ORIGINAL ARTICLE

Multistate Modeling to Analyze Nosocomial Infection Data: An Introduction and Demonstration

Martin Wolkewitz, PhD; Maja von Cube, MSc; Martin Schumacher, PhD

OBJECTIVE. Multistate and competing risks models have become an established and adequate tool with which to quantify determinants and consequences of nosocomial infections. In this tutorial article, we explain and demonstrate the basics of these models to a broader audience of professionals in health care, infection control, and hospital epidemiology.

METHODS. Using a publicly available data set from a cohort study of intensive care unit patients, we show how hospital infection data can be displayed and explored graphically and how simple formulas are derived under some simplified assumptions for illustrating the basic ideas behind multistate models. Only a few simply accessible values (event counts and patient days) and a pocket calculator are needed to reveal basic insights into cumulative risk and clinical outcomes of nosocomial infection in terms of mortality and length of stay.

RESULTS. We show how to use these values to perform basic multistate analyses in own data or to correct biased estimates in published data, as these values are often reported. We also show relationships between multistate-based hazard ratios and odds ratios, which are derived from the popular logistic regression model.

CONCLUSIONS. No sophisticated statistical software is required to apply a basic multistate model and to avoid typical pitfalls such as time-dependent or competing-risks bias.

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To analyze risk factors of nosocomial infections and the impact of nosocomial infection on mortality in cohort studies, the logistic regression model is the dominant approach.[1] Recently, Pierce et al[1] provided an excellent overview of statistical models (eg, Poisson and survival models), which extend the logistic regression model by accounting for time-at-risk, time-dependency of nosocomial infection, other risk factors, and competing events. As noted by Pierce et al,[1] different models often simply address different questions. However, for readers of published results, it is often not transparent which approaches lead to bias (and should therefore be avoided) and how the results from different models are linked.

Biased results seem to be common in articles about nosocomial infection. For instance, ignoring the time dependency of nosocomial infection in length-of-stay analyses can lead to a serious overestimation of the additional length of stay due to nosocomial infection.[2,3] Competing events are another serious source of bias.[4] When calculating the risk of nosocomial infection depending on the time at risk, ignoring discharge and death as competing events leads to an overestimation of cumulative nosocomial infection risk.[2,4]

Multistate models have become an attractive tool to accommodate the time dependency of nosocomial infection and death or discharge as competing events. Indeed, multistate models are well suited to avoiding time-dependent and competing-risks biases, and they further provide deep time-dependent insights into the determinants and consequences of nosocomial infection (see recent examples in Ong et al,[5] Ong et al,[6] van Vught et al,[7] De Angelis et al,[8] and Stewardson et al[9]).

In this article, we aim to make the basic mechanisms of competing risks and multistate models transparent to professionals who draw conclusions from published studies of nosocomial infection. We make use of simplified assumptions (ie, time-constant hazard rates) to illustrate the basic ideas behind multistate models. With time-constant hazard rates, a first-step analysis of the multistate model for nosocomial infection can be performed easily; this is a useful tool for avoiding competing-risks bias and time-dependent bias. The corresponding mathematical proofs and the contrast with multistate models using time-dependent hazards are provided in a statistical companion paper.

METHODS

The multistate model is displayed in Figure 2. Each arrow represents a time-homogeneous hazard rate λ_{ij} from state i to j. The hazards λ_{ij} are interpreted as the daily risk of moving from state i to state j and are estimated by

$$\hat{\lambda}_{ij} = \frac{\text{Number of patients moving from state } i \text{ to } j}{\text{Summed patient}-\text{days in state i}}$$

Affiliation: Faculty of Medicine and Medical Center, Institute for Medical Biometry and Statistics, University of Freiburg, Freiburg, Germany.

