k-1})(1 - D_{k-1})(1 - A_{k-1})]
\]

\[
d_{1k} = \sum_{i=1}^{n} 1_{\tilde{T}_i \in (t_{k-1}, t_k), \tilde{\epsilon}_i = 1} = nE_n[Y_k(1 - D_k)(1 - A_k)(1 - Y_{k-1})]
\]

\[
d_{2k} = \sum_{i=1}^{n} 1_{\tilde{T}_i \in (t_{k-1}, t_k), \tilde{\epsilon}_i = 2} = nE_n[D_k(1 - A_k)(1 - Y_{k-1})(1 - D_{k-1})]
\]

\[
d_k = \sum_{i=1}^{n} 1_{\tilde{T}_i \in (t_{k-1}, t_k)} = nE_n[(1 - Y_{k-1})(1 - D_{k-1})(1 - A_{k-1}) - (1 - Y_k)(1 - D_k)(1 - A_k)]
\]

\[
r_k = \sum_{i=1}^{n} 1_{\tilde{T}_i > t_{k-1}} = nE_n[(1 - Y_{k-1})(1 - D_{k-1})(1 - A_{k-1})].
\]

30
Define discrete-time cause-specific hazards \( \tilde{\lambda}_k^0, \tilde{\lambda}_k^1 \) and \( \tilde{\lambda}_k^2 \) as

\[
\begin{align*}
\tilde{\lambda}_k^0 &= \Pr(A_k = 1|Y_{k-1} = D_{k-1} = A_{k-1} = 0) = \frac{E[A_k(1-Y_{k-1})(1-D_{k-1})(1-A_{k-1})]}{E[(1-Y_{k-1})(1-D_{k-1})(1-A_{k-1})]}, \\
\tilde{\lambda}_k^1 &= \Pr(Y_k = 1|D_k = A_k = Y_{k-1} = 0) = \frac{E[Y_k(1-D_k)(1-A_k)(1-Y_{k-1})]}{E[(1-D_k)(1-A_k)(1-Y_{k-1})]}, \\
\tilde{\lambda}_k^2 &= \Pr(D_k = 1|A_k = Y_{k-1} = D_{k-1} = 0) = \frac{E[D_k(1-A_k)(1-Y_{k-1})(1-D_{k-1})]}{E[(1-A_k)(1-Y_{k-1})(1-D_{k-1})]},
\end{align*}
\]

and their respective estimators

\[
\begin{align*}
\hat{\lambda}_k^0 &= \frac{E_n[A_k(1-Y_{k-1})(1-D_{k-1})(1-A_{k-1})]}{E_n[(1-Y_{k-1})(1-D_{k-1})(1-A_{k-1})]} = \tilde{\lambda}_k^0, \\
\hat{\lambda}_k^1 &= \frac{E_n[Y_k(1-D_k)(1-A_k)(1-Y_{k-1})]}{E_n[(1-D_k)(1-A_k)(1-Y_{k-1})]} = \tilde{\lambda}_k^1(1-\tilde{\lambda}_k^0)(1-\tilde{\lambda}_k^1), \\
\hat{\lambda}_k^2 &= \frac{E_n[D_k(1-A_k)(1-Y_{k-1})(1-D_{k-1})]}{E_n[(1-A_k)(1-Y_{k-1})(1-D_{k-1})]} = \tilde{\lambda}_k^2(1-\tilde{\lambda}_k^0),
\end{align*}
\]

We then have

\[
\begin{align*}
\hat{\lambda}_{dkk} &= \frac{E_n[A_k(1-Y_{k-1})(1-D_{k-1})(1-A_{k-1})]}{E_n[(1-Y_{k-1})(1-D_{k-1})(1-A_{k-1})]} = \tilde{\lambda}_k^0, \\
\hat{\lambda}_{dk} &= \frac{E_n[Y_k(1-D_k)(1-A_k)(1-Y_{k-1})]}{E_n[(1-D_k)(1-A_k)(1-Y_{k-1})]} = \tilde{\lambda}_k^1(1-\tilde{\lambda}_k^0), \\
\hat{\lambda}_k &= \frac{E_n[D_k(1-A_k)(1-Y_{k-1})(1-D_{k-1})]}{E_n[(1-A_k)(1-Y_{k-1})(1-D_{k-1})]} = \tilde{\lambda}_k^2(1-\tilde{\lambda}_k^0),
\end{align*}
\]

so that, in the absence of censoring due to loss to follow-up or administrative end of study, the Aalen-Johansen estimator \([3]\) with \( j \) set to 1 reduces to the empirical distribution function of exposure-free hospital mortality:

\[
\begin{align*}
\sum_{k=1}^{K} \hat{\lambda}_{dkk} = \sum_{k=1}^{K} \frac{E_n[Y_k(1-D_k)(1-A_k)(1-Y_{k-1})]}{E_n[(1-Y_{k-1})(1-D_{k-1})(1-A_{k-1})]} = \sum_{k=1}^{K} \frac{E_n[(1-Y_k)(1-D_k)(1-A_k)]}{E_n[(1-Y_{k-1})(1-D_{k-1})(1-A_{k-1})]}
\end{align*}
\]  

(17)

(18)

\[
\begin{align*}
&= n^{-1} \sum_{k=1}^{K} \sum_{i=1}^{n} \mathbb{1}_{\bar{t}_i \in (t_{k-1}, t_k], \bar{\epsilon}_i = 1} \\
&= n^{-1} \sum_{k=1}^{K} \hat{\lambda}_{dkk}
\end{align*}
\]  

31
Define counterfactual discrete-time cause-specific hazards $\lambda_{k}^{0}$, $\lambda_{k}^{1}$, and $\lambda_{k}^{2}$ where the second equality holds because for each $k \leq 0$ we have $Y_{k} = D_{k} = A_{k} = 0$.

The Aalen-Johansen estimator with $j$ set to 1 can again be expressed as the following function of the non-parametrically estimated cause-specific hazards $\tilde{\lambda}_{k}^{0}$, $\tilde{\lambda}_{k}^{1}$, and $\tilde{\lambda}_{k}^{2}$

$$
\sum_{k=1}^{K} \frac{d_{ik}}{r_{k}} \prod_{s=1}^{k-1} \left(1 - \frac{\tilde{d}_{s}}{r_{s}}\right) = \sum_{k=1}^{K} \tilde{\lambda}_{k}^{1} (1 - \tilde{\lambda}_{k}^{1}) (1 - \tilde{\lambda}_{k}^{0}) \prod_{s=1}^{k-1} (1 - \tilde{\lambda}_{s}^{0})(1 - \tilde{\lambda}_{s}^{1})(1 - \tilde{\lambda}_{s}^{2}).
$$

(19)

A.3 Counterfactual cumulative incidence of hospital death $Pr(T^{\pi=0} \leq t_{k}, \epsilon^{0} = 1) = Pr(Y_{k}^{\pi=0} = 1)$

Suppose, hypothetically speaking, that for each subject, we could observe their counterfactual data. Following the definitions from Section 2 in the main text, under the assumed temporal ordering $(D_{k}^{\pi=0}, Y_{k}^{\pi=0})$, we would then have

$$
1_{T^{\pi=0} \in (t_{k-1}, t_{k}], \epsilon^{0}=1} = Y_{k}^{\pi=0}(1 - D_{k}^{\pi=0})(1 - Y_{k-1}^{\pi=0})
$$

$$
1_{T^{\pi=0} \in (t_{k-1}, t_{k}], \epsilon^{0}=2} = D_{k}^{\pi=0}(1 - Y_{k-1}^{\pi=0})(1 - D_{k-1}^{\pi=0})
$$

$$
1_{T^{\pi=0} > t_{k-1}} = (1 - Y_{k-1}^{\pi=0})(1 - D_{k-1}^{\pi=0})
$$

$$
1_{T^{\pi=0} \in (t_{k-1}, t_{k}]} = 1_{T^{\pi=0} > t_{k-1}} - 1_{T^{\pi=0} > t_{k}}
$$

$$
= (1 - Y_{k-1}^{\pi=0})(1 - D_{k-1}^{\pi=0}) - (1 - Y_{k}^{\pi=0})(1 - D_{k}^{\pi=0}),
$$

such that

$$
d_{1k}^{\pi=0} = \sum_{i=1}^{n} 1_{T_{i}^{\pi=0} \in (t_{k-1}, t_{k}], \epsilon_{i}^{0}=1} = nE_{n}[Y_{k}^{\pi=0}(1 - D_{k}^{\pi=0})(1 - Y_{k-1}^{\pi=0})]
$$

$$
d_{2k}^{\pi=0} = \sum_{i=1}^{n} 1_{T_{i}^{\pi=0} \in (t_{k-1}, t_{k}], \epsilon_{i}^{0}=2} = nE_{n}[D_{k}^{\pi=0}(1 - Y_{k-1}^{\pi=0})(1 - D_{k-1}^{\pi=0})]
$$

$$
d_{k}^{\pi=0} = \sum_{i=1}^{n} 1_{T_{i}^{\pi=0} \in (t_{k-1}, t_{k}]} = nE_{n}[(1 - Y_{k-1}^{\pi=0})(1 - D_{k-1}^{\pi=0}) - (1 - Y_{k}^{\pi=0})(1 - D_{k}^{\pi=0})]
$$

$$
y_{k}^{\pi=0} = \sum_{i=1}^{n} 1_{T_{i}^{\pi=0} > t_{k-1}} = nE_{n}[(1 - Y_{k}^{\pi=0})(1 - D_{k}^{\pi=0})].
$$

Define counterfactual discrete-time cause-specific hazards $\lambda_{k}^{1,\pi=0}$ and $\lambda_{k}^{2,\pi=0}$ as

$$
\lambda_{k}^{1,\pi=0} = Pr(Y_{k}^{\pi=0} = 1 | D_{k}^{\pi=0} = Y_{k-1}^{\pi=0} = 0) = \frac{E[Y_{k}^{\pi=0}(1 - D_{k}^{\pi=0})(1 - Y_{k-1}^{\pi=0})]}{E[(1 - D_{k}^{\pi=0})(1 - Y_{k-1}^{\pi=0})]}
$$

$$
\lambda_{k}^{2,\pi=0} = Pr(D_{k}^{\pi=0} = 1 | Y_{k-1}^{\pi=0} = D_{k-1}^{\pi=0} = 0) = \frac{E[D_{k}^{\pi=0}(1 - Y_{k-1}^{\pi=0})(1 - D_{k-1}^{\pi=0})]}{E[(1 - Y_{k-1}^{\pi=0})(1 - D_{k-1}^{\pi=0})]},
$$

and their respective estimators

$$
\hat{\lambda}_{k}^{1,\pi=0} = \frac{E_{n}[Y_{k}^{\pi=0}(1 - D_{k}^{\pi=0})(1 - Y_{k-1}^{\pi=0})]}{E_{n}[(1 - D_{k}^{\pi=0})(1 - Y_{k-1}^{\pi=0})]}
$$

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where the second equality holds because for each $k \leq 0$ we have $Y^\pi=0 = D^\pi=0 = 0$.

