Marginal structural models for partial exposure regimes

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SUMMARY
Intensive care unit (ICU) patients are highly susceptible to hospital-acquired infections due to their poor health and many invasive therapeutic treatments. The effect on mortality of acquiring such infections is, however, poorly understood. Our goal is to quantify this using data from the National Surveillance Study of Nosocomial Infections in ICUs (Belgium). This is challenging because of the presence of time-dependent confounders, such as mechanical ventilation, which lie on the causal path from infection to mortality. Standard statistical analyses may be severely misleading in such settings and have shown contradictory results. Inverse probability weighting for marginal structural models may instead be used but is not directly applicable because these models parameterize the effect of acquiring infection on a given day in ICU, versus “never” acquiring infection in ICU, and this is ill-defined when ICU discharge precedes that day. Additional complications arise from the informative censoring of the survival time by hospital discharge and the instability of the inverse weighting estimation procedure. We accommodate this by introducing a new class of marginal structural models for so-called partial exposure regimes. These describe the effect on the hazard of death of acquiring infection on a given day \( s \), versus not acquiring infection “up to that day,” had patients stayed in the ICU for at least \( s \) days.

Keywords: Causal inference; Direct effect; ICU; Intermediate variables; Marginal structural models; Nosocomial infection; Time-dependent confounding.

1. INTRODUCTION
Intensive care unit (ICU) patients are estimated to have 5–10 times higher risk of acquiring nosocomial, that is, hospital acquired, infections than patients in other hospital units, due to their poor health and many invasive therapeutic treatments. These infections are believed to account for 50% of all major

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complications of hospitalization and are considered to have a substantial impact on morbidity, mortality, and medical costs (Gaynes, 1997). In 1985, the Study on the Efficacy of Nosocomial Infection Control (Haley and others, 1985) demonstrated that surveillance of nosocomial infections can reduce infection rates by as much as 30%, provided that sufficient infection control staff and adequate surveillance are available. Since then, surveillance of nosocomial infections has played a fundamental role in assessing and improving the quality of medical care.

In 1995, the Scientific Institute of Public Health—Louis Pasteur (Belgium)—set up a national surveillance network in ICUs in collaboration with the Belgian Society for Intensive Care and Emergency Medicine (Suetens, Jans and others, 1999). The aim of this network is twofold: to assist individual ICU’s to obtain local incidence statistics for ICU-acquired nosocomial pneumonia (NP, one of the main nosocomial infections) and bloodstream infection and to offer national statistics in parallel to guide the interpretation of each ICU’s performance. Surveillance and the definition of NP that we will adopt follow a standard protocol based on a Europe-wide consensus reached in the Hospitals in Europe Link for Infection Control through Surveillance project (Suetens, Savey and others, 2003).

In this article, we will use data collected through the network to quantify the effect of NP on mortality in ICU patients. This is a complex problem for various reasons. First, the association between infection and mortality is disturbed by time-dependent confounders. For instance, daily exposure to invasive treatments such as mechanical ventilation or the presence of a central vascular catheter increases the risk of NP, and the poor health conditions leading to these treatments are also indicative of an increased mortality risk. These confounders lie on the causal path from infection to mortality because infection makes it more likely that the patient will receive invasive therapeutic treatments. Standard adjustment approaches, such as time-dependent proportional hazards regression, will then usually give biased results (see, e.g. Andersen, 1986; Bryan and others, 2004; Kalbfleisch and Prentice, 2002; Robins, 1986, 1997b; Robins, Hernán and Brumback, 2000; Vansteelandt, 2007). Second, the censoring of the survival time upon hospital discharge may be informative because the decision to discharge patients is closely related to their health status, so that mortality rates may differ substantially between those who are discharged on a given day and those who are not.

The problem of estimating the mortality rate attributable to NP has received much attention in the intensive care literature (see, e.g. Carlet, 2001; Vincent, 2003; Schumacher and others, 2007) as a reliable estimate is not only of theoretical interest but also important for determining the potential benefits of new drugs. Common practice is to fit logistic regression models for mortality in ICU, adjusting for NP status upon ICU discharge, for length of stay in ICU, and possibly for time-dependent variables measured prior to infection (Mertens, Suetens and others, 2006). An alternative approach is to base inference on proportional hazards models for time to death, adjusting for either NP status upon ICU discharge or time-dependent NP status and additionally for time-dependent variables measured prior to infection. These analyses ignore the aforementioned problems and empirical results are therefore highly controversial, with several studies reporting relative risk estimates for mortality ranging from neutral to severely harmful. The present study addresses the above problems by using marginal structural models (Hernán and others, 2000; van der Laan and Robins, 2003; Bryan and others, 2004).