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Only the following 7 simple numbers are needed to estimate the hazards of the multistate model: (1) the number of patients who acquire nosocomial infection, (2) the number of patients who are discharged without nosocomial infection, (3) the number of patients who are discharged with nosocomial infection, (4) the number of patients who die without nosocomial infection, (5) the number of patients who die with nosocomial infection, (6) the total patient days without nosocomial infection, and (7) the total patient days with nosocomial infection.

Based on the 5 hazards from the multistate model, it is now possible to quantify cumulative risk and clinical outcomes of nosocomial infection in terms of mortality and length of stay.

RESULTS

Displaying Raw Nosocomial Infection Data

Figure 1 shows the data of a German cohort study with 756 intensive care unit (ICU) patients; it is a random sample of a larger study[10] and is publicly available.[11] All patients enter the ICU, and as long as they stay alive in the ICU without a nosocomial infection (which is pneumonia in this example), they are at risk to acquire a nosocomial infection, to die, or to be discharged alive uninfected (marked as a gray line). Notably, due to the definition of nosocomial infection, discharge without nosocomial infection constitutes the end of the at-risk period for nosocomial infection. This at-risk condition for the 3 competing events corresponds to state 0 from the multistate model (Figure 2). After some time at risk, each patient will either acquire a nosocomial infection (n = 124, lower panels of Figure 1), be discharged without nosocomial infection (n = 475, left upper panel of Figure 1), or die without nosocomial infection (n = 157, right upper panel of Figure 1), meaning that he or she moves to state 1, 2, or 3, respectively. The gray patient days from all 4 panels in Figure 1 contribute to the state 0; the total of all patient days in state 0 is 6,442 patient days. Notably, this sum equals the product of number of patients and the mean duration time of staying alive at the ICU without nosocomial infection of 8.52 ($6{,}442 = 756 \times 8.52$). All patients were followed-up until discharge or death; there was no administrative censoring.

Patients with a nosocomial infection (marked with a black line after nosocomial infection acquisition) are still at risk to die or will be discharged. The black patient days (of the same patients) contribute to the state 1 in the multistate model (Figure 1). Thus, infected patients contribute both to the at-risk time in state 0 (ie, the pre-nosocomial infection time marked in gray) as well as in state 1 (ie, the post-NI time marked in black). The sum of all (black) at-risk times is