We then have

\[
\frac{d_{1,k}^\pi=0}{r_k} = \frac{E_n[Y^\pi=0(1 - D^\pi=0)(1 - Y_{k-1}^\pi=0)]}{E_n[(1 - Y_{k-1}^\pi=0)(1 - D_{k-1}^\pi=0)]} = \hat{\lambda}_{1,k}^\pi=0 (1 - \hat{\lambda}_{k}^2, \pi=0),
\]

\[
\frac{d_{2,k}^\pi=0}{r_k} = \frac{E_n[D^\pi=0(1 - Y^\pi=0)(1 - D_{k-1}^\pi=0)]}{E_n[(1 - Y_{k-1}^\pi=0)(1 - D_{k-1}^\pi=0)]} = \hat{\lambda}_{2,k}^\pi=0
\]

\[
= 1 - (1 - \hat{\lambda}_{1,k}^\pi=0)(1 - \hat{\lambda}_{k}^2, \pi=0),
\]

so that, in the absence of censoring due to loss to follow-up or administrative end of study, the Aalen-Johansen estimator $\hat{\lambda}_k$ with $j$ set to 1 reduces to the empirical distribution function of counterfactual exposure-free hospital mortality:

\[
\sum_{k=1}^{K} \frac{d_{1,k}^\pi=0}{r_k} \prod_{s=1}^{k-1} \left( 1 - \frac{d_{s}^\pi=0}{r_s} \right) = \sum_{k=1}^{K} \frac{E_n[Y^\pi=0(1 - D^\pi=0)(1 - Y_{k-1}^\pi=0)]}{E_n[(1 - Y_{k-1}^\pi=0)(1 - D_{k-1}^\pi=0)]} \prod_{s=1}^{k-1} \frac{E_n[(1 - Y_{s-1}^\pi=0)(1 - D_{s-1}^\pi=0)]}{E_n[(1 - Y_{s-1}^\pi=0)(1 - D_{s-1}^\pi=0)]}
\]

\[
= \sum_{k=1}^{K} E_n[Y^\pi=0(1 - D^\pi=0)(1 - Y_{k-1}^\pi=0)]
\]

\[
= n^{-1} \sum_{k=1}^{K} \sum_{i=1}^{n} (1 - Y_i^\pi=0 \in (t_{k-1}, t_k] \cap \pi=0 = 1)
\]

\[
= n^{-1} \sum_{k=1}^{K} d_{1,k}^\pi=0,
\]

where the second equality holds because for each $k \leq 0$ we have $Y^\pi=0 = D^\pi=0 = 0$.

Note that the Aalen-Johansen estimator $\hat{\lambda}_k$ with $j$ set to 1 can again be expressed as the following function of the non-parametrically estimated counterfactual discrete-time cause-specific hazards $\hat{\lambda}_{k,\pi=0}$ and $\hat{\lambda}_{k}^2, \pi=0$

\[
\sum_{k=1}^{K} \frac{d_{1,k}^\pi=0}{r_k} \prod_{s=1}^{k-1} \left( 1 - \frac{d_{s}^\pi=0}{r_s} \right) = \sum_{k=1}^{K} \hat{\lambda}_{1,k}^\pi=0 (1 - \hat{\lambda}_{k}^2, \pi=0) \prod_{s=1}^{k-1} (1 - \hat{\lambda}_{s}^\pi=0)(1 - \hat{\lambda}_{k}^2, \pi=0).
\]
B Weighting-based characterization of estimators based on multistate models

B.1 Treating exposure onset as a (non-informative) censoring event: the Aalen-Johansen estimator as an IPC weighted average

Following the definitions from Sections 2 and 3 in the main text and building on Appendix A.2 under the assumed temporal ordering \((A_k, \tilde{D}_k, \tilde{Y}_k)\) and upon treating HAI onset as non-informative or independent censoring, we have

\[
\begin{align*}
  d'_{1k} &\equiv \hat{d}_{1k} = \sum_{i=1}^{n} 1_{\tilde{T}_i \in (t_{k-1}, t_k), \tilde{e}_i = 1} = nE_n[Y_k(1 - D_k)(1 - A_k)(1 - Y_{k-1})] \\
n'_{1k} &\equiv \hat{n}_{1k} = \sum_{i=1}^{n} 1_{\tilde{T}_i \in (t_{k-1}, t_k), \tilde{e}_i = 1} = nE_n[Y_k(1 - D_k)(1 - A_k)(1 - Y_{k-1})] \\
  d'_{2k} &\equiv \hat{d}_{2k} = \sum_{i=1}^{n} 1_{\tilde{T}_i \in (t_{k-1}, t_k), \tilde{e}_i = 2} = nE_n[D_k(1 - A_k)(1 - Y_{k-1})(1 - D_{k-1})] \\
n'_{2k} &\equiv \hat{n}_{2k} = \sum_{i=1}^{n} 1_{\tilde{T}_i \in (t_{k-1}, t_k), \tilde{e}_i = 2} = nE_n[D_k(1 - A_k)(1 - Y_{k-1})(1 - D_{k-1})] \\
  d'_k &\equiv \hat{d}_k - \hat{d}_{0k} = \sum_{i=1}^{n} 1_{\tilde{T}_i \in (t_{k-1}, t_k), \tilde{e}_i = 0} - \sum_{i=1}^{n} 1_{\tilde{T}_i \in (t_{k-1}, t_k), \tilde{e}_i = 0} \\
    = nE_n[(1 - Y_{k-1})(1 - D_{k-1})(1 - A_{k-1}) - (1 - Y_k)(1 - D_k)(1 - A_k)] \\
    - nE_n[A_k(1 - Y_{k-1})(1 - D_{k-1})(1 - A_{k-1})] \\
    = nE_n[(1 - A_k)(1 - Y_{k-1})(1 - D_{k-1}) - (1 - Y_k)(1 - D_k)(1 - A_k)] \\
  r'_k &\equiv \hat{r}_k - \hat{r}_{0k} = \sum_{i=1}^{n} 1_{\tilde{T}_i > t_{k-1}} - \sum_{i=1}^{n} 1_{\tilde{T}_i \in (t_{k-1}, t_k), \tilde{e}_i = 0} \\
    = nE_n[(1 - Y_{k-1})(1 - D_{k-1})(1 - A_{k-1})] \\
    - nE_n[A_k(1 - Y_{k-1})(1 - D_{k-1})(1 - A_{k-1})] \\
    = nE_n[(1 - A_k)(1 - Y_{k-1})(1 - D_{k-1})]
\end{align*}
\]

We then have

\[
\begin{align*}
  \frac{d'_{1k}}{n'_{1k}} &\equiv \frac{\hat{d}_{1k}}{\hat{n}_{1k}} = \frac{E_n[Y_k(1 - D_k)(1 - A_k)(1 - Y_{k-1})]}{E_n[(1 - A_k)(1 - Y_{k-1})(1 - D_{k-1})]} = \hat{\lambda}_k(1 - \hat{\lambda}_k), \\
  \frac{d'_{2k}}{n'_{2k}} &\equiv \frac{\hat{d}_{2k}}{\hat{n}_{2k}} = \frac{E_n[D_k(1 - A_k)(1 - Y_{k-1})(1 - D_{k-1})]}{E_n[(1 - A_k)(1 - Y_{k-1})(1 - D_{k-1})]} = \hat{\lambda}_k, \\
  \frac{d'_k}{n'_k} &\equiv \frac{\hat{d}_k - \hat{d}_{0k}}{\hat{n}_k - \hat{n}_{0k}} = \frac{E_n[(1 - A_k)(1 - Y_{k-1})(1 - D_{k-1}) - (1 - Y_k)(1 - D_k)(1 - A_k)]}{E_n[(1 - A_k)(1 - Y_{k-1})(1 - D_{k-1})]} \\
    = 1 - \frac{E_n[(1 - Y_{k-1})(1 - D_{k-1})(1 - A_{k-1})]}{E_n[(1 - A_k)(1 - Y_{k-1})(1 - D_{k-1})]} = 1 - (1 - \hat{\lambda}_k)(1 - \hat{\lambda}_k),
\end{align*}
\]

so that, in the absence of censoring due to loss to follow-up or administrative end of study, we can rewrite the Aalen-Johansen estimator \([\hat{\Lambda}^{\hat{n}}]\) in the main text as

\[
\sum_{k=1}^{K} \frac{d'_{1k}}{n'_{1k}} \prod_{s=1}^{k-1} \left(1 - \frac{d'_s}{n'_s}\right) = \sum_{k=1}^{K} \frac{\hat{d}_{1k}}{\hat{n}_{1k}} \prod_{s=1}^{k-1} \left(1 - \frac{\hat{d}_s - \hat{d}_{0s}}{\hat{n}_s - \hat{n}_{0s}}\right)
\]

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\[
= \sum_{k=1}^{K} \sum_{i=1}^{n} \mathbf{1}_{i \in \{t_{k_1}, t_k\}, \hat{r}_i = 1} \hat{W}_{ik}^0
\]

with
\[
\hat{W}_{ik}^0 = W_{ik}^0 = \frac{1}{\prod_{s=1}^{k} \Pr(T \in \{t_{s_1}, t_s\}, \hat{1} = 0 | T > t_{s-1})}
\]

The third equality follows from the fact that we have \(Y_k = D_k = A_k = 0\) for every \(k \leq 0\). The fourth equality only holds if for each \(s \in \{1, ..., k\}, we have \)
\[
\hat{\Pr}(A_s = 0 | Y_{s-1} = D_{s-1} = A_{s-1} = 0) = P_n(A_s = 0 | Y_{s-1} = D_{s-1} = A_{s-1} = 0) = \frac{E_n[(1 - Y_{s-1})(1 - D_{s-1})(1 - A_s)]}{E_n[(1 - Y_{s-1})(1 - D_{s-1})(1 - A_s)]}
\]

with \(P_n(X = x | Z = z)\) as defined in Appendix A.1, which implies non-parametric estimation of the weights \(W_{ik}^0\). The last equality in the expression of \(\hat{W}_{ik}^0\) is proven in Appendix C. Note that even
though a subscript $i$ is used in the summation, the weights $\hat{W}_{ik}^\circ$ are not subject-dependent, as clarified by their definition $\hat{W}_{ik}^\circ \equiv \hat{W}_{ik}^\bullet$.

Recall that (22) corresponds to the Aalen-Johansen estimator (2) discussed in Appendix A.1 upon treating HAI onset as a censoring event and assuming that, within an interval $k$, censoring precedes events. In the absence of remaining censoring due to loss to follow-up or administrative end of study, the Aalen-Johansen estimator (15) reduces to the empirical cumulative distribution function (16) (see Appendix A.1). The above equalities illustrate that, in accordance with Satten and Datta (2001), in the presence of censoring, the Aalen-Johansen estimator (22) for the cumulative incidence function corresponds to an inverse probability of censoring (IPC) weighted empirical cumulative distribution function (23) with weights $\hat{W}_{ik}^\bullet$ equal to the inverse of Kaplan-Meier estimates for the censoring event by interval $k$ (upon reversing the roles of censoring events and events of interest). This may become more apparent upon rewriting the reciprocal of $\hat{W}_{ik}^\circ$ in the more usual notation

$$\prod_{s=1}^{k} \{1 - \bar{P}(T \in (t_{s-1}, t_s], \bar{\epsilon} = 0|T > t_{s-1})\} = \prod_{s=1}^{k} \left(1 - \frac{\bar{d}_{0s}}{\bar{r}_s}\right).$$

More specifically, note that (23) is a weighted version of the empirical cumulative distribution function of hospital death (16) with weights $\hat{W}_{ik}^\circ$ and a weighted version of the empirical cumulative distribution function of infection-free hospital death (18) with weights $\hat{W}_{ik}^\bullet = (1 - A_{ik})\hat{W}_{ik}^\circ$.

Furthermore note that Aalen-Johansen estimator (22) could be considered a weighted version of the Aalen-Johansen estimators (15) and (17) with weight $1 - A_{ik}$ for subject $i$ at interval $k$. Upon substituting this weight by $\hat{W}_{ik}^\bullet$, which is licensed by the fact that $\hat{W}_{ik}^\circ$ only depends on $i$, we obtain an IPC weighted version of the Aalen-Johansen estimators (15) and (17) that is algebraically equivalent to (22). Algebraic equivalence of estimators (22) and (23) then alternatively follows from the following equality

$$\sum_{k=1}^{K} E_n[Y_k(1 - Y_{k-1})(1 - D_k)\hat{W}_{ik}^\bullet] \prod_{s=1}^{k-1} E_n[(1 - Y_s)(1 - D_s)\hat{W}_{is}^\bullet] = \sum_{k=1}^{K} E_n[Y_k(1 - Y_{k-1})(1 - D_k)\hat{W}_{ik}^\circ]$$

where the first equality again follows from the fact that we have $Y_k = D_k = A_k = 0$ for every $k \leq 0$, and

$$E_n[(1 - Y_k)(1 - D_k)\hat{W}_{ik+1}^\bullet] = E_n \left[ \frac{(1 - Y_k)(1 - D_k)(1 - A_{k+1})\hat{W}_{ik}^\bullet}{P_n(A_{k+1} = 0|Y_k = D_k = A_k = 0)} \bigg| Y_k = D_k = A_k = 0 \right] P_n(\nabla_k = \overline{D}_k = \overline{A}_k = \overline{0})$$

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with \( E_n(X|Z = z) \) as defined in Appendix A.1. The proof of this equality is also given in Lemma 2 in Young et al. (2020).