We review the Belgian National Surveillance Study in Section 2 and marginal structural models in Section 3.2. Standard inference for such models cannot be used for estimating the effect of ICU-acquired infection on death for the following reasons. First, these models describe the hazard of death for ICU patients had they acquired infection in the ICU at a given number of days since admission, but this is ill-defined when ICU discharge comes earlier. Second, infection status and confounders were only recorded until ICU discharge, whereas survival times were recorded until hospital discharge to alleviate the problem of informative censoring. Similar difficulties arise in observational studies with a mortality end point where exposures are incompletely measured due to loss to follow-up or end-of-study, but survival times are assessed over a much longer time period (e.g. using death registers).
To accommodate both problems, we propose a new class of marginal structural models in Section 3.3, which express the effect on the hazard of death of acquiring infection on a given day \( s \), versus not acquiring infection up to that day, had patients stayed in the ICU for at least \( s \) days. We call the models in our class marginal structural models for partial exposure regimes as each considered “exposure regime” specifies the “exposures” (i.e. infections) for a given patient only up to the chosen time point \( s \). This has the added advantage of yielding more stable inferences since we merely aim to infer the effect of avoiding infection during the first \( s \) days since admission and not during the entire ICU stay. It thus makes the new models useful even in settings where standard marginal structural models can be applied. We derive a class of consistent and asymptotically normal (CAN) estimators for the parameters indexing our models and provide a reasonably efficient estimator in that class. In Section 4, we present the results obtained for the surveillance data. In Section 5, we discuss the usefulness of marginal structural models for partial exposure regimes in more general settings.

2. NATIONAL ICU SURVEILLANCE STUDY

All ICUs in Belgian hospitals were invited to participate in this surveillance study on a voluntary basis. For all patients admitted to the ICU, data were recorded on personal characteristics, reasons for ICU admission, baseline health status, and daily indicators of received invasive treatments and acquired infections in the ICU. Nosocomial infections were defined as infections acquired by patients after the second day of ICU stay to exclude infections that were in incubation upon enrollment in the ICU. The third day of stay in ICU will thus be the starting point for our analysis, excluding patients who stayed less than 3 days. We will restrict the analysis to the surveillance data collected for the year 2002 in one of the largest hospitals which has accurate daily measurements of received invasive treatments and acquired infections. A total of 1072 ICU patients were analysed. Of the 100 (9.3%) patients who acquired NP in ICU and stayed more than 2 days, 41 (41%) died in hospital, of whom 27 in ICU, as compared to 183 (18.8%) deaths among the 972 patients who remained NP-free in ICU, of whom 99 died in ICU. Among patients who stayed more than 2 days in ICU, the median length of stay in ICU was 4 days (interquartile range [IQR] 3, 95th percentile 13) for those without a history of NP and 16 days (IQR 13, 95th percentile 54.5) for the remaining patients. Additional background details can be found in Mertens, Suetens and others (2006).

A preliminary causal analysis (Mertens, Vansteelandt and others, 2006) using marginal structural models revealed highly unstable results when survival times were censored upon ICU discharge as a result of high censoring rates. Using patient registers, the survival status of each patient was therefore assessed upon hospital discharge.

3. MARGINAL STRUCTURAL MODELS FOR PARTIAL EXPOSURE REGIMES

3.1 Notation

Throughout, we use the following notation. For each patient, let \( A_t \) be a counting process that indicates 1 for ICU-acquired infection at or prior to time \( t \) and 0 otherwise, where \( A_0 = 0 \) by definition (see Figure 1). Likewise, let \( D_t \) (\( C_t \)) be a counting process that indicates 1 if ICU (hospital) discharge happened at or prior to time \( t \) and 0 otherwise. Define \( L_0 \) to be a vector of baseline variables collected upon admission to the ICU. In our analyses, \( L_0 \) consists of age, gender, reason for ICU admission, acute coronary care, multiple trauma, presence and type of infections upon ICU admission, prior surgery, baseline antibiotic use, and the simplified acute physiology score (SAPS), a severity-of-illness score based on a set of 15 clinical parameters predicting the mortality risk of a patient admitted to the ICU (Le Gall and others, 1993). Further, for \( t > 0 \), define \( L_t \) to be a vector of invasive therapeutic treatment indicators collected on
Fig. 1. Multistate model: directed arrows show the possible transitions from one state to another.

day $t$, consisting of indicators of exposure to mechanical ventilation, central vascular catheter, parenteral feeding, presence and/or feeding through naso- or oro-intestinal tube, tracheotomy intubation, nasal intubation, oral intubation, stoma feeding, and surgery. Discharge from the ICU defines the end of follow-up for all measured variables, except survival time, so that $A_t$ and $L_t$ are observed for all $t$ with $D_t = 0$, but not otherwise. Survival time $T$ is censored by discharge from the hospital. We define $K$ to be the end of follow-up time and, for any vector $Z = (Z_0, \ldots, Z_K)$ and $t \leq K$, $\overline{Z}_t = (Z_0, \ldots, Z_t)$. Throughout, we assume that infection and discharge on day $t$ can only be affected by time-dependent variables measured on previous days (and thus not by those measured on the same day).