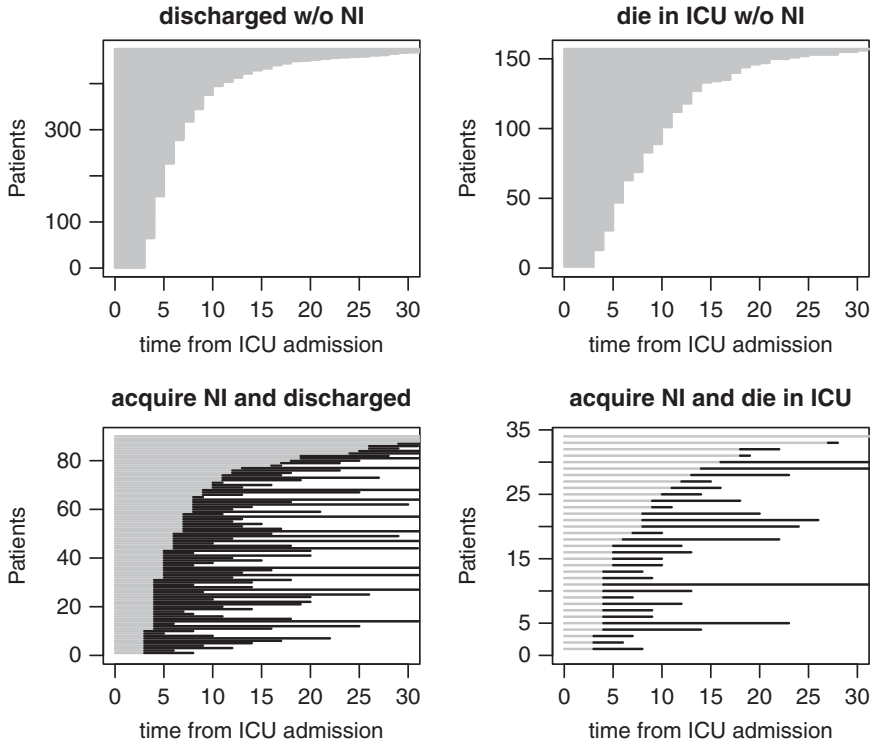


FIGURE 1. Real data from a German hospital cohort study that are publicly available. Each line represents 1 patient admission. The gray line means that the patient is not infected with nosocomial infection, black means that the patient is infected (usually assumed until death or discharge).

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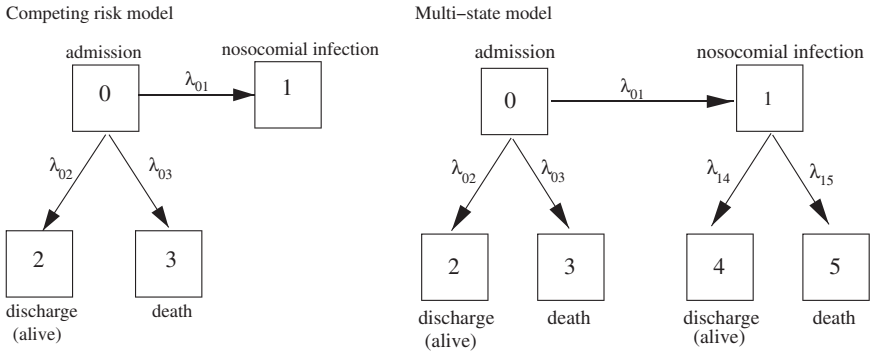


FIGURE 2. Competing risks (left) and multistate model (right). We assume constant hazards λij (hazard from state i to j).

1,527 patient days in state 1; the mean duration time of staying alive at the ICU with nosocomial infection is 12.5 days.

Incidence Density, Risk, and Odds of Nosocomial Infection

The 5 hazards can now be used to perform basic multistate analyses (Tables 1 and 2). The incidence density of nosocomial infection per patient days is simply λ_{01}, which is interpreted as the daily probability to acquire a nosocomial infection during the hospital stay. The risk of nosocomial infection, however, is $\frac{\lambda_{01}}{\lambda_{01}+\lambda_{02}+\lambda_{03}}$, the probability that a nosocomial infection will occur during hospital stay. In the data example, it is $124/(124+475+157)=16.4\%$ because the denominators (summed patient days in state 0) cancel out. The formula shows how the risk of nosocomial infection depends not only on the incidence density λ_{01} but also on the discharge and death without nosocomial infection hazards λ_{02} and λ_{03}. The odds of nosocomial infection are $\frac{\lambda_{01}}{\lambda_{02}+\lambda_{03}}=19.6\%$, the probability that a nosocomial infection will occur during the hospital stay divided by the probability that a nosocomial infection will not occur during hospital stay. It is often similar to the risk of nosocomial infection if the nosocomial infection is rare (ie, a risk <10%).

Analysis of Risk Factors Associated With Nosocomial Infection

The first step to performing an analysis of risk factors for nosocomial infection (eg, older age or invasive devices) is to study the effect on the 3 event-specific hazards λ_{01}, λ_{02}, and λ_{03}. Thus, for a binary risk factor (1 = present, 0 = absent), one calculates the event-specific hazard ratios