Following the results of Appendix A.3, (22) and (23) are consistent estimators of \( \Pr(T^\pi = 0 \leq t_K, \epsilon^\pi = 0) = \Pr(Y^\pi_k = 1) \) under non-informative (artificial) censoring by HAI onset or, equivalently, the assumption that the observable cause-specific hazards of hospital death and discharge among patients who have remained uninfected equal the counterfactual infection-free cause-specific hazards of hospital death and discharge, respectively. That is, for every \( k \), we have

\[
\begin{align*}
\lambda^{1, \pi = 0}_k &= \hat{\lambda}_k^1 \\
\lambda^{2, \pi = 0}_k &= \hat{\lambda}_k^2.
\end{align*}
\]

Finally, note that the Aalen-Johansen estimator upon considering HAI onset as a censoring event (21), corresponds to the Aalen-Johansen estimator (19) from Appendix A.2 upon setting the cause-specific hazard of the competing event HAI onset (or transition intensity) \( \hat{\lambda}_k^0 \) to 0 (Arjas and Eerola, 1993; Keiding et al., 2001).

**B.2 Treating HAI as an exclusion criterion**

A naive multistate model based approach ignores HAI onset and (implicitly) assumes the counterfactual cumulative incidence \( \Pr(T^\pi = 0 \leq t_K, \epsilon^{\pi = 0} = 1) \) can be substituted by \( \Pr(T \leq t_K, \epsilon = 1|\epsilon^{\pi = 0} \neq 0) = \Pr(\bar{T} \leq t_K, \tilde{\epsilon} = 1|\tilde{\epsilon}^{\pi = 0} \neq 0) \). This quantity can, in turn, be estimated using the Aalen-Johansen estimators (15) or (17) after exclusion of ever exposed patients (for whom \( \tilde{\epsilon} = 0 \) or \( A_r = 1 \)) from the analysis or equivalently, weighing each patient \( i \) at each time interval \( k \) by \( 1 - A_{i, r} \). In the absence of censoring due to loss to follow-up or administrative end of study, this estimator reduces to a weighted empirical cumulative distribution function

\[
\begin{align*}
\sum_{k=1}^{K} & \frac{E_n[Y_k(1 - Y_{k-1})(1 - D_k)(1 - A_k)(1 - A_r)]}{E_n[(1 - Y_{k-1})(1 - D_{k-1})(1 - A_{k-1})(1 - A_r)]} \times \\
& \prod_{s=1}^{k-1} \frac{E_n[(1 - Y_s)(1 - D_s)(1 - A_s)(1 - A_r)]}{E_n[(1 - Y_{s-1})(1 - D_{s-1})(1 - A_{s-1})(1 - A_r)]} \\
& = \sum_{k=1}^{K} \frac{E_n[Y_k(1 - Y_{k-1})(1 - D_k)(1 - A_r)]}{E_n[(1 - Y_{k-1})(1 - D_{k-1})(1 - A_r)]} \prod_{s=1}^{k-1} \frac{E_n[(1 - Y_s)(1 - D_s)(1 - A_r)]}{E_n[(1 - Y_{s-1})(1 - D_{s-1})(1 - A_r)]} \\
& = \sum_{k=1}^{K} \frac{E_n[Y_k(1 - Y_{k-1})(1 - D_k)(1 - A_r)]}{E_n[(1 - Y_{k-1})(1 - D_{k-1})(1 - A_r)]} \\
& \times \prod_{s=1}^{k-1} \frac{E_n[(1 - Y_s)(1 - D_s)(1 - A_r)]}{E_n[(1 - Y_{s-1})(1 - D_{s-1})(1 - A_r)]}
\end{align*}
\] (24)
\[
E_n \left[ Y_k (1 - Y_{k-1}) (1 - D_k) (1 - A_k) \hat{W}^* \right]
\]

with

\[
d_{ik}^w \equiv n \sum_{i=1}^{n} \mathbb{1}_{t_i \in (t_{k-1}, t_k], \tilde{\epsilon}_i = 1} \hat{W}^*_i
\]

the weighted number of HAI-free hospital deaths in interval \(k\) and

\[
\hat{W}^*_i \equiv \hat{W}^* = \frac{1}{1 - P_n(\tilde{\epsilon} = 0)} = \frac{1}{P_n(A_r = 1)} = 1 + \frac{P_n(A_r = 1)}{P_n(A_r = 0)}.
\]

The first equality above holds because, for each \(k\), we have \((1 - A_k)(1 - A_r) = (1 - A_r)\). The fourth equality holds because, for each \(k \leq \tau\), we have

\[
Y_k (1 - A_r) = \begin{cases} 
1 & \text{iff } Y_k (1 - A_k) = 1; \\
0 & \text{otherwise}.
\end{cases}
\]

The latter holds because

1. \(Y_k (1 - A_k) = 1\) iff \(Y_k = 1\) and \(A_k = 0\), in which case we have \(A_{k+1} = 0\), and so \(Y_k (1 - A_r) = 1\), due to the deterministic relation between the competing events.

2. \(Y_k (1 - A_r) = 1\) iff \(Y_k = 1\) and \(A_r = 0\), in which case we have \(A_k = 0\), and so \(Y_k (1 - A_k) = 1\), due to the fact that by definition, for any \(k \leq \tau\), we have \(A_k \leq A_r\).

Note that, even though a subscript \(i\) is used in the summation, the weights \(\hat{W}^*_i\) are not subject-dependent, as clarified by their definition \(\hat{W}^*_i \equiv \hat{W}^*\). Expression (25) is again a weighted version of the empirical cumulative distribution of infection-free hospital death (18) with weights \(\hat{W}^*_i\) equal to the inverse probability of remaining without HAI until hospital death or discharge (or, equivalently, being included in the final sample for this naive analysis), but also a weighted version of the empirical cumulative distribution of hospital death (16) with weights \((1 - A_{ik})\hat{W}^*_i\).

**B.3 Treating HAI onset as a time-dependent exclusion criterion**

Schumacher et al. (2007) describe a method to estimate the counterfactual risk \(\Pr(T^\pi=0 \leq t_K, \pi=0 = 1)\) from an extended or progressive illness death model, as depicted in Figure 6.
Let $P_{ij}(s,t)$ denote the transition probability $\Pr(X_t = j | X_s = i)$ for $s \leq t$, with $X_s$ the observed state at time $s$ and $X_t$ the observed state at time $t$. In the considered setting, we have that $\Pr(X_0 = 0) = 1$, such that, for each pair $(j,t)$, $P_{0j}(0,t)$ corresponds to a so-called state occupation probability (or cumulative incidence) $\Pr(X_t = j)$. Schumacher et al. (2007) target the following quantity

$$P_{01}(0,t) P_{00}(0,t) + P_{01}(0,t) + P_{02}(0,t) = 1 - P_{03}(0,t) - P_{04}(0,t) - P_{05}(0,t),$$

which, given that

$$\Pr(\tilde{T} > t) = P_{00}(0,t),$$
$$\Pr(\tilde{T} \leq t, \tilde{\epsilon} = 1) = P_{01}(0,t),$$
$$\Pr(\tilde{T} \leq t, \tilde{\epsilon} = 2) = P_{02}(0,t),$$
$$\Pr(\tilde{T} \leq t, \tilde{\epsilon} = 0) = 1 - P_{00}(0,t) - P_{01}(0,t) - P_{02}(0,t),$$

equals

$$\frac{\Pr(\tilde{T} \leq t, \tilde{\epsilon} = 1)}{1 - \Pr(\tilde{T} \leq t, \tilde{\epsilon} = 0)} = \frac{\Pr(\tilde{T} \leq t, \tilde{\epsilon} = 1)}{\Pr(\tilde{T} > t \cup (\tilde{T} \leq t, \tilde{\epsilon} \neq 0))} = \Pr(\tilde{T} \leq t, \tilde{\epsilon} = 1 | \tilde{T} > t \cup (\tilde{T} \leq t, \tilde{\epsilon} \neq 0)).$$

In other words, Schumacher et al. (2007) implicitly assume that

$$\Pr(T^\pi = 0 \leq t_K, \epsilon^\pi = 0 = 1) = \Pr(\tilde{T} \leq t_K, \tilde{\epsilon} = 1 | \tilde{T} > t_K \cup (\tilde{T} \leq t_K, \tilde{\epsilon} \neq 0)).$$

The relevant state occupation probabilities for estimating this targeted observable quantity can also be obtained from a simpler competing risk model with three absorbing states (and no transient states), as depicted in Figure 2, which is obtained by collapsing HAI onset and subsequent hospital death or discharge into a single absorbing state. This corresponds to the competing risk model with observed event time $\tilde{T}$ and event types $\tilde{\epsilon} \in \{0, 1, 2\}$, discussed in the main text. Let $P'_{0k}(0,t)$ denote the state occupation probability $\Pr(X'_t = k | X'_0 = 0)$ for $0 \leq t$, with $X'_t$ the observed state at time $t$, as defined in the competing risk model depicted in Figure 2 under the careful consideration that event types $\tilde{\epsilon} = 1$ and $\tilde{\epsilon} = 2$ correspond to states 1 and 2, respectively, but event type $\tilde{\epsilon} = 0$ corresponds to state 3. The targeted quantity can then be expressed as

$$\frac{P'_{01}(0,t)}{P'_{00}(0,t) + P'_{01}(0,t) + P'_{02}(0,t)} = \frac{P'_{01}(0,t)}{1 - P'_{03}(0,t)}.$$

In other words, each probability (the cumulative risk of HAI-free death and the cumulative risk of HAI onset, respectively) in the targeted functional

$$\Pr(\tilde{T} \leq t_K, \tilde{\epsilon} = 1) \over 1 - \Pr(\tilde{T} \leq t_K, \tilde{\epsilon} = 0)$$

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can be estimated by their corresponding Aalen-Johansen estimator, such that the estimator proposed by [Schumacher et al., 2007] can be expressed as

\[
\sum_{k=1}^{K} \frac{E_n[Y_k(1 - Y_{k-1})(1 - D_k)(1 - A_k)]}{E_n[1 - (1 - Y_{k-1})(1 - D_k)(1 - A_k)]} \prod_{s=1}^{k-1} \frac{E_n[(1 - Y_s)(1 - D_s)(1 - A_s)]}{E_n[(1 - Y_{s-1})(1 - D_{s-1})(1 - A_{s-1})]} \frac{E_n[(1 - Y_s)(1 - D_s)(1 - A_s)]}{E_n[(1 - Y_{s-1})(1 - D_{s-1})(1 - A_{s-1})]}. \tag{26}
\]