3.2 Marginal structural models

Time-dependent multistate models for event history analysis (Andersen and Keiding, 2002; Schumacher and others, 2007) may appear well matched to the multistate nature (see Figure 1) of our problem. However, they are likely to yield biased estimates of the effect of ICU-acquired NP on mortality whether or not one adjusts for the relevant past confounder history (Robins, 1997b). For the unadjusted analysis, this is so because these analyses ignore time-varying confounders like mechanical ventilation, which increases the risk of infection and is also associated with death. For the adjusted analysis, this is so when these time-varying confounders lie on the causal path from infection to mortality because standard regression adjustment for such postinfection measurements may introduce bias. This problem of adjusting for internal (or endogenous) time-dependent covariates has long been recognized in the survival literature (see, e.g. Andersen, 1986, and the discussion in Kalbfleisch and Prentice, 2002), but solutions to it have emerged only recently. One such solution, which is becoming increasingly popular among statisticians and epidemiologists, is to use marginal structural Cox regression models (Hernán and others, 2000). We briefly review these models in this section.

Let $T_{\pi}$ express the counterfactual survival time (Rubin, 1978; Robins, 1986) which an ICU patient would, possibly contrary to fact, have had under a given infection path $\pi = (a_1, a_2, \ldots, a_K)$ following which the patient is infected on day $t$ since ICU admission if $a_t = 1$ and uninfected if $a_t = 0$. Then, a marginal structural Cox regression model is a Cox regression model for the counterfactual survival time $T_{\pi}$, possibly conditional on the baseline covariates $V$. It thus expresses how the hazard of death would
have been if all ICU patients had followed infection path \(\bar{a}\). A simple example is

\[
\lambda_\pi(t|V) = \lambda_0(t) \exp(\beta_1 a_t + \beta_2 V),
\]

(3.1)

where \(\lambda_\pi(t|V)\) is the hazard function that characterizes the conditional survival function of \(T_\pi\), given \(V\). It thus represents the hazard of death at time \(t\) among patients with baseline covariates \(V\) had they all followed infection path \(\bar{a}\). Further, \(\lambda_0(t)\) is an unknown baseline hazard of death at time \(t\) and \(\beta_1\) and \(\beta_2\) are unknown parameters. In model (3.1), \(\exp(\beta_1)\) expresses the causal rate ratio at time \(t\) due to acquiring infection at time \(t\). This represents the ratio of the mortality rate at any time \(t\) had all patients with baseline covariates \(V\) acquired infection at time \(t\) compared to the mortality rate at time \(t\) had these patients acquired no infection up to time \(t\). Further, \(\lambda_0(t)\) expresses the hazard of death at time \(t\) for patients with \(V = 0\) had they followed an infection path in which they never acquired infection in ICU. The model’s name “marginal” expresses that the model does not involve time-dependent confounders. Adjustment for such confounders happens by fitting the model to data from a pseudo-population in which there are no time-varying confounders, but the target effect is the same. This pseudo-population is constructed by reweighting subjects in the risk set at each time \(t\) by the reciprocal of the product of the conditional probabilities of the observed infection status at each time before time \(t\), given the history of time-varying confounders at that time (see expression (3.4) below) (Hernán and others, 2000).

The considered marginal structural Cox models are not directly applicable in our study because the exposure “ICU-acquired infection” (and, likewise, \(T_\pi\)) is ill-defined between ICU discharge and death or censoring of the survival time. Since our goal is to estimate the effect of “ICU-acquired” infection on mortality, it may seem natural to define patients as uninfected when they were not infected upon ICU discharge. However, this would make standard estimators for marginal structural models irregular (Robins, Hernán and Brumback, 2000) because there would be patients with certain prognostic factors (namely, those who are discharged uninfected from ICU) who are precluded from becoming infected under this definition. This irregularity results from the failure of the implicit assumption of experimentation in the “assignment” of infection (van der Laan and Robins, 2003), according to which, at each time \(t = 1, \ldots, K\), it must be true that

\[
0 < P(A_t = 1|\bar{A}_{t-1}, \bar{L}_{t-1}, D_t, V) < 1 \text{ with probability 1}.
\]

This assumption is needed to avoid inverse weighting by zero (see expression (3.4) below).

