STATISTICAL NOTE

Jan Beyersmann
Petra Gastmeier
Martin Schumacher

Incidence in ICU populations: how to measure and report it?

J. Beyersmann (✉)
Institute of Statistics, University of Ulm,
Ulm, Germany
e-mail: jan.beyersmann@uni-ulm.de
Tel.: +49-731-5033100
Fax: +49-731-5033109

P. Gastmeier
Institute of Hygiene and Environmental
Medicine, Charité University Medicine
Berlin, Berlin, Germany

M. Schumacher
Institute of Medical Biometry and Statistics,
University Hospital Freiburg, Freiburg,
Germany

Abstract Incidence of ICU events is mostly measured in one of two ways which differ by the denominator only. Either the number of incident events divided by the number of ICU patients is reported or the number of incident events per 1,000 ICU days is calculated. The difference is relevant, but a connection is rarely made. We give an example where pneumonia diagnosis on admission has no effect on one measure of mortality incidence, but increases the other. We demonstrate how to connect the two measures of incidence. The conclusion is that so-called 'competing incidences' should also be reported.

Keywords Competing risks ·
Incidence rate · Incidence proportion ·
Adverse event

Introduction

Incidence of (not just) ICU events such as ICU mortality, ICU-acquired infections, etc., is typically measured in one of two ways. Either the *incidence proportion*

$$\frac{\text{number of incident events}}{\text{number of patients}}$$

or the *incidence rate*