Alternatively, since the targeted quantity \( \Pr \left[ \bar{T} \leq t_K, \bar{\epsilon} = 1 \mid \bar{T} > t_K \cup (\bar{T} \leq t_K, \bar{\epsilon} \neq 0) \right] \) equals the risk of infection-free hospital death in patients that have not acquired infection by interval \( K \), the proposed estimator by [Schumacher et al., 2007] can be shown to correspond to the Aalen-Johansen estimators \((15)\) and \((17)\) after exclusion of patients infected by \( t_K \) (for whom \( T \leq t_K, \epsilon = 0 \) or \( A_K = 1 \)) from the analysis (or equivalently, application of weights \( 1 - A_iK \) for each patient \( i \) at each interval \( k \)). In the absence of censoring due to loss to follow-up or administrative end of study, this estimator reduces to a weighted empirical cumulative distribution function

\[
\sum_{k=1}^{K} \frac{E_n[Y_k(1 - Y_{k-1})(1 - D_k)(1 - A_k)]}{E_n[(1 - Y_{k-1})(1 - D_{k-1})(1 - A_{k-1})(1 - A_K)]} \times \prod_{s=1}^{k-1} \frac{E_n[(1 - Y_s)(1 - D_s)(1 - A_s)(1 - A_K)]}{E_n[(1 - Y_{s-1})(1 - D_{s-1})(1 - A_{s-1})(1 - A_K)]} \tag{27}
\]

\[
= \sum_{k=1}^{K} \frac{E_n[Y_k(1 - Y_{k-1})(1 - D_k)(1 - A_K)]}{E_n[(1 - Y_{k-1})(1 - D_{k-1})(1 - A_K)]} \prod_{s=1}^{k-1} \frac{E_n[(1 - Y_s)(1 - D_s)(1 - A_K)]}{E_n[(1 - Y_{s-1})(1 - D_{s-1})(1 - A_K)]}
\]

\[
= \sum_{k=1}^{K} \frac{E_n[Y_k(1 - Y_{k-1})(1 - D_k)(1 - A_K)]}{E_n[(1 - Y_{k-1})(1 - D_{k-1})(1 - A_K)]} \frac{E_n[(1 - Y_s)(1 - D_s)(1 - A_K)]}{E_n[(1 - Y_{s-1})(1 - D_{s-1})(1 - A_K)]}
\]

\[
= \sum_{k=1}^{K} \frac{E_n[Y_k(1 - Y_{k-1})(1 - D_k)(1 - A_K)]}{P_n(A_K = 0)}
\]

\[
= \sum_{k=1}^{K} \frac{E_n[Y_k(1 - Y_{k-1})(1 - D_k)(1 - A_K)\hat{W_k}^i]}{n^{-1} \sum_{k=1}^{K} \tilde{d}_{1k}^i}, \tag{28}
\]
\[ \hat{d}_{1k}^{wK} = \sum_{i=1}^{n} 1_{T_i \in (t_{k-1}, t_k], \hat{\epsilon}_i = 1} \hat{W}_{iK}^\dagger \]

\[ = nE_n [Y_k(1 - Y_{k-1})(1 - D_k)(1 - A_k)\hat{W}_K^\dagger] \]

is the weighted number of HAI-free hospital deaths in interval \( k \) and

\[ \hat{W}_{iK}^\dagger \equiv \hat{W}_K^\dagger \equiv \frac{1}{1 - P_n(T \leq t_K, \hat{\epsilon} = 0)} - \frac{1}{P_n(A_K = 0)} = 1 + \frac{P_n(A_K = 1)}{P_n(A_K = 0)}. \]

The first equality holds because, for each \( k \leq K \), we have \((1 - A_k)(1 - A_K) = (1 - A_K)\). The fourth equality holds because, for each \( k \leq K \), we have

\[ Y_k(1 - A_K) = \begin{cases} 1 & \text{iff } Y_k(1 - A_k) = 1; \\ 0 & \text{otherwise.} \end{cases} \]

The latter holds because

1. \( Y_k(1 - A_k) = 1 \) iff \( Y_k = 1 \) and \( A_k = 0 \), in which case we have \( A_{k+1} = 0 \), and so \( Y_k(1 - A_K) = 1 \), due to the deterministic relation between the competing events.

2. \( Y_k(1 - A_K) = 1 \) iff \( Y_k = 1 \) and \( A_K = 0 \), in which case we have \( A_k = 0 \), and so \( Y_k(1 - A_k) = 1 \), due to the fact that by definition, for any \( k \leq K \), we have \( A_k \leq A_K \).

Note again that, even though a subscript \( i \) is used in the summation, the weights \( \hat{W}_{iK}^\dagger \) are not subject-dependent, as clarified by their definition \( \hat{W}_{iK}^\dagger \equiv \hat{W}_K^\dagger \). Also important to note is that events (in interval \( k \)) are not weighed according to a function that depends on the time of the event, but according to a function that depends on the landmark interval \( K \) at which the cumulative incidence function is evaluated. This implies that the same event is weighed differently according to the chosen landmark.

Expression (28) is again a weighted version of the empirical cumulative distribution of infection-free hospital death (18) with weights \( \hat{W}_{iK}^\dagger \) equal to the inverse probability of remaining without HAI up to (and including) interval \( K \) (irrespective of hospitalization status), but also a weighted version of the empirical cumulative distribution of hospital death (16) with weights \((1 - A_{ik})\hat{W}_{iK}^\dagger\).

B.4 Treating HAI onset as informative, explainable censoring:

the weighted Aalen-Johansen estimator as an IPC weighted average

Define weights

\[ W_{ik} = \prod_{s=1}^{k} \frac{1}{1 - \Pr(T \in (t_{s-1}, t_s], \hat{\epsilon} = 0|T \geq t_{s-1}, L_{is-1})} \]
censoring conditional on the history of a set of baseline and/or time-dependent covariates under the assumed temporal ordering (\(A_k, \tilde{D}_k, \tilde{Y}_k, L_j\)) and upon treating HAI onset as independent censoring conditional on the history of a set of baseline and/or time-dependent covariates \(\bar{L}_k\), we have

\[
\begin{align*}
\hat{d}_{1ik}^w &= \frac{1}{n} \sum_{i=1}^{n} 1_{\hat{T}_i \in (t_{k-1}, t_k), \hat{\epsilon}_i = 1} \hat{W}_{ik} = n E_n[Y_k(1 - D_k)(1 - A_k)(1 - Y_{k-1})\hat{W}_k]
\end{align*}
\]

\[
\begin{align*}
\hat{d}_{2ik}^w &= \frac{1}{n} \sum_{i=1}^{n} 1_{\hat{T}_i \in (t_{k-1}, t_k), \hat{\epsilon}_i = 2} \hat{W}_{ik} = n E_n[D_k(1 - A_k)(1 - Y_{k-1})(1 - D_{k-1})\hat{W}_k]
\end{align*}
\]

\[
\begin{align*}
\hat{d}_{0ik}^w &= \frac{1}{n} \sum_{i=1}^{n} 1_{\hat{T}_i \in (t_{k-1}, t_k), \hat{\epsilon}_i = 0} \hat{W}_{ik} = n E_n[A_k(1 - Y_{k-1})(1 - D_{k-1})(1 - A_{k-1})\hat{W}_k]
\end{align*}
\]

\[
\begin{align*}
\hat{r}_{ik}^w &= \frac{1}{n} \sum_{i=1}^{n} 1_{\hat{T}_i > t_{k-1}} \hat{W}_{ik} = n E_n[(1 - Y_{k-1})(1 - D_{k-1})(1 - A_{k-1})\hat{W}_k]
\end{align*}
\]

Define

\[
\hat{\lambda}_{ik}^w = \frac{E[Y_k(1 - D_k)(1 - A_k)(1 - Y_{k-1})W_k]}{E[(1 - D_k)(1 - A_k)(1 - Y_{k-1})W_k]} \tag{29}
\]
\[ \lambda_{2,ik} \equiv \frac{E[D_k(1 - A_k)(1 - Y_{k-1})(1 - D_{k-1})W_k]}{E[(1 - A_k)(1 - Y_{k-1})(1 - D_{k-1})W_k]}, \tag{30} \]

and their respective estimators

\[ \hat{\lambda}_{2,ik} \equiv \frac{E_n[Y_k(1 - D_k)(1 - A_k)(1 - Y_{k-1})\hat{W}_k]}{E_n[(1 - D_k)(1 - A_k)(1 - Y_{k-1})\hat{W}_k]} \tag{31} \]

\[ \tilde{\lambda}_{2,ik} \equiv \frac{E_n[D_k(1 - A_k)(1 - Y_{k-1})(1 - D_{k-1})\hat{W}_k]}{E_n[(1 - A_k)(1 - Y_{k-1})(1 - D_{k-1})\hat{W}_k]} \tag{32} \]

We then have

\[ \frac{d_{ik}^{w_{ik}}}{r_{ik}^{w_{ik}}} = \frac{E_n[Y_k(1 - D_k)(1 - A_k)(1 - Y_{k-1})\hat{W}_k]}{E_n[(1 - A_k)(1 - Y_{k-1})(1 - D_{k-1})\hat{W}_k]} = \lambda_{2,ik}(1 - \hat{\lambda}_{2,ik}) \]

\[ \frac{d_{ik}^{w_{ik}}}{r_{ik}^{w_{ik}}} = \frac{E_n[D_k(1 - A_k)(1 - Y_{k-1})(1 - D_{k-1})\hat{W}_k]}{E_n[(1 - A_k)(1 - Y_{k-1})(1 - D_{k-1})\hat{W}_k]} = \tilde{\lambda}_{2,ik} \]

\[ \frac{d_{ik}^{w_{ik}}}{r_{ik}^{w_{ik}}} = \frac{E_n[(1 - A_k)(1 - Y_{k-1})(1 - D_{k-1})\hat{W}_k - (1 - Y_k)(1 - D_k)(1 - A_k)\hat{W}_k]}{E_n[(1 - A_k)(1 - Y_{k-1})(1 - D_{k-1})\hat{W}_k]} = 1 - \left(1 - \lambda_{2,ik}\right)(1 - \tilde{\lambda}_{2,ik}) \]

so that, in the absence of censoring due to loss to follow-up or administrative end of study, we can write the IPC weighted Aalen-Johansen estimator \cite{12} in the main text as

\[ \sum_{k=1}^{K} \frac{d_{ik}^{w_{ik}}}{r_{ik}^{w_{ik}}} \prod_{s=1}^{k-1} \left(1 - \frac{d_{is}^{w_{is}}}{r_{is}^{w_{is}}}\right) = \sum_{k=1}^{K} \frac{d_{ik}^{w_{ik}}}{r_{ik}^{w_{ik}}} \prod_{s=1}^{k-1} \left(1 - \frac{d_{is}^{w_{is}}}{r_{is}^{w_{is}}} - \frac{\hat{d}_{is}^{w_{is}}}{\hat{r}_{is}^{w_{is}}}\right) \]

\[ = \sum_{k=1}^{K} \lambda_{2,ik}(1 - \hat{\lambda}_{2,ik}) \prod_{s=1}^{k-1} \left(1 - \lambda_{2,is}(1 - \hat{\lambda}_{2,is})\right) \tag{33} \]

\[ = \sum_{k=1}^{K} \left[ \frac{E_n[Y_k(1 - D_k)(1 - A_k)(1 - Y_{k-1})\hat{W}_k]}{E_n[(1 - A_k)(1 - Y_{k-1})(1 - D_{k-1})\hat{W}_k]} \right] \prod_{s=1}^{k-1} \left[ \frac{E_n[(1 - Y_s)(1 - D_s)(1 - A_s)\hat{W}_s]}{E_n[(1 - A_s)(1 - Y_{s-1})(1 - D_{s-1})\hat{W}_s]} \right]. \tag{34} \]

Under non-parametric estimation of the weights, we have (also see Lemma 2 in [Young et al., 2020])

\[ E_n[(1 - Y_k)(1 - D_k)(1 - A_{k+1})\hat{W}_{k+1}] \]

\[ = E_n \left[ \frac{(1 - Y_k)(1 - D_k)(1 - A_{k+1})\hat{W}_k}{P_n(A_{k+1} = 0)T_k, Y_k = D_k = A_k = 0} \right] \]

\[ = \sum_{l_k} E_n \left[ \frac{(1 - Y_k)(1 - D_k)(1 - A_{k+1})\hat{W}_k}{P_n(A_{k+1} = 0|T_k = l_k, Y_k = D_k = A_k = 0)} \right] \times P_n(T_k = l_k, Y_k = D_k = A_k = 0) \]

\[ = \sum_{l_k} E_n \left[ (1 - Y_k)(1 - D_k)(1 - A_k)\hat{W}_k | T_k = l_k, Y_k = D_k = A_k = 0 \right] \times P_n(T_k = l_k, Y_k = D_k = A_k = 0) \]

\[ = E_n[(1 - Y_k)(1 - D_k)(1 - A_k)\hat{W}_k]. \tag{35} \]
In this case, this IPC weighted Aalen-Johansen estimator \ref{equation:34} is algebraically equivalent with
\[ \sum_{k=1}^{K} E_n[Y_k(1 - D_k)(1 - A_k)(1 - Y_{k-1})\hat{W}_k] \] (36)
\begin{align*}
&= n^{-1} \sum_{k=1}^{K} \sum_{i=1}^{n} 1_{\tilde{F}_i \in (t_{k-1}, t_k], \tilde{e}_i = 1} \hat{W}_{ik} \\
&= n^{-1} \sum_{k=1}^{K} \tilde{d}^{w}_{1ik} .
\end{align*}
(37)

However, if \( L_k \) is high-dimensional, or contains non-categorical covariates, non-parametric estimation of the weights becomes practically infeasible due to the curse of dimensionality. Parametric (or semi-parametric) weight estimation then gives rise to two different estimators.