$\lambda^1{}_{01}/\lambda^0{}_{01}$, $\lambda^1{}_{02}/\lambda^0{}_{02}$ and $\lambda^1{}_{03}/\lambda^0{}_{03}$. The superscripts 1 or respectively 0 indicate the corresponding hazard with or respectively without the risk factor. Such an analysis, usually done with event-specific Cox or Poisson regression models, provides information on the way the risk factor is associated with the instantaneous risk (or the speed) to acquire a nosocomial infection, to be discharged, or to die in the hospital. This etiological approach does not study the effect on the cumulative risk of nosocomial infection. For this cumulative metric, the risk odds ratio is a commonly used association measure and can be calculated with the logistic regression model. The dependency on λ_{02} and λ_{03} is the reason that risk odds ratios often differ from hazard ratios because risk factors of nosocomial infection are also often associated with discharge and death without nosocomial infection hazards

TABLE 1. Overview of Basic Multistate Analysis of Nosocomial Infection That Can Be Done With Constant Hazards[a]

Constant Hazards From Multistate Model	
NI hazard	λ_{01}
Discharge hazard w/o NI	λ_{02}
Death hazard w/o NI	λ_{03}
Discharge with NI	λ_{14}
Death hazard with NI	λ_{15}
Occurrence of nosocomial infection	
Incidence rate of NI per patient day	λ_{01}
Risk (incidence proportion) of NI	λ_{01}/λ_0
Odds of NI	$\lambda_{01}/(\lambda_{02}+\lambda_{03})$
Cumulative risk of NI until day t	$(\lambda_{01}/\lambda_0)\ (1 - \exp(-\lambda_0\ t))$
Cumulative risk of death w/o NI until day t	$(\lambda_{02}/\lambda_0)\ (1 - \exp(-\lambda_0\ t))$
Cumulative risk of discharge w/o NI until day t	$(\lambda_{03}/\lambda_0)\ (1 - \exp(-\lambda_0\ t))$
Mortality / Length of Stay Due to NI	
Hazard ratio of NI (death)	$\lambda_{15}/\lambda_{03}$
Hazard ratio of NI (discharge)	$\lambda_{14}/\lambda_{02}$
ICU mortality risk of infected	$\lambda_{15}/(\lambda_{14}+\lambda_{15})$
ICU mortality risk of uninfected	$\lambda_{03}/(\lambda_{02}+\lambda_{03})$
ICU mortality risk ratio	$\frac{\lambda_{15}/\lambda_{03}}{(\lambda_{14}+\lambda_{15})/(\lambda_{02}+\lambda_{03})}$
ICU mortality odds of infected	$\lambda_{15}/\lambda_{14}$
ICU mortality odds of uninfected	$\lambda_{03}/\lambda_{02}$
ICU mortality odds ratio	$\frac{\lambda_{15}/\lambda_{03}}{\lambda_{14}/\lambda_{02}}=\frac{\lambda_{15}\lambda_{02}}{\lambda_{14}\lambda_{03}}$
Change in length of stay due to NI	$\frac{1}{\lambda_0}*\left[\frac{(\lambda_{02}+\lambda_{03})}{(\lambda_{14}+\lambda_{15})}-1\right]$
Change in length of stay (death)	$\frac{\lambda_{15}}{\lambda_{14}+\lambda_{15}}*$ cLOS
Change in length of stay (discharge alive)	$\frac{\lambda_{14}}{\lambda_{14}+\lambda_{15}}*$ cLOS

NOTE. NI, nosocomial infection; ICU, intensive care unit; cLOS, change in length of stay.
[a]Short notation: $\lambda_0=\lambda_{01}+\lambda_{02}+\lambda_{03}$, $\lambda_1=\lambda_{14}+\lambda_{15}$

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TABLE 2. Real Data Example From a German Cohort Study[a]