Alternatively, one could consider the infection and ICU discharge status of a patient as a joint exposure. Specifically, one could redefine an infection path to be any path \((d, a, as)\) in which a patient, while alive, will be discharged from the ICU on day \(d\) and either acquire infection on a given earlier day \(s < d\) (if \(a = 1\)) or stay uninfected during his/her stay in the ICU (if \(a = 0\)). The joint causal effect of discharge and infection in the ICU on the hazard of death can be expressed as a function of baseline covariates \(V\) through marginal structural Cox models for multiple interventions (Hernán and others, 2001; Robins, Hernán and Siebert, 2003). The following is a simple example of such a model:

\[
\lambda_{(d,a,as)}(t|V) = \lambda_0(t) \exp((\beta_1 + \beta_2(t-s))aI(t \geq s) + (\beta_3 + \beta_4(t-d))I(t \geq d) + \beta_5 V)
\]

with \(d > s\). Here, \(\lambda_{(d,a,as)}(t|V)\) is the hazard that characterizes the conditional survival function of the counterfactual survival time, given \(V\), under infection path \((d, a, as)\) \(\lambda_0(t)\) is an unknown baseline hazard of death at time \(t\), and \(\beta_1, \beta_2, \beta_3, \beta_4, \beta_5\) are unknown parameters. In particular, \(\exp(\beta_1 + \beta_2(t-s))\) is the causal rate ratio at time \(t\) due to acquiring infection at time \(s, s \leq t, s < d\). This represents the ratio of the mortality rate at any time \(t\) had all patients with baseline covariates \(V\) acquired infection at time \(s\)
compared to the mortality rate at time $t$ had these patients experienced the same discharge time but no infection up to time $t$. Note that this causal effect parameter has limited relevance from a public health perspective. First, it expresses the effect of acquiring NP at a given time on mortality in the hypothetical and unrealistic scenario where we would keep the patients in the ICU until some given, later time. Second, by comparing the same group of patients under 2 possible infection histories, the time of discharge from the ICU being equal, $\exp(\beta_1 + \beta_2(t - s))$ represents only the direct effect of acquiring infection at time $s$ on mortality at time $t$. As such, it does not capture the indirect effect of infection on death that may arise when infection prolongs the time of stay in the ICU, which may itself affect mortality risk. Furthermore, preliminary analyses (not displayed) showed that estimates for the parameters in the above model are highly unstable as a result of inverse weighting by small probabilities in the estimation procedure. This is due to a lengthy follow-up for a limited number of patients and because many time-dependent variables are strongly predictive for ICU discharge.

### 3.3 Marginal structural models for partial infection paths

To accommodate the foregoing problems, we will infer mortality rates under infection paths $(s, a)$ in which patients stay in the ICU for “at least” $s$ days and acquire infection (if $a = 1$) or not (if $a = 0$) on day $s$. Thus, under path $(s, a) = (s, 0)$, patients are uninfected in the ICU up to day $s$, their infection status being unspecified thereafter; under path $(s, a) = (s, 1)$, patients are uninfected in the ICU up to day $s$ and acquire infection on day $s$. By analysing mortality rates of ICU patients under each such infection path, we will be able to answer causal questions like “What would be the effect on the mortality rate of ICU patients of acquiring infection at time $s$, versus not acquiring infection up to that time, had they stayed in the ICU for at least $s$ days?” At the same time, we will be solving the problem that the infection status is unknown or ill-defined after ICU discharge because we only consider infection paths which specify the infection status of patients during their stay in the ICU. As such, these infection paths generalize the deterministic treatment regimes of Robins (1997a) which specify the treatment at each time from start until end of study.

For a given path $(s, a)$, let $T_{(s,a)}$ be the random variable representing the subject’s time from admission in the ICU to death had they experienced infection path $(s, a)$ rather than their own infection history, all other things being equal. We can then express the causal effect of infection in the ICU on the hazard of death through the marginal structural Cox model:

$$
\lambda_{(s,a)}(t|V) = \lambda_0(t) \exp(\beta_1 \min(t, s) + \beta_2 a I(t \geq s) + \beta_3 V).
$$

(3.2)

Here, $\lambda_{(s,a)}(t|V)$ is the hazard that characterizes the conditional survival function, given $V$, of the counterfactual survival time under infection path $(s, a)$, $\lambda_0(t)$ is an unknown baseline hazard of death at time $t$, and $\beta_1, \beta_2$, and $\beta_3$ are unknown parameters. Note that $\lambda_0(t) = \lambda_{(0,0)}(t|0)$ is the hazard of death at time $t$ among patients with $V = 0$ and is hence directly identifiable from the observed data distribution. In addition, note that $\exp(\beta_2)$ is the causal rate ratio at time $t$ of acquiring infection at any time $s, s \leq t$. It represents the ratio of the mortality (hazard) rate at any time $t$ had all patients with baseline covariates $V$ stayed in the ICU up to at least time $s$ and acquired infection at that time compared to the mortality (hazard) rate at time $t$ had these patients also stayed in the ICU up to at least time $s$ but acquired no infection up to that time. By specifying only whether infection comes before discharge, $\exp(\beta_2)$ represents the overall effect of acquiring infection at time $s$ on mortality at time $t$ under model (3.2). We call (3.2) a marginal structural model for partial exposure regimes to express that it determines each exposure regime (i.e., each infection path) only for a limited time period, contrary to the more standard marginal structural models of Section 3.2.
3.4 Inference