Again note that \( \text{(36)} \) is a weighted version of the empirical cumulative distribution of hospital death \( \text{(16)} \) with weights \( \hat{W}_{ik} \) and a weighted version of the empirical cumulative distribution of infection-free hospital death \( \text{(18)} \) with weights \( \hat{W}'_{ik} \). Furthermore note that Aalen-Johansen estimator \( \text{(34)} \) is a weighted version of both Aalen-Johansen estimators \( \text{(15)} \) and \( \text{(17)} \) with weights \( \hat{W}'_{ik} \).

Following the results of Appendix A.3 under correct specification of the weights, \( \text{(34)} \) and \( \text{(36)} \) are consistent estimators of \( \Pr(T_{\pi=0} \leq t_K, e_{\pi=0} = 1) \equiv \Pr(Y_{K_{\pi=0}} = 1) \) under the assumption that, for every \( k \),
\begin{align*}
\hat{\lambda}^{1,\pi=0}_{k} &= \hat{\lambda}^{1,w}_{k} \\
\hat{\lambda}^{2,\pi=0}_{k} &= \hat{\lambda}^{2,w}_{k}.
\end{align*}

In Appendix B.4.1, however, we give a set of weaker assumptions for non-parametric identification that is implied by these equalities, but does not warrant interpretation of \( \hat{\lambda}^{1,w}_{k} \) and \( \hat{\lambda}^{2,w}_{k} \) in terms of counterfactual cause-specific hazards. In Appendix B.4.2, building on recent work by Young et al. (2020) we review an additional assumption that does warrant this interpretation.

B.4.1 Assumptions for non-parametric identification of \( \Pr(Y_{K_{\pi=0}} = 1) \)

Expressions \( \text{(34)} - \text{(36)} \) are consistent estimators of \( \Pr(Y_{K_{\pi=0}} = 1) = \Pr(T_{\pi=0} \leq t_K, e_{\pi=0} = 1) \) under correct specification of a (parametric) working model for the IPC weights \( W_k \) and under the following structural assumptions.

- Sequential exchangeability
  \[ Y_{K_{\pi=0}} \perp \perp A_k | L_{k-1}, D_{k-1}, Y_{k-1} = A_{k-1} = 0 \] \( \text{(38)} \)

- Positivity
  \[ \Pr(A_k = 0 | L_{k-1}, A_{k-1} = D_{k-1} = Y_{k-1} = 0) > 0 \text{ w.p.1} \] \( \text{(39)} \)
Consistency

\[
\text{If } A_k = 0 \text{ then } \mathcal{L}_k = L_{k=0}, \mathcal{D}_k = D_{k=0} \text{ and } Y_k = Y_{k=0}. \quad (40)
\]

Under these assumptions we have

\[
\begin{align*}
\Pr(Y_{k=0}^* = 1) &= K \sum_{k=1}^{K} \Pr(Y_{k=0}^* = 1, Y_{k-1}^* = 0) \\
&= K \sum_{k=1}^{K} \Pr(Y_{k=0}^* = 1, Y_{k-1}^* = \ldots = Y_1^* = 0) \\
&= \sum_{k=1}^{K} \sum_{l_0} \Pr(Y_{k=0}^* = 1, Y_{k-1}^* = \ldots = Y_1^* = 0 | L_0 = l_0) f(L_0 = l_0) \\
&= \sum_{k=1}^{K} \sum_{l_0} \Pr(Y_{k=0}^* = 1, Y_{k-1}^* = \ldots = Y_1^* = 0 | L_0 = l_0, A_1 = 0) f(L_0 = l_0) \\
&= \sum_{k=1}^{K} \sum_{l_0, d_1} \Pr(Y_1 = 0 | L_0 = l_0, D_1 = d_1, A_1 = 0) \\
&\quad \times \Pr(Y_{k=0}^* = 1, Y_{k-1}^* = \ldots = Y_2^* = 0 | L_0 = l_0, D_1 = d_1, A_1 = Y_1 = 0) \\
&\quad \times \Pr(D_1 = d_1 | L_0 = l_0, A_1 = 0) f(L_0 = l_0) \\
&= \sum_{k=1}^{K} \sum_{l_0, d_1, A_1} \Pr(Y_1 = 0 | L_0 = l_0, D_1 = d_1, A_1 = 0) \\
&\quad \times \Pr(Y_{k=0}^* = 1, Y_{k-1}^* = \ldots = Y_2^* = 0 | L_1 = l_1, D_1 = d_1, A_1 = Y_1 = 0) \\
&\quad \times f(L_1 = l_1 | L_0 = l_0, D_1 = d_1, A_1 = Y_1 = 0) \Pr(D_1 = d_1 | L_0 = l_0, A_1 = 0) f(L_0 = l_0) \\
&= \sum_{k=1}^{K} \sum_{l_0, d_1, A_1} \Pr(Y_1 = 0 | L_0 = l_0, D_1 = d_1, A_1 = 0) \\
&\quad \times \Pr(Y_{k=0}^* = 1, Y_{k-1}^* = \ldots = Y_2^* = 0 | L_1 = l_1, D_1 = d_1, A_2 = Y_1 = 0) \\
&\quad \times f(L_1 = l_1 | L_0 = l_0, D_1 = d_1, A_1 = Y_1 = 0) \Pr(D_1 = d_1 | L_0 = l_0, A_1 = 0) f(L_0 = l_0) \\
&= \sum_{k=1}^{K} \sum_{l_0, d_1, A_1} \Pr(Y_1 = 0 | L_0 = l_0, D_1 = d_1, A_1 = 0) \\
&\quad \times \Pr(Y_{k=0}^* = 1, Y_{k-1}^* = \ldots = Y_2^* = 0 | L_1 = l_1, D_1 = d_1, A_2 = Y_1 = 0) \\
&\quad \times f(L_1 = l_1 | L_0 = l_0, D_1 = d_1, A_1 = Y_1 = 0) \Pr(D_1 = d_1 | L_0 = l_0, A_1 = 0) f(L_0 = l_0)
\end{align*}
\]

(41)
\[
\sum_{k=1}^{K} \sum_{\bar{l}_k, \bar{d}_k} \Pr(Y_k = 0| L_0 = l_0, \bar{D}_1 = \bar{d}_1, A_1 = 0) \\
\times \Pr(Y_2 = 0| L_1 = l_1, \bar{D}_2 = \bar{d}_2, A_2 = Y_1 = 0) \\
\times \Pr(Y_k^{\pi=0} = 1, Y_{k-1}^{\pi=0} = \cdots = Y_3^{\pi=0} = 0| L_1 = l_1, \bar{D}_2 = \bar{d}_2, A_2 = Y_2 = 0) \\
\times \Pr(D_2 = d_2| L_1 = l_1, \bar{D}_1 = \bar{d}_1, A_1 = Y_1 = 0) f(L_1 = l_1| L_0 = l_0, \bar{D}_1 = \bar{d}_1, A_1 = Y_1 = 0) \\
\times \Pr(D_1 = d_1| L_0 = l_0, A_1 = 0) f(L_0 = l_0)
\]

\[
= \cdots
\]

\[
= \sum_{k=1}^{K} \sum_{\bar{l}_{k-1}, \bar{d}_k} \Pr(Y_k = 1| L_{k-1} = l_{k-1}, \bar{D}_k = \bar{d}_k, A_k = Y_{k-1} = 0) \\
\times \prod_{s=1}^{k} \Pr(D_s = d_s| L_{s-1} = l_{s-1}, \bar{D}_{s-1} = \bar{d}_{s-1}, A_s = Y_{s-1} = 0) \\
\times f(L_{s-1} = l_{s-1}| L_{s-2} = l_{s-2}, \bar{D}_{s-1} = \bar{d}_{s-1}, A_{s-1} = Y_{s-1} = 0) \\
\times \Pr(Y_{s-1} = 0| L_{s-2} = l_{s-2}, \bar{D}_{s-2} = \bar{d}_{s-2}, A_{s-1} = Y_{s-2} = 0)
\]

\[
= \sum_{k=1}^{K} \sum_{\bar{l}_{k-1}, \bar{d}_k} \Pr(Y_k = 1, Y_{k-1} = 0| L_{k-1} = l_{k-1}, \bar{D}_k = \bar{d}_k, A_0 = 0, L_{k-1} = l_{k-1}) \\
\times \prod_{s=1}^{K} \Pr(A_s = 0| L_{s-1} = l_{s-1}, A_{s-1} = D_{s-1} = Y_{s-1} = 0)
\]

\[
= \sum_{k=1}^{K} \mathbb{E} \left\{ \frac{Y_k(1 - D_k)(1 - A_k)(1 - Y_{k-1})}{\prod_{s=1}^{K} \Pr(A_s = 0| L_{s-1} = l_{s-1}, A_{s-1} = D_{s-1} = Y_{s-1} = 0)} \right\}
\]

\[
= \sum_{k=1}^{K} \mathbb{E} \left\{ Y_k(1 - D_k)(1 - A_k)(1 - Y_{k-1})W_k \right\},
\]

where the fourth and eighth equality hold under sequential exchangeability \[38\] and positivity \[39\], the sixth and 10th equality hold under consistency \[40\], the 11th equality holds under all three assumptions, and the 13th equality follows from the deterministic relation between the competing events \( D = 1 \) and \( Y = 1 \).

Along the same lines as \[35\], the following algebraic equivalence holds

\[
\sum_{k=1}^{K} \mathbb{E} \left\{ Y_k(1 - D_k)(1 - A_k)(1 - Y_{k-1})W_k \right\} \prod_{s=1}^{k-1} \mathbb{E} \left\{ (1 - Y_s)(1 - D_s)(1 - A_s)W_s \right\}
\]

\[
= \sum_{k=1}^{K} \mathbb{E} \left\{ Y_k(1 - D_k)(1 - A_k)(1 - Y_{k-1})W_k \right\} \prod_{s=1}^{k-1} \mathbb{E} \left\{ (1 - Y_s)(1 - Y_{s-1})(1 - D_{s-1})W_s \right\}
\]
Under an additional sequential exchangeability assumption

\[ \Pr(Y_k^{\pi=0} = 1) = \sum_{k=1}^{K} \frac{E[Y_k(1 - D_k)(1 - A_k)(1 - Y_{k-1})W_k]}{E[(1 - Y_s)(1 - D_s)(1 - A_s)W_s]} \prod_{s=1}^{k-1} \frac{E[(1 - Y_s)(1 - D_s)(1 - A_s)W_s]}{E[(1 - Y_s)(1 - D_s)(1 - A_s)W_s]} \]  

(44)

under assumptions (38)-(40).