Descriptive Data Needed for Analysis	
No. of patients	756 patients
Total patient days in state 0	6,442 patient days
Total patient days in state 1	1527 patient days
No. of NI	124 infected patients
No. of discharges without NI	475 uninfected patients
No. of deaths without NI	157 uninfected patients
No. of discharges with NI	90 infected patients
No. of deaths with NI	34 infected patients
Constant Hazards From Multistate Model	
λ_{01}	0.019 per patient day
λ_{02}	0.074 per patient day
λ_{03}	0.024 per patient day
λ_{14}	0.059 per patient day
λ_{15}	0.022 per patient day
Occurrence of NI	
Incidence rate	0.019 per patient day
Risk of NI	$0.019/(0.019+0.074+0.024) = 124/(124+475+157) = 16.4\ \%$
Odds of NI	$0.019/(0.074+0.024) = 124/(475+157) = 19.6\ \%$
Cumulative risk of NI and competing events	See Figure 3
Mortality/Length of Stay Due to NI	
ICU mortality risk of infected	$0.022/(0.059+0.022) = 27.4\%$
ICU mortality risk of uninfected	$0.024/(0.074+0.024) = 24.8\%$
ICU mortality risk ratio	$\frac{0.022/0.024}{(0.059+0.022)/(0.074+0.024)} = 1.11$
ICU mortality odds of infected	$0.022/0.059 = 37.8\%$
ICU mortality odds of uninfected	$0.024/0.074 = 33.1\%$
ICU mortality odds ratio of NI	$\frac{0.022/0.024}{0.059/0.074} = 1.14$
Hazard ratio of NI (death)	$0.022/0.024 = 0.91$
Hazard ratio of NI (discharge)	$0.059/0.074 = 0.80$
Change in length of stay due to NI, d	$\frac{1}{0.019+0.074+0.024} \times \left[\frac{(0.074+0.024)}{(0.059+0.022)} - 1 =\right] 1.77$ ICU days
Change in length of stay leading to death, d	$[0.059/(0.059+0.022)] \times 1.77 = 0.48$ ICU days
Change in length of stay leading to discharge alive, d	$[0.022/(0.059+0.022)] \times 1.77 = 1.29$ ICU days

NOTE. NI, nosocomial infection; ICU, intensive care unit.
[a]For calculations, we used the exact values; constant hazards have been rounded.

(and thus a Cox or Poisson is often different from a logistic regression analysis). However, the following relationship exists between the odds ratio of a binary risk factor for nosocomial infection and the hazard ratios of the multistate model in the simple setting of time-constant hazards:

$$\text{odds ratio of risk factor (NI)} = \frac{\text{hazard ratio of risk factor (NI)}}{\text{hazard ratio of risk factor (discharge or death)}}$$

which equals more formally $\frac{\lambda_{01}^1 / \lambda_{01}^0}{\left(\lambda_{02}^1 + \lambda_{03}^1\right) / \left(\lambda_{02}^0 + \lambda_{03}^3\right)}$. Notably, the sum of the 2 hazards λ_{02} and λ_{03} is the hazard of the combined end point of death and discharge. The formula shows that a decreasing or increasing effect of a risk factor on the discharge or death hazard leads to increasing or decreasing nosocomial infection odds.

Cumulative Risk of Nosocomial Infection Depending on Time

The cumulative risk of nosocomial infection is the probability of acquiring nosocomial infection until day t and can be written as $(\lambda_{01}/(\lambda_{01}+\lambda_{02}+\lambda_{03})) \times (1-\exp(-(\lambda_{01}+\lambda_{02}+\lambda_{03}) \times t))$ (see also Schumacher et al[12] and Beyersmann et al[13]). In other words, it displays the way the risk of nosocomial infection increases with time, up to the proportion $\lambda_{01}/(\lambda_{01}+\lambda_{02}+\lambda_{03})$ (Table 1 and Figure 3).

The impact of competing risk bias can be seen easily if these estimates are compared to the estimate where competing events are treated as censored observation. For instance, censoring competing events for nosocomial infection means setting λ_{02} and λ_{03} to zero. Thus, the biased measures are $1-\exp(-\lambda_{01}t)$ for nosocomial infection, $1-\exp(-\lambda_{02}t)$ for discharge, and $1-\exp(-\lambda_{03}t)$ for death without nosocomial infection.