In this section, we develop inference for the parameters indexing marginal structural models for partial infection paths under the assumption of no unmeasured confounders. Specifically, we assume that at each time \( t \leq s \), survivors with prognostic factors \( \bar{L}_{t-1}, \bar{A}_{t-1}, D_{t-1} = 0 \) and \( V \) have the same hazard of infection and ICU discharge at time \( t \) regardless of their counterfactual survival time \( T_{(s,a)} \), for each infection path \((s, a)\) that is compatible with the observed history \((\bar{A}_{t-1}, D_{t-1} = 0)\). That is, for each such path \((s, a)\) and each \( t \leq s \),

\[
(A_t, D_t) \perp T_{(s,a)} | \bar{L}_{t-1}, \bar{A}_{t-1}, D_{t-1} = 0, \quad T > t,
\]

where \( U \perp V|W \) for random variables \( U, V \), and \( W \) indicates that \( U \) is conditionally independent of \( V \), given \( W \). This assumption is reasonable when the physician’s decision to discharge a patient from the ICU at time \( t \) is based solely on daily patient characteristics which were recorded in \( \bar{L}_{t-1}, \bar{A}_{t-1} \), and \( V \), and, in addition, all time-dependent confounders for the association between infection and death are accounted for.

Even if all patients were observed until the study end or death, analysis tools for marginal structural Cox models (Hernán and others, 2000) would not be directly applicable to fit model (3.2) under these assumptions because each infection path is specified for only a limited period of time. Below, we give a practical algorithm for obtaining a CAN estimator for the parameter \( \beta = (\beta_1, \beta_2, \beta_3)' \) indexing model (3.2) in the absence of unmeasured time-dependent confounders. The motivation for this algorithm is given in the supplementary material available at Biostatistics online (http://www.biostatistics.oxfordjournals.org), where the resulting estimate is defined via weighted partial likelihood estimation.

First, we identify, for each infection path \((s, a)\), those patients whose observed infection history is compatible with the path \((s, a)\). For each time \( t \), we thus construct a vector of variables \((S_t, A^*_t)\) which takes the value \((s, a)\) for a given patient at that time if that patient’s observed infection path up to time \( t \) could have been obtained under the path \((s, a)\). That is, for given \( s \), \((S_t, A^*_t) = (s, 1)\) (or \((S_t, A^*_t) = (s, 0)\)) for a given patient at time \( t \) if that patient was in the ICU at time \( s \leq t \) and acquired NP at that time (or did not acquire NP up to and including that time). In contrast to inference for ordinary marginal structural models, the data for a given patient at a given time may be compatible with multiple infection paths and may thus carry information about more than one path. This is because the considered paths are only partially specified. For instance, if a patient’s data are compatible with infection path \((s, 0)\) at time \( t \), then they are compatible with all infection paths \((u, 0)\) for \( u < s \) and may thus appear multiple times in the database corresponding to different values of \( S_t \).

Next, for all infection paths \((s, a)\) jointly, we fit a proportional hazards model using only the data compatible with the given path and weighting each observation by the reciprocal probability of following that path to account for the selective nature of our subsample. Specifically, we substitute \((s, a)\) by \((S_t, A^*_t)\) in the marginal structural model (3.2) by fitting the time-dependent Cox model

\[
\lambda(t | S_t, A^*_t, V) = \lambda^*_0(t) \exp(\beta_1^* \min(t, S_t) + \beta_2^* A^*_t + \beta_3^* V)
\]

and weight the contribution of a patient to the risk set at time \( t \) by the stabilized weights

\[
swi(t, S_t, \bar{A}_t, \bar{D}_t, \bar{L}_{t-1}, V) = \prod_{k=1}^{S_t} \frac{P(A_k | A_{k-1} = D_k = 0, V)}{P(A_k | A_{k-1} = D_k = 0, \bar{L}_{k-1}, V)} \times \frac{P(D_k = 0 | A_{k-1} = D_{k-1} = 0, V)}{P(D_k = 0 | A_{k-1} = D_{k-1} = 0, \bar{L}_{k-1}, V)}.
\]

These weights differ from the usual stabilized weights for marginal structural models (Hernán and others, 2000, 2001) in that they consider the joint treatment process given by infection and discharge at each time.
and do this only up to the artificial time $S_t$. Note that they involve the discharge process to account for the fact that, at each time $t$, those subjects who are still in the ICU (i.e. those for whom we have information on the infection history) may form a selective subset of the study population. The impact of weighting is to eliminate time-varying confounders by removing their association with exposure $(A_t, D_t)$ at each time $t$, while leaving the causal effect of interest unchanged. The numerator probabilities in (3.4) are included for stabilization of the weights and are allowed to be misspecified by the fact that model (3.2) is postulated conditional on $V$.