B.4.2 Additional assumption for non-parametric identification of counterfactual cause-specific hazards

Under an additional sequential exchangeability assumption

\[ D_{k}^{\pi=0} \perp A_{k} | L_{k-1}, Y_{k-1}, D_{k-1} = A_{k-1} = 0, \]  

(45)

\( \tilde{\lambda}_{k}^{1,w_{ik}} \) (29) and \( \tilde{\lambda}_{k}^{2,w_{ik}} \) (30) can be interpreted as discrete-time counterfactual cause-specific hazards. That is, the time-dependent counterfactual cause-specific hazards \( \lambda_{k}^{j,\pi=0} (j \in \{ 1, 2 \}) \) are defined and identified as

\[ \lambda_{k}^{1,\pi=0} = \Pr(Y_{k}^{\pi=0} = 1 | Y_{k-1}^{\pi=0} = D_{k}^{\pi=0} = 0) = \tilde{\lambda}_{k}^{1,w_{ik}} \]  

(46)

\[ \lambda_{k}^{2,\pi=0} = \Pr(D_{k}^{\pi=0} = 1 | Y_{k-1}^{\pi=0} = D_{k-1}^{\pi=0} = 0) = \tilde{\lambda}_{k}^{2,w_{ik}} \]  

(47)

under assumptions (38)-(40) and (45), because under these assumptions we have

1.

\[ \Pr(Y_{k}^{\pi=0} = 1, D_{k}^{\pi=0} = Y_{k-1}^{\pi=0} = 0) = E[Y_k(1 - D_k)(1 - A_k)(1 - Y_{k-1})W_k], \]

as illustrated above,

2.

\[ \Pr(D_{k}^{\pi=0} = Y_{k-1}^{\pi=0} = 0) = \sum_{l_0} \Pr(Y_1 = D_1 = 0 | L_0 = l_0, A_1 = 0) \]

\[ \times \Pr(D_{k}^{\pi=0} = Y_{k-1}^{\pi=0} = D_{k-1}^{\pi=0} = \cdots = Y_{1}^{\pi=0} = D_{1}^{\pi=0} = 0 | L_0 = l_0, A_1 = 0, D_1 = Y_1 = 0) \]

\[ \times f(L_0 = l_0) \]
\[
\sum_{l_i} \Pr(Y_1 = D_1 = 0|L_0 = l_0, A_1 = 0) \\
\times \Pr(D_k = 0 = Y_{k-1}^\pi = D_{k-1}^\pi = \cdots = Y_2 = D_2^\pi = 0|L_1 = \bar{l}_1, A_1 = D_1 = Y_1 = 0) \\
\times f(L_1 = l_1|L_0 = l_0, A_1 = D_1 = Y_1 = 0) f(L_0 = l_0)
\]

\[
\sum_{l_i} \Pr(Y_1 = D_1 = 0|L_0 = l_0, A_1 = 0) \\
\times \Pr(D_k = 0 = Y_{k-1}^\pi = D_{k-1}^\pi = \cdots = Y_2 = D_2^\pi = 0|L_1 = \bar{l}_1, A_2 = D_1 = Y_1 = 0) \\
\times f(L_1 = l_1|L_0 = l_0, A_1 = D_1 = Y_1 = 0) f(L_0 = l_0)
\]

\[
\sum_{l_k-1} \Pr(D_k = 0|L_{k-1} = \bar{l}_{k-1}, A_k = D_{k-1} = Y_{k-1} = 0)
\]

\[
\times \prod_{s=1}^{k} \Pr(Y_{s-1} = D_{s-1} = 0|L_{s-2} = \bar{l}_{s-2}, A_{s-1} = D_{s-2} = Y_{s-2} = 0) \\
\times f(L_{s-1} = l_{s-1}|L_{s-2} = \bar{l}_{s-2}, A_{s-1} = D_{s-1} = Y_{s-1} = 0)
\]

\[
= \sum_{l_{k-1}} \prod_{s=1}^{k} \Pr(Y_{s-1} = D_{s-1} = \bar{A}_k = 0, L_{s-1} = \bar{l}_{s-1}, A_{s-1} = D_{s-1} = Y_{s-1} = 0)
\]

\[
= E \left[ \frac{(1 - Y_{k-1})(1 - D_k)(1 - A_k)}{\prod_{s=1}^{k} \Pr(A_s = 0|L_{s-1} = \bar{l}_{s-1}, A_{s-1} = D_{s-1} = Y_{s-1} = 0)} \right]
\]

\[
= E \left[ (1 - Y_{k-1})(1 - D_k)(1 - A_k)W_k \right],
\]

where the third and sixth equality hold under positivity (39) and the fact that sequential exchangeability assumptions (38) and (45) together imply

\[
(Y_{k-1}^\pi, D_{k-1}^\pi) \perp\!
\perp A_k|L_{k-1}, Y_{k-1} = D_{k-1} = A_{k-1} = 0,
\]

the 4th and 7th equality hold under consistency (40) and the 9th equality holds under all four assumptions, and similarly

3.

\[
\Pr(Y_{k-1}^\pi = D_{k-1}^\pi = \bar{0})
\]

\[
= E \left[ (1 - Y_{k-1})(1 - D_{k-1})(1 - A_{k-1})W_{k-1} \right]
\]

\[
= E \left[ (1 - Y_{k-1})(1 - D_{k-1})(1 - A_k)W_k \right],
\]

where the last equality follows along the same lines as (35).
It is important to note that sequential exchangeability assumption (45) is not necessary for identification of \( \Pr(Y_{K}^a = 0) \) by (43) or (44), but that it is nonetheless necessary for identification of the counterfactual cause-specific hazards \( \lambda_{k}^{j=0}(j \in \{1, 2\}) \) by (46) and (47), or, similarly, for interpretation of the factors in (33) in terms of (estimated) counterfactual cause-specific hazards. Along with the other three assumptions, assumption (45) thus permits to reconstruct the hypothetical population in which no one were exposed from the observed data in such a way that each factor of the Aalen-Johansen characterization of \( \Pr(Y_{K}^a = 0) \) (20) that involves unobserved counterfactual data \( (D_{a}^{\pi=0}_k, Y_{a}^{\pi=0}_k) \) (for \( k \leq K \)) can be estimated from the observed factual data \((L_k, A_k, D_k, Y_k)\) by an IPC weighted equivalent.

However, as noted elsewhere (Hernán, 2010; Young et al., 2020; Martinussen et al., 2020), the contrasts of these counterfactual cause-specific hazards, although counterfactual, cannot generally be endowed a causal interpretation due to a built-in selection bias when comparing two distinct (counterfactual) populations that cannot be identified at baseline.

### B.4.3 Single world intervention graphs

Although sequential exchangeability conditions (38) and (45) may be quite difficult to interpret, these conditional independencies involving counterfactuals can be graphically interrogated from single world intervention graphs (SWIGs) (Richardson and Robins, 2013b). Intuitively, a SWIG can be thought of as a causal diagram that explicitly depicts a hypothetical world in which certain nodes have been intervened upon according a pre-specified hypothetical intervention. For more details about SWIGs and how to construct them, we refer the reader to Richardson and Robins (2013a), Richardson and Robins (2013b), or Appendix A in Young et al. (2020), for a shorter and more targeted description in the context of competing and censoring events.

In this section, we specifically focus on a causal diagram that graphically represents a set of assumptions under which sequential exchangeability conditions (38) and (45) hold, as can be evaluated from its corresponding SWIG obtained under a hypothetical intervention that eliminates exposure or, in other words, sets \( A_{k} \) to 0. Consider the causal diagram template depicted in Figure 7. We refer to it as a template because it is meant as a simplification that only explicitly depicts two time waves \( k-1 \) and \( k \), but that suffices for illustrative purposes. The node \( U \) represents a (possibly vector-valued) set of unmeasured confounders of the relation between measured confounders \( L_{k} \), on the one hand, and hospital death and discharge, on the other hand. In time-to-event settings, \( U \) is often conceived of an unobserved ‘frailty’ component. The edge from \( L_{0} \) to \( A_{k-1} \) is dashed to imply the existence of previous time waves between baseline and interval \( k-1 \). Figure 8 depicts the SWIG template derived from Figure 7 obtained under a hypothetical intervention that eliminates exposure.
Under consistency (40), the causal diagram in Figure 7 implies sequential exchangeability (38) for any \( k \in \{0, ..., K\} \) by the absence of unblocked backdoor paths on the SWIG in Figure 8 between the observed value \( A_k \) and future counterfactual outcomes \( Y_{k=0} \) conditional on \( (L_{k-1}, D_{k-1}, A_{k-1} = Y_{k-1} = 0) \). Furthermore, under consistency (40), also sequential exchangeability (45) is implied for any \( k \in \{0, ..., K\} \) by the absence of unblocked backdoor paths on the SWIG between the observed value \( A_k \) and future counterfactual outcomes \( D_{k=0} \) conditional on \( (L_{k-1}, Y_{k-1}, A_{k-1} = D_{k-1} = 0) \).

Importantly, this graphical representation illustrates that exchangeability conditions (38) and (45)
do not preclude unmeasured confounding of the relation between the outcome of interest and its competing event, nor of the relation between the outcome (competing event) at time interval \( k - 1 \) and the outcome (competing event) at later intervals \( \geq k \).

### B.4.4 Connection with other estimators

Upon re-weighing patient time contributions of each patient \( i \) in the risk set of each considered interval \( k \) by \( \hat{W}_{ik}' = (1 - A_{ik}) \hat{W}_{ik} \), both estimators (22) and (26) (Appendices B.1 and B.3) can, in the absence of censoring due to loss to follow-up or administrative end of the study, be shown to be algebraically equivalent to the IPC weighted Aalen-Johansen estimator (34) and the IPC weighted empirical cumulative distribution function (36) under non-parametric estimation of the weights.

**Treating HAI onset as a non-informative censoring event**  This is readily apparent for (22) (36) in the main text; see Appendix B.1 from the above results. Moreover, under assumptions (38)-(40) and (45), the (marginal) counterfactual cause-specific hazards \( \lambda_k^{1, \pi = 0} \) \((j \in \{1, 2\})\) can be expressed as weighted sums of the corresponding (conditional) observable cause-specific hazards \( \lambda_k^j(\bar{r}_{k-1}) \) within strata defined by the history of confounders \( \bar{L}_{k-1} \):

\[
\begin{align*}
\lambda_k^{1, \pi = 0} &= \frac{\Pr(Y_k^{\pi = 0} = 1, D_k^{\pi = 0} = Y_{k-1}^{\pi = 0} = \emptyset)}{\Pr(D_k^{\pi = 0} = Y_{k-1}^{\pi = 0} = 0)} = \frac{\sum \lambda_k^1(\bar{r}_{k-1}) g(\bar{r}_{k-1})}{\sum \lambda_{k-1} g(\bar{r}_{k-1})} \\
\lambda_k^{2, \pi = 0} &= \frac{\Pr(D_k^{\pi = 0} = 1, Y_k^{\pi = 0} = D_{k-1}^{\pi = 0} = 0)}{\Pr(Y_{k-1}^{\pi = 0} = D_{k-1}^{\pi = 0} = 0)} = \frac{\sum \lambda_k^2(\bar{r}_{k-1}) h(\bar{r}_{k-1})}{\sum \lambda_{k-1} h(\bar{r}_{k-1})},
\end{align*}
\]

with

\[
\begin{align*}
\lambda_k^1(\bar{r}_{k-1}) &= \Pr(Y_k = 1 \mid Y_{k-1} = D_k = A_k = 0, \bar{L}_{k-1} = \bar{r}_{k-1}) \\
\lambda_k^2(\bar{r}_{k-1}) &= \Pr(D_k = 1 \mid Y_{k-1} = D_{k-1} = A_k = 0, \bar{L}_{k-1} = \bar{r}_{k-1}) \\
g(\bar{r}_{k-1}) &= \frac{\prod_{s=1}^k \Pr(A_s = 0 \mid \bar{L}_{s-1} = \bar{r}_{s-1}, A_{s-1} = D_{s-1} = Y_{s-1} = 0)}{\prod_{s=1}^k \Pr(A_s = 0 \mid \bar{L}_{s-1} = \bar{r}_{s-1}, A_{s-1} = D_{s-1} = Y_{s-1} = 0)} \\
h(\bar{r}_{k-1}) &= \frac{\prod_{s=1}^k \Pr(Y_{k-1} = D_{k-1} = A_k = 0, \bar{L}_{k-1} = \bar{r}_{k-1})}{\prod_{s=1}^k \Pr(A_s = 0 \mid \bar{L}_{s-1} = \bar{r}_{s-1}, A_{s-1} = D_{s-1} = Y_{s-1} = 0)}.
\end{align*}
\]

This characterization clarifies that (22) is a special case of (34) under the stronger assumption that the marginal counterfactual hazards equal the marginal factual observable hazards (as clarified at the end of Appendix B.1) or, in other words that \( \bar{L}_k \) equals the empty set for every \( k \), such that the hazards \( \lambda_k^1(\bar{r}_{k-1}) \) and \( \lambda_k^2(\bar{r}_{k-1}) \), and weights \( g(\bar{r}_{k-1}) \) and \( h(\bar{r}_{k-1}) \) are rendered dependent of only \( k \).