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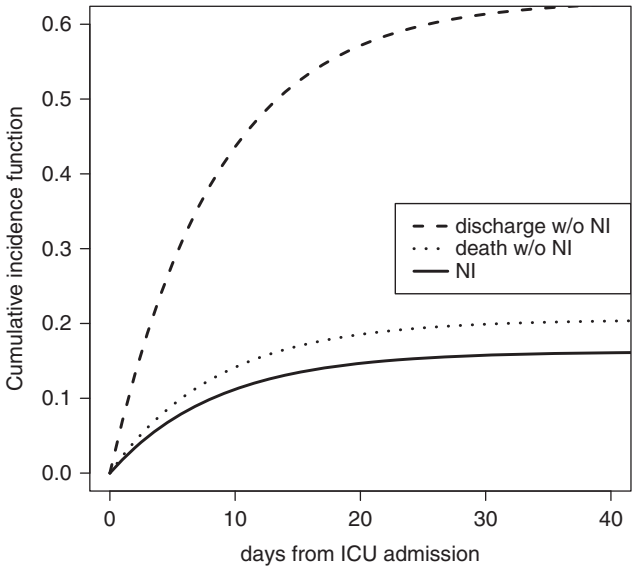


FIGURE 3. Cumulative risk of nosocomial infections and their corresponding competing events (death and discharge without nosocomial infection). Estimates were derived by plugging in the hazard values from Table 2 into the formula from Table 1.

Impact of Nosocomial Infection on ICU Mortality

The first step in quantifying the consequences of nosocomial infection is to model the association between nosocomial infection and the death and discharge hazards. Our data example shows that nosocomial infection patients are associated with a decreased discharge as well as death hazard (hazard ratios $\lambda_{14}/\lambda_{02} = 0.80$ and $\lambda_{15}/\lambda_{03} = 0.91$, respectively). Notably, this analysis is a simplified version of 2 event-specific Cox or Poisson regression models (one for outcome death with censoring discharged patients and another for outcome discharge with censoring the deaths) with nosocomial infection treated as a time-dependent variable. The hazard ratios show that patients with nosocomial infection stay longer at the ICU (hazard ratio of nosocomial infection, ie, discharge, is much lower than 1) and that the daily probability to die in the ICU is almost not influenced by nosocomial infection (hazard ratio of nosocomial infection, ie, death, is close to 1). In contrast, a logistic regression model estimates the odds ratio of nosocomial infection regarding death. This model ignores any timings of nosocomial infection, death, and discharge and can be regarded as a snapshot at the end of stay in the ICU.[14] In the data, the estimated odds ratio for ICU death of 1.14 (ie, $=(34\times475)/(90\times157)$) shows that nosocomial infection increases ICU mortality meaning that more patients with nosocomial infection eventually die in the ICU than without nosocomial infection. Thus, even though the death hazard ratio of nosocomial infection is lower than 1, the odds ratio for ICU death is >1. In the simple setting of time-constant hazards, the dependency between the odds ratio and the hazard ratios (and thus between logistic and 2 time-dependent Cox or Poisson regression models) can be displayed as follows:

$$\text{odds ratio of NI (death)} = \frac{\text{hazard ratio of NI (death)}}{\text{hazard ratio of NI (discharge)}}$$

which equals more formally $\frac{\lambda_{15}/\lambda_{03}}{\lambda_{14}/\lambda_{02}}$. Both OR as well as RR, are summary measures of both event-specific hazards for ICU death and discharge. From the formula, it follows that a reducing/increasing effect on the discharge hazard has an increasing/decreasing effect on the ICU mortality risk and odds. It also follows that if there is no effect of nosocomial infection on the death or discharge hazard (ie, $\lambda_{03}=\lambda_{15}$ and $\lambda_{02}=\lambda_{14}$), the odds ratio (OR) and risk ratio (RR) equals 1. If there is no effect on the death hazard ($\lambda_{03}=\lambda_{15}$) and the nosocomial infection is associated with a reduced discharge hazard ($\lambda_{14}<\lambda_{02}$) (meaning that nosocomial infection patients stay longer at the ICU), then the risk ratio and odds ratio are >1 (OR > RR > hazard ratio [HR] = 1). Analogously, an increased discharge hazard ($\lambda_{14}>\lambda_{02}$) leads to reduced risk and odds ratios (OR < RR < HR = 1).