To deal with censoring of the survival status due to hospital discharge, we proceed under the additional assumption of sequentially ignorable censoring (van der Laan and Robins, 2003). For our data, this assumption states that among subjects with a given observed past $\bar{A}_{td}, \bar{D}_t, \bar{L}_{td}, V$, where $t_D = \min(t, D - 1)$ and $t_{D-} = \min(t, D) - 1$, the censored and uncensored subjects at time $t$ have the same survival time distribution; that is, $C \perp T | \bar{A}_{td}, \bar{D}_t, \bar{L}_{td}, V, T > t, C > t$ for each time $t$. At a given time $t$, this assumption could be reasonable for short-term survival rates because we have available a large and detailed collection of prognostic factors for survival that also predict time of discharge from the ICU. However, for given $t$, it is questionable for the longer term because we lack data monitoring the health status of patients after leaving the ICU. In our study, the median length of stay in hospital after ICU discharge was 8 days (IQR 10, 5% percentile 0, 95% percentile 50).

We can correct the above analysis for sequentially ignorable censoring by further weighting each patient’s contribution to the risk set at time $t$ by the stabilized weights

$$swc(t, \bar{A}_{td}, \bar{D}_t, \bar{C}_{t-1}, \bar{L}_{td}) = \prod_{k=1}^{t} \frac{P(C_k = 0|\bar{A}_{kd}, \bar{D}_k, C_{k-1} = 0, V)}{P(C_k = 0|\bar{A}_{kd}, D_k, C_{k-1} = 0, \bar{L}_{kd-}, V)},$$

(3.5)

where the numerator and denominator probabilities equal 1 when $D_k = 0$. Here, we implicitly assume that hospital discharge does not causally affect survival. Under this assumption and provided that the measured time-dependent covariates are sufficient to adjust for time-dependent confounding and censoring due to hospital discharge, fitting model (3.3) and weighting each patient’s contribution to the risk set at time $t$ by the product of (3.4) and (3.5) produce a consistent estimator for the causal rate ratio.

4. DATA ANALYSIS

We first consider the unadjusted time-dependent proportional hazards (PH) model

$$\lambda(t|\bar{A}_t) = \lambda_0(t) \exp(\beta_1 A_t).$$

To enhance comparability with later results, we fitted this model via unweighted pooled logistic regression with regression splines for the time effect. The estimate of the hazard ratio (HR) of death comparing patients who acquired infection prior to time $t$ and those who did not was 1.89 (95% confidence interval [CI] [1.32, 2.71]). When adding baseline covariates (SAPS score and reasons for admission to the ICU), the estimated HR was no longer significant and equaled 1.37 (95% CI [0.93, 2.04]). A detailed overview of conventional analysis results for these data and the biases incurred by different standard regression methods can be found in Mertens, Suetens and others (2006).

To adjust for time-dependent confounding, we extended our data set to include $S_t$ and $A_t^*$ for each patient at each time $t$. Next, we calculated stabilized weights by means of 6 pooled logistic regression models for the numerator and denominator weights in (3.4) and (3.5). To avoid unstable weights, we included baseline covariates $(V)$ in the numerator weights and then later also in the marginal structural model. Specifically, we considered the type of admission allowing for effect modification by acute coronary care and multiple trauma, presence and type of infection and surgery at admission, SAPS score and
age (allowing for quadratic effects on both), gender, antibiotic use during the first 48 hours of ICU stay, and baseline values for all previously listed invasive therapeutic treatment indicators. Time-dependent information on exposure to invasive treatments was summarized in terms of the presence/absence of the treatment on each of the 2 previous days and by the total number of previous days on invasive treatments. In addition, we allowed for quadratic effects of the number of previous days on mechanical ventilation additionally allowing for effect modification by antibiotic use during the first 48 hours of ICU stay and on central vascular catheter. To build parsimonious models, we used the following conservative approach. In the first stage, all main effects were added and then sequentially removed if nonsignificant at the 10% level (ignoring correlations between outcomes from the same patient). In the second stage, the suggested interaction terms and quadratic effects were added if significant following the same criterion. Splines were used to model the time effect in all models.

Using the estimated predicted values from these models, we calculated the probability of each patient having their observed infection status up to time $t$, given baseline variables and then also given time-dependent variables $\bar{L}_{t-1}$. We calculated similar estimates for the probability of ICU discharge and hospital discharge, the latter after also adjusting for the infection and ICU discharge history. To avoid unstable weights, we considered only infection paths $(s, a)$ with $3 \leq s \leq 11$. This implies that the estimated effect of infection on the hazard of death pertains only to infection paths where infection is acquired during the first 11 days starting from day 3. Note, however, that we included all observed person-days in the analysis.

Figure 2 displays the distribution of the natural logarithm of the stabilized weights as a function of time. The stabilized weights had a median and mean of 0.81 and 0.93, an interquartile range and standard deviation of 0.48 and 1.94, and 1% and 99% percentiles of 0.048 and 3.89 (minimum 0.0039, maximum 123.48). Among weights greater than 5, the 99th, 75th, and 50th percentiles are 100.59, 11.70, and 8.69. Among weights smaller than 0.2, the 1st, 25th, and 50th percentiles are 0.0066, 0.069, and 0.12.

Because standard software for PH regression does not allow us to reweight the risk sets at each time, we fit the discrete-time analog of (3.3) via a weighted pooled logistic regression model using generalized

![Fig. 2. Box plots of the natural logarithm of the stabilized weights in function of time $t$ (with whiskers extending to 2.5 times the interquartile range).](https://academic.oup.com/biostatistics/article-abstract/10/1/46/269536)
Fig. 3. Marginal survival curve (upper solid line) (directly estimated from the observed data) with 95% CIs (dashed) and predicted survival curve following immediate infection (lower solid line) (based on the marginal structural model) with approximate 95% CIs (dotted). The latter intervals acknowledge imprecision on the estimated causal effect but ignore imprecision on the estimated survival curve. Left: from 3 to 140 days after ICU admission; right: from 3 to 20 days after ICU admission.

estimating equations, treating each patient-day as an observation and using regression splines to fit the time effect (Hernán and others, 2000). Unbiasedness of the estimating equations under this logistic regression model requires use of the independence working correlation (Vansteelandt, 2007). Note that by using generalized estimating equations to fit model (3.3), we account for the potentially strong correlation arising in the augmented data set. This may contain the same observations multiple times corresponding to different values of \( S_t \). Because the effect on the hazard of death at time \( t \) of keeping the patient in the ICU up to time \( S_t \) was considered a nuisance, we modeled the effect of \( S_t \) in model (3.3) using regression splines. Our causal estimate of the HR for infection was 2.74 (95% conservative CI [1.48, 5.09]). We conclude that under any infection path in which patients stay in the ICU for at least a given number of days \( s \), the effect of acquiring infection on day \( s \) is to multiply the hazard of death by 2.74. CIs were obtained using the robust standard error. By not taking into account the estimation of the weights, this yields an asymptotically conservative CI for our causal parameters (Robins, Hernán and Brumback, 2000). Figure 3 shows the estimated survival curves for the study population along with 95% CIs and predicted survival curves in the hypothetical scenario where all patients acquire infection at the third day of their stay in the ICU. It illustrates the severe estimated impact of ICU-acquired infection on mortality.

To examine the stability of the results to extreme weights, we additionally evaluated the effect of infection on mortality for infection paths with \( 3 \leq s \leq s_{\text{max}} = 7, 8, 9, \) and 10. The weights are more stable for these analyses because the product in (3.4) runs over a smaller number of time points. The results are displayed in Table 1 and show that the effect size and significance stay the same with increasing stability of the weights. Finally, we performed an ad hoc procedure whereby stabilized weights smaller
Table 1. Distribution of the stabilized weights (1% and 99% percentiles, minimum and maximum), HRs, and 95% CIs in marginal structural models for partial infection paths with $3 \leq s \leq s_{\text{max}}$

<table>
<thead>
<tr>
<th>$s_{\text{max}}$</th>
<th>1% Percentile</th>
<th>99% Percentile</th>
<th>Minimum</th>
<th>Maximum</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>0.065</td>
<td>3.50</td>
<td>0.0071</td>
<td>25.94</td>
<td>2.75</td>
<td>(1.48, 5.12)</td>
</tr>
<tr>
<td>8</td>
<td>0.064</td>
<td>3.49</td>
<td>0.0061</td>
<td>35.91</td>
<td>2.66</td>
<td>(1.43, 4.94)</td>
</tr>
<tr>
<td>9</td>
<td>0.060</td>
<td>3.51</td>
<td>0.0053</td>
<td>54.14</td>
<td>2.70</td>
<td>(1.46, 5.00)</td>
</tr>
<tr>
<td>10</td>
<td>0.054</td>
<td>3.72</td>
<td>0.0046</td>
<td>81.88</td>
<td>2.71</td>
<td>(1.47, 5.01)</td>
</tr>
<tr>
<td>11</td>
<td>0.048</td>
<td>3.89</td>
<td>0.0039</td>
<td>123.48</td>
<td>2.74</td>
<td>(1.48, 5.09)</td>
</tr>
</tbody>
</table>

than 0.2 or greater than 5 were truncated at 0.2 and 5, respectively. This yielded a HR of 2.50 (95% conservative CI [1.45, 4.31]), suggesting once more robustness to the extreme weights. Allowing for an interaction between the infection status and the number of days since acquiring the infection revealed that, on the hazard scale, the effect of acquiring infection on a given day $s$ increases nonsignificantly by 2.8% (95% conservative CI [$-1.2\%, 6.7\%$], $P = 0.17$) per day since acquiring infection. Likewise, there was no indication that the effect of ICU-acquired infection on the hazard of death depends on the time at which it was acquired ($P = 0.29$).

5. DISCUSSION

The effect on mortality of acquiring NP in ICU continues to raise controversy among clinicians because standard statistical analyses have shown contradictory results. Because this is partly due to inappropriate adjustment for intermediate time-varying confounders, we have proposed to use analyses of marginal structural models. These take into account the time order in which infection, mortality data, and time-dependent confounders were collected and correct appropriately for time-dependent confounders that lie on the causal path from NP to mortality. Inference for such models was, however, not directly applicable to our data for the following 2 reasons: (a) the infection status of patients was ill-defined subsequent to ICU discharge, an event which lies on the causal path from infection to mortality; (b) the usual weights in the weighted estimating equations for standard marginal structural models were highly unstable because there was a lengthy follow-up for several patients and many collected time-dependent variables were strongly predictive of ICU discharge.

To accommodate these problems, we have proposed to model mortality rates under “partially specified” infection paths. The resulting models solve the problem mentioned in (a) without fixing the discharge time after the event of infection and thus without fixing variables on the causal path from infection to mortality. In addition, inference under these models tends to be more stable because each infection path is specified only up to a given time $s$ (rather than up to the study end). As such, the weights in the inverse weighting procedure merely involve the first $s$ time points and are thus less affected by lengthy follow-up with frequent infection measurements. Alternatively, weight instability may be intercepted by inferring only the effect of late infections, along the lines of Joffe and others (2004) and Petersen and others (2007), or by using doubly robust estimators which allow better for truncating extreme weights (Yu and van der Laan, 2006). Finally, note that our results directly accommodate situations where exposures are not collected up to the time where outcomes are assessed. This may happen in settings where the mortality status of patients is assessed at the time of data analysis, that is, later than end-of-follow-up, through death registers, or where each patient’s treatment or treatment compliance is closely monitored for only a limited time period. By not fixing treatment levels observed after this time period, the proposed models isolate the overall effect of treatment over the given period on outcome and extrapolate much less from the observed data than standard marginal structural models.
Alternatively, we could have chosen to assess the effect of avoiding infection among patients who acquired infection on a given day. This effect estimand has greater relevance since physicians are primarily interested in the effect of “preventing” infection among the infected. Also, by restricting the focus to those who acquired infection in the ICU, one avoids the difficulty that the effect of acquiring infection on a given day in ICU is ill-defined for those who get discharged before that day. Structural nested accelerated failure time models (Robins and Tsiatis 1992, Robins 1997b, Keiding and others 1999) can be used for modeling this effect estimand. These are models for the effect of a change in infection status on survival time among patients with a given history of measured time-dependent confounders and infection. Because inference for these models is more complicated, does not allow the use of standard software, and typically suffers more from censoring of the survival time, we have chosen to adopt marginal structural models in this article and plan to report on structural nested models elsewhere.

Finally, it remains to be seen how sensitive conclusions are to the untestable assumptions that there are no unmeasured time-varying confounders for the effect of infection on mortality and that censoring is sequentially ignorable. The former assumption implies that among patients with prognostic factors $L_{t-1}, A_{t-1}, D_{t-1} = 0$, the causal effect of infection and ICU discharge is the same regardless of their infection and ICU discharge status at time $t$. This may not be entirely realistic because we anticipate the causal effect of infection to be greater among the infected and we may lack sufficient prognostic factors conditional on which this is no longer so. The assumption of sequentially ignorable censoring may also be questioned because the decision to discharge patients from hospital is intimately connected with their health status, about which no information was recorded after ICU discharge. In future work, we plan to accommodate this by estimating the effect of acquiring infection in ICU on “30-day ICU mortality”. This end point is uncensored and of even greater interest to clinicians because time to death in ICU patients can be greatly extended by invasive therapeutic treatments.

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REFERENCES


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