Estimation by expression (34), on the other hand, is done under the assumption that the conditional counterfactual hazards \( \lambda_k^{j, \pi = 0}(\bar{r}_{k-1}) \) equal the conditional factual observable hazards \( \lambda_k^j(\bar{r}_{k-1}) \) under a sufficient set \( \bar{L}_k \)

\[
\lambda_k^{1, \pi = 0}(\bar{r}_{k-1}) = \Pr(Y_k^{\pi = 0} = 1 \mid \bar{L}_{k-1} = \bar{r}_{k-1}, D_k^{\pi = 0} = Y_{k-1}^{\pi = 0} = 0) = \lambda_k^1(\bar{r}_{k-1})
\]
\[ \lambda_k^{2,\pi=0}(t_{k-1}) \equiv \Pr(D_k^{\pi=0} = 1 | \overline{L}_k = t_{k-1}, Y_k = 0, D_{k-1}^{\pi=0} = 0) = \lambda_k^2(t_{k-1}). \]

Likewise, under assumptions (38)-(40) and (45), the (marginal) counterfactual cause-specific hazards \( \lambda_k^{j,\pi=0} \) \((j \in \{1, 2\})\) are identified by \( \tilde{\lambda}_k^{1,\pi=0} \) and \( \lambda_k^{2,\pi=0} \). If \( \overline{L}_k \) equals the empty set for every \( k \leq K \), then \( W_k \) is rendered dependent of only \( k \) and the weights cancel out in the numerator and denominator of (29) and (30), such that, for every \( k \leq K \), we have

\[
\tilde{\lambda}_k^{1,\pi=0} = \lambda_k^1 \\
\lambda_k^{2,\pi=0} = \lambda_k^2.
\]

Treating HAI onset as a time-dependent exclusion criterion (Schumacher et al., 2007) To provide some intuition into the impact of re-weighing patient time contributions by \( \hat{W}_i' \) in application of the estimator originally proposed by Schumacher et al. (2007), recall that this estimator can be expressed as (see Appendix B.3)

\[
\hat{\Pr}(\tilde{T} \leq t_K, \tilde{\epsilon} = 1) \over \hat{\Pr}(\tilde{T} > t_K) + \hat{\Pr}(\tilde{T} \leq t_K, \tilde{\epsilon} = 1) + \hat{\Pr}(\tilde{T} \leq t_K, \tilde{\epsilon} = 2) = \frac{\hat{\Pr}(\tilde{T} \leq t_K, \tilde{\epsilon} = 1)}{1 - \hat{\Pr}(\tilde{T} \leq t_K, \tilde{\epsilon} = 0)},
\]

where each probability is estimated non-parametrically by the Aalen-Johansen estimator. In the absence of censoring due to loss to follow-up or administrative end of the study, these correspond to the following empirical cumulative distribution functions (see Appendix A.2)

\[
\hat{\Pr}(\tilde{T} \leq t_K, \tilde{\epsilon} = 0) = \sum_{k=1}^{K} E_n[A_k(1 - A_{k-1})(1 - Y_{k-1})(1 - D_{k-1})]
\]

\[
\hat{\Pr}(\tilde{T} \leq t_K, \tilde{\epsilon} = 1) = \sum_{k=1}^{K} E_n[Y_k(1 - Y_{k-1})(1 - D_k)(1 - A_k)]
\]

\[
\hat{\Pr}(\tilde{T} \leq t_K, \tilde{\epsilon} = 2) = \sum_{k=1}^{K} E_n[D_k(1 - D_{k-1})(1 - A_k)(1 - Y_{k-1})]
\]

\[
\hat{\Pr}(\tilde{T} > t_K) = E_n[(1 - Y_K)(1 - D_K)(1 - A_K)].
\]

Upon weighing the contribution of each patient \( i \) at each interval \( k \) by \( \hat{W}_i' \), the numerator of expression (48) becomes

\[
\sum_{k=1}^{K} E_n[Y_k(1 - Y_{k-1})(1 - D_k)(1 - A_k)\hat{W}_i']
\]

and the denominator becomes

\[
E_n[(1 - Y_K)(1 - D_K)(1 - A_K)\hat{W}_i'] + \sum_{k=1}^{K} E_n[Y_k(1 - Y_{k-1})(1 - D_k)(1 - A_k)\hat{W}_i'] + D_k(1 - D_{k-1})(1 - A_k)(1 - Y_{k-1})\hat{W}_i'.
\]
\[ E_n[(1 - Y_K)(1 - D_K)(1 - A_K)\hat{W}_K'] \]
\[ + \sum_{k=1}^{K} E_n[(Y_k(1 - D_k) + D_k)(1 - A_k)(1 - Y_{k-1})(1 - D_{k-1})\hat{W}_k'] \]
\[ = E_n[(1 - Y_K)(1 - D_K)(1 - A_K)\hat{W}_K'] \]
\[ + \sum_{k=1}^{K} E_n[(1 - (1 - Y_k)(1 - D_k))(1 - A_k)(1 - Y_{k-1})(1 - D_{k-1})\hat{W}_k'] \]
\[ = E_n[(1 - Y_K)(1 - D_K)(1 - A_K)\hat{W}_K'] \]
\[ + \sum_{k=1}^{K} E_n[(1 - A_k)(1 - Y_{k-1})(1 - D_{k-1})\hat{W}_k'] - \sum_{k=1}^{K} E_n[(1 - Y_k)(1 - D_k)(1 - A_k)\hat{W}_k'] \]
\[ = \sum_{k=1}^{K} E_n[(1 - Y_{k-1})(1 - D_{k-1})(1 - A_k)\hat{W}_k] - \sum_{k=1}^{K-1} E_n[(1 - Y_k)(1 - D_k)(1 - A_k)\hat{W}_k'] \]
\[ = \sum_{k=0}^{K-1} E_n[(1 - Y_k)(1 - D_k)(1 - A_{k+1})\hat{W}_{k+1}] - \sum_{k=1}^{K-1} E_n[(1 - Y_k)(1 - D_k)(1 - A_k)\hat{W}_k'] \]
\[ = E_n[(1 - Y_0)(1 - D_0)(1 - A_1)\hat{W}_1] \]
\[ = E_n[(1 - Y_0)(1 - D_0)(1 - A_0)\hat{W}_0'] = 1. \]

The last two equalities follow from the fact that, for every \( k \leq 0 \), we have \( Y_k = D_k = A_k = 0 \), and from (35).

Or shorter, after IPC weighting, the denominator reduces to 1 simply because
\[ 1 - \sum_{k=1}^{K} E_n[A_k(1 - A_{k-1})(1 - Y_{k-1})(1 - D_{k-1})\hat{W}_k'] \]
\[ = 1 - \sum_{k=1}^{K} E_n[A_k(1 - A_k)(1 - Y_{k-1})(1 - D_{k-1})\hat{W}_k] = 1 - 0 = 1. \]

Expression (48) clearly illustrates that the estimator proposed by Schumacher et al. (2007) expresses the fraction of deceased patients by landmark interval \( K \) among patients who have not acquired an infection by interval \( K \). In other words, at each successive landmark interval \( K \), the considered population is implicitly reduced to those patients who either remained hospitalized and uninfected until the end of interval \( K \) or have died or been discharged by interval \( K \) while being uninfected, as indicated by the scaling factor in the denominator, which sums the probability of belonging to each of these mutually exclusive groups, i.e. \( \Pr(\hat{T} > t_K) + \Pr(\hat{T} < t_K, \tilde{c} = 1) + \Pr(\hat{T} < t_K, \tilde{c} = 2) \).

IPC weighting by \( \hat{W}_k' \), on the other hand, aims to construct a pseudo-population that equals the original population under the scenario where no patient would have acquired an infection by interval \( K \) or, equivalently, all patients would have remained uninfected until interval \( K \) or would have died or been discharged by interval \( K \) while being uninfected, so as to evaluate which fraction of this hypothetical cohort of patients would have died at the hospital by interval \( K \). Note that the scaling
factor in the denominator in this weighted population reduces to 1 at each landmark interval $K$, because after weighting, each patient in this hypothetical cohort belongs to one of these mutually exclusive (hypothetical) groups at each landmark interval $K$. In other words, after weighting, the considered population at each landmark interval $K$ corresponds to the original population under the aforementioned hypothetical scenario.

**Connection with alternative estimators in Bekaert et al. (2010)**

To illustrate the connection with the estimators of $\Pr(Y^K = 0) \equiv \Pr(T^K = 0, \epsilon^K = 0 = 1)$ from Bekaert et al. (2010), we first introduce some additional notation. Let $A'_k = A_k$ for every $k$: $t_k \leq T$. For every $k$: $t_k > T$, $A'_k$ is undefined. Furthermore, let $\epsilon'_{ik} = j, j \in \{0, 1, 2\}$, denote the event status of patient $i$ by interval $k$, where $j = 0$ in the absence of an event, $j = 1$ in case of hospital death, or $j = 2$ in case of hospital discharge.

The naive estimator from Bekaert et al. (2010) (expression (2) in their paper) for the counterfactual exposure path $a = 0$ then corresponds with

$$\sum_{i=1}^{n} 1_{\epsilon'_{ik} = 1} \prod_{k=1}^{K} \{1_{A'_k = 0} 1_{\epsilon'_{i,k-1} = 0} + 1_{\epsilon'_{i,k-1} \neq 0}\}$$

which, in our discrete time process notation, can be re-expressed as

$$\frac{\sum_{i=1}^{n} 1_{\epsilon'_{ik} = 1} \prod_{k=1}^{K} 1_{A_k = 0}}{\sum_{i=1}^{n} \prod_{k=1}^{K} 1_{A_k = 0}} = \frac{\sum_{i=1}^{n} 1_{T_i \leq t_K, \epsilon_i = 1} 1_{A_{i,k} = 0}}{\sum_{i=1}^{n} 1_{A_{i,k} = 0}} = \frac{E_n[Y_K(1 - A_K)]}{E_n[1 - A_K]}.$$

Upon further rewriting the latter expression, it can be shown to correspond with the estimator proposed by Schumacher et al. (2007) [28]

$$\frac{E_n[Y_K(1 - A_K)]}{E_n[1 - A_K]} = \sum_{k=1}^{K} E_n\left[\frac{Y_k(1 - Y_{k-1})(1 - A_k)}{P_n(A_K = 0)}\right]$$

$$= \sum_{k=1}^{K} E_n\left[\frac{Y_k(1 - Y_{k-1})(1 - D_k)(1 - A_k)}{P_n(A_K = 0)}\right]$$

$$= \sum_{k=1}^{K} E_n\left[Y_k(1 - Y_{k-1})(1 - D_k)(1 - A_k)\hat{W}_K^{\dagger}\right],$$

where the first equality holds because as before (see Appendix [B.3]), for each $k \leq K$, we have

$$Y_k(1 - A_K) = \begin{cases} 1 & \text{iff } Y_k(1 - A_k) = 1; \\ 0 & \text{otherwise}, \end{cases}$$

and the second equality follows from the deterministic relation between $D_k$ and $Y_k$. This equivalence has also been highlighted by von Cube et al. (2020a) and is demonstrated in their Appendix B.2.2.
The IP weighted estimator from [Bekaert et al. (2010)](expression (3) in their paper) for the counterfactual exposure path \( \pi = 0 \) (expression (34) and (36) since this IP weighted estimator of Bekaert et al. (2010) is again algebraically equivalent with the IPC weighted estimators (34) and (36) since

\[
\sum_{i=1}^{n} \frac{1_{i',k=1} \prod_{k=1}^{K} \frac{1_{A'_k=0} 1_{i',k-1=0} + 1_{i',k-1 \neq 0}}{\Pr(A'_k = 0|\epsilon_{i',k-1}, \overline{A}_{i',k-1}, \overline{T}_{i,k-1})}}{\sum_{i=1}^{n} \prod_{k=1}^{K} \frac{1_{A'_k=0} 1_{i',k-1=0} + 1_{i',k-1 \neq 0}}{\Pr(A'_k = 0|\epsilon_{i',k-1}, \overline{A}_{i',k-1}, \overline{T}_{i,k-1})}},
\]

with \( \Pr(A'_k = 0|\epsilon_{i',k-1}, \overline{A}_{i',k-1}, \overline{T}_{i,k-1}) \) defined to equal 1 whenever \( (\epsilon_{i',k-1} \neq 0, A'_i,k-1 = 0) \). In our discrete time process notation, this IP weighted estimator can be re-expressed as

\[
\sum_{i=1}^{n} \frac{1_{i',k=1} \prod_{k=1}^{K} \frac{1_{A_i,k=0}}{\Pr(A_i,k = 0|\epsilon_{i',k-1}, \overline{A}_{i',k-1}, \overline{T}_{i,k-1})}}{\sum_{i=1}^{n} \prod_{k=1}^{K} \frac{1_{A_i,k=0}}{\Pr(A_i,k = 0|\epsilon_{i',k-1}, \overline{A}_{i',k-1}, \overline{T}_{i,k-1})}} = \frac{E_n}{E_n} \left[ \frac{Y (1 - A_K)}{\prod_{k=1}^{K} \Pr(A_k = 0|\overline{L}_{k-1}, \overline{A}_{k-1}, \overline{D}_{k-1}, Y_{k-1})} \right] = \frac{E_n}{E_n} \left[ \frac{1 - A_K}{\prod_{k=1}^{K} \Pr(A_k = 0|\overline{L}_{k-1}, \overline{A}_{k-1}, \overline{D}_{k-1}, Y_{k-1})} \right]
\]