Change in Length of ICU Stay Due to Nosocomial Infection

Allignol et al[15] showed the way how the change in the length of the ICU stay due to nosocomial infection depends on the 5 hazards, including the distinction between patients being discharged and dying in the ICU (Table 1). Applied to the data, patients with nosocomial infection stay 1.77 days longer in the ICU than patients without nosocomial infection; 0.48 additional ICU days regarding death; and 1.29 additional days regarding discharge. These estimates consider the time-dependency of nosocomial infection (patient days before infection belong to the 'uninfected group' and not to the 'infected group') and therefore avoid the time-dependent bias. In the data, the time-dependent biased estimate would be the difference of 21.0 days (eventually with nosocomial infection) and 8.5 days (eventually without nosocomial infection), resulting in 12.5 additional ICU days. In the time-dependent biased analysis, the patient days before infection are incorrectly counted as 'infected' patient days.

DISCUSSION

In this article, we provided the concept and framework of basic multistate modeling for nosocomial infection. Without sophisticated software, a first-step analysis of risk and consequences of nosocomial infection can be performed easily using the plug-in values of 5 accessible hazard rates. This procedure has been demonstrated with real ICU data. At least, the results are free of time-dependent and competing-risk biases. Even if the assumption of time-constant hazards is not realistic, the plug-in analysis can give good approximations. The formulas shown herein can be used to reconstruct analyses from published articles if the values are available (see examples in Wolkewitz et al[16] and Wolkewitz et al[17]).

The following quantities can also be displayed in dependency of the constant hazards and time: mortality risk

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of patients with and without nosocomial infection, attributable mortality, and population-attributable fraction (unpublished data). All time-dependent measurements approximate eventually (for large time points) the ones shown in Table 2.

The basic multistate model can be extended in several ways. The first extension is that the hazards themselves might depend on time. From our experience, the discharge hazard λ_{02} often starts large at earlier time points and then decreases because the proportion of shorter-stay patients is usually large.[18] Even though a simple mathematical form (as shown in this article) is then intractable, all time-dependent measurements can be estimated with nonparametric estimation methods allowing for time-dependent hazards.[15,19,20] Notably, the exact relationships between the event-specific hazard ratios and the odds ratio (as shown in this paper) do not hold if the hazards depend on time. The next extension is to allow for confounding adjustments and control. Time-independent potential confounders can be easily included in the corresponding regression models (ie, logistic, Cox, and/or Poisson). The time-dependent extension of the logistic regression model for nosocomial infection is the Fine and Gray model, which yields so-called subdistribution hazard ratios and quantifies effects in terms of the cumulative risk of nosocomial infection (see examples in Wolkewitz et al[21]). If cohort data from many ICUs are available, frailty models account for the fact that patients are clustered within ICUs.[21,22] In the presence of time-dependent variables (eg, invasive devices such as mechanical ventilation), some approaches aim to adjust for time-dependent confounding via marginal structural models.[23]

These techniques are not restricted to nosocomial infection and can also be applied to other time-dependent complications in the hospital such as delirium during ICU stay.[24] To improve reports from cohort studies about nosocomial infection, we recommend that the corresponding event counts be provided as well as the total patient days so that a simple multistate model reanalysis can be performed.

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Address correspondence to Martin Wolkewitz, PhD, Freiburg Center of Data Analysis and Modelling, Eckerstr 1, Room 105, 79104 Freiburg, Germany (wolke@imbi.uni-freiburg.de).

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