From this alternative expression, it is clear that, under non-parametric estimation of the weights, this IP weighted estimator of [Bekaert et al. (2010)](expression (34) and (36) since

\[
E_n \left[ \frac{Y (1 - A_K)}{\prod_{k=1}^{K} P_n(A_k = 0|\overline{L}_{k-1}, \overline{A}_{k-1}, \overline{D}_{k-1}, Y_{k-1})} \right] = \sum_{k=1}^{K} E_n \left[ \frac{Y (1 - Y_{k-1})(1 - A_k)}{\prod_{s=1}^{k} P_n(A_s = 0|\overline{L}_{s-1}, \overline{A}_{s-1}, \overline{D}_{s-1}, Y_{s-1})} \right] = \sum_{k=1}^{K} E_n \left[ \frac{Y (1 - Y_{k-1})(1 - D_K)(1 - A_k)}{\prod_{s=1}^{k} P_n(A_s = 0|\overline{L}_{s-1}, \overline{A}_{s-1}, \overline{D}_{s-1}, Y_{s-1})} \right] = \sum_{k=1}^{K} E_n \left[ \frac{Y (1 - Y_{k-1})(1 - D_K)(1 - A_K)}{\prod_{s=1}^{k} P_n(A_s = 0|\overline{L}_{s-1}, A_{s-1} = D_{s-1} = Y_{s-1} = 0)} \right] = \sum_{k=1}^{K} E_n \left[ Y (1 - Y_{k-1})(1 - D_K)(1 - A_K) \overline{W}_k \right],
\]

55
where the first equality again holds because, for each \( k \leq K \), we have \( Y_k(1 - A_K) = Y_k(1 - A_k) \), and the second equality follows from the deterministic relation between \( D_k \) and \( Y_k \).

**Connection with alternative estimators in **[Young et al. (2020)](https://www.example.com) Following [Young et al. (2020)](https://www.example.com), it can be shown that assumptions [38]-[40] give rise to yet another IPC weighted estimator for \( \Pr(Y^\tau = 0) = \Pr(T^\tau = 0, \epsilon^\tau = 0) = 1 \):

\[
\sum_{k=1}^{K} \sum_{s=1}^{k-1} \frac{E_n \left[ Y_k(1 - Y_{k-1})(1 - A_k)\hat{W}_k^* \right]}{E_n \left[ (1 - Y_{k-1})(1 - A_k)\hat{W}_k^* \right]} \prod_{s=1}^{k-1} \frac{E_n \left[ (1 - Y_s)(1 - A_s)\hat{W}_s^* \right]}{E_n \left[ (1 - Y_{s-1})(1 - A_s)\hat{W}_s^* \right]},
\]

with weights

\[
\hat{W}_k^* = \prod_{s=1}^{k} \frac{1}{\Pr(A_s = 0|T_{s-1}, D_{s-1}, A_{s-1} = Y_{s-1} = 0)}
\]

instead of \( \hat{W}_k \). In the absence of censoring due to loss to follow-up or administrative end of the study and using a non-parametric estimator for \( \hat{W}_k^* \), this alternative IPC weighted estimator is again algebraically equivalent to [34] and [36] since

\[
\sum_{k=1}^{K} \sum_{s=1}^{k-1} \frac{E_n \left[ Y_k(1 - Y_{k-1})(1 - A_k)\hat{W}_k^* \right]}{E_n \left[ (1 - Y_{k-1})(1 - A_k)\hat{W}_k^* \right]} \prod_{s=1}^{k-1} \frac{E_n \left[ (1 - Y_s)(1 - A_s)\hat{W}_s^* \right]}{E_n \left[ (1 - Y_{s-1})(1 - A_s)\hat{W}_s^* \right]}
\]

\[
= \sum_{k=1}^{K} E_n \left[ Y_k(1 - Y_{k-1})(1 - A_k)\hat{W}_k^* \right]
\]

\[
= \sum_{k=1}^{K} E_n \left[ Y_k(1 - Y_{k-1})(1 - D_k)(1 - A_k)\hat{W}_k^* \right]
\]

\[
= \sum_{k=1}^{K} E_n \left[ Y_k(1 - Y_{k-1})(1 - D_k)(1 - A_k)\hat{W}_k \right],
\]

where the first equality holds because

\[
E_n \left[ (1 - Y_k)(1 - A_{k+1})\hat{W}_{k+1}^* \right] \]

\[
= E_n \left[ \frac{(1 - Y_k)(1 - A_{k+1})\hat{W}_{k+1}^*}{P_n(A_{k+1} = 0|\bar{T}_k, D_k, Y_k = A_k = 0)} \right]
\]

\[
= \sum_{\bar{t}_k, \bar{d}_k} E_n \left[ \frac{(1 - Y_k)(1 - A_{k+1})\hat{W}_k^*}{P_n(A_{k+1} = 0|\bar{T}_k = \bar{t}_k, D_k = \bar{d}_k, Y_k = A_k = 0)} \right]  
\times P_n(\bar{T}_k = \bar{t}_k, \bar{D}_k = \bar{d}_k, Y_k = A_k = 0)
\]

\[
= \sum_{\bar{t}_k, \bar{d}_k} E_n \left[ (1 - Y_k)(1 - A_k)\hat{W}_k^* \right]  
\times P_n(\bar{T}_k = \bar{t}_k, \bar{D}_k = \bar{d}_k, Y_k = A_k = 0)
\]

\[
= E_n \left[ (1 - Y_k)(1 - A_k)\hat{W}_k^* \right],
\]

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the second equality holds because \( Y_k = Y_k(1 - D_k) \) by the deterministic relation between \( Y_k \) and \( D_k \), and the last equality holds because

\[
(1 - D_k)\hat{W}_k^* = \frac{1 - D_k}{\prod_{s=1}^{k} P_n(A_s = 0|L_{s-1}, D_s - 1, A_{s-1} = Y_{s-1} = 0)} \prod_{s=1}^{k} P_n(A_s = 0|L_{s-1}, A_{s-1} = D_{s-1} = Y_{s-1} = 0)
\]

Moreover, under assumptions (38)-(40), the factors of this alternative IPC weighted estimator can be interpreted in terms of counterfactual discrete time subdistribution hazard estimates (Young et al., 2020).

\[
\sum_{k=1}^{K} E_n \left[ Y_k(1 - Y_{k-1})(1 - A_k)\hat{W}_k^* \right] \prod_{s=1}^{k-1} E_n \left[ (1 - Y_s)(1 - A_s)\hat{W}_s^* \right] \prod_{s=1}^{k-1} \left\{ 1 - E_n \left[ Y_s(1 - Y_{s-1})(1 - A_s)\hat{W}_s^* \right] \right\}
\]

\[
= \sum_{k=1}^{K} \hat{\lambda}_k^{*\pi=0} \prod_{s=1}^{k-1} (1 - \hat{\lambda}_s^{*\pi=0}),
\]

with \( \hat{\lambda}_k^{*\pi=0} \equiv \Pr(Y_k^{\pi=0} = 1|Y_{k-1}^{\pi=0} = 0) \).
C Decomposition of accumulated weight

Censoring leads to weight being transferred in the analysis from censored to uncensored individuals. In this section we illustrate more formally how the weight that gets transferred can be expressed as part of the total weight accumulated by individuals that have remained uncensored until interval \( k \).

Following Appendix B.1 we have

\[
W^o_k = \prod_{s=1}^{k} \frac{1}{1 - \Pr(T \in (t_{s-1}, t_s], \tilde{c} = 0 | T > t_{s-1})}
\]

\[
= \prod_{s=1}^{k} \frac{1}{1 - \Pr(A_s = 1 | Y_{s-1} = D_{s-1} = A_{s-1} = 0)}
\]

\[
= 1 + \frac{1 - \prod_{s=1}^{k} \Pr(A_s = 1 | Y_{s-1} = D_{s-1} = A_{s-1} = 0)}{\prod_{s=1}^{k} \Pr(A_s = 1 | Y_{s-1} = D_{s-1} = A_{s-1} = 0)}
\]

For instance, in the special case where \( k = 3 \), we have

\[
W^o_3 = 1 + \frac{1 - (1 - P_1)(1 - P_2)(1 - P_3)}{(1 - P_1)(1 - P_2)(1 - P_3)}
\]

\[
= 1 + \frac{1 - (1 - P_3) + (1 - P_3) - (1 - P_2)(1 - P_3) + (1 - P_2)(1 - P_3) - (1 - P_1)(1 - P_2)(1 - P_3)}{(1 - P_1)(1 - P_2)(1 - P_3)}
\]

\[
= 1 + \frac{P_3 + P_2(1 - P_3) + P_1(1 - P_2)(1 - P_3)}{(1 - P_1)(1 - P_2)(1 - P_3)}
\]

\[
= 1 + \frac{P_1}{1 - P_1} + \frac{P_2}{1 - P_2} + \frac{P_3}{1 - P_3}
\]

with \( P_s \) shorthand notation for \( \Pr(A_s = 1 | Y_{s-1} = D_{s-1} = A_{s-1} = 0) \).

Alternatively, we can obtain

\[
W^o_3 = 1 + \frac{1 - (1 - P_3) + (1 - P_3) - (1 - P_1)(1 - P_2) + (1 - P_1)(1 - P_2) - (1 - P_1)(1 - P_2)(1 - P_3)}{(1 - P_1)(1 - P_2)(1 - P_3)}
\]

\[
= 1 + \frac{P_1 + P_2(1 - P_1) + P_3(1 - P_2)(1 - P_1)}{(1 - P_1)(1 - P_2)(1 - P_3)}
\]

\[
= 1 + \frac{P_1}{1 - P_1} + \frac{P_2}{1 - P_2} + \frac{P_3}{1 - P_3}
\]

Generalizing from the special case where \( k = 3 \), we can see that in the general case, upon re-writing the numerator of the fraction as a telescoping sum, we obtain the following (retrospective) decomposition in terms of the weight directly received from patients censored in each interval \( s \leq k \) and the indirect weight received through the same patients who have, in turn, also accumulated/received from patients censored in earlier intervals \( s' < s \):

\[
W^o_k = 1 + \frac{1 - \sum_{s=2}^{k} \prod_{s'=s}^{k} (1 - P_{s'}) + \sum_{s=2}^{k} \prod_{s'=s}^{k} (1 - P_{s'}) - \sum_{s=1}^{k} \prod_{s'=1}^{k} (1 - P_{s'})}{\prod_{s=1}^{k} (1 - P_s)}
\]

\[
= 1 + \frac{\sum_{s=1}^{k} P_s \prod_{s'=s+1}^{k} (1 - P_{s'})}{\prod_{s=1}^{k} (1 - P_s)}
\]

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\[ W_k^\circ = 1 + \frac{1}{1 - P_k} \prod_{s=1}^{k-1} (1 - P_s) + \sum_{s=1}^{k-1} \prod_{s'=1}^{s-1} (1 - P_{s'}) - \prod_{s=1}^{k} (1 - P_s) \]

An alternative (prospective) decomposition in terms of the weight patients censored in interval \( s \leq k \) transfer forward in time until interval \( k \) can be obtained upon re-writing the numerator of the fraction as an alternative telescoping sum.

The weight directly transferred by patients censored in interval \( s \) is cumulatively carried forward over time to patients censored in later intervals \( s' > s \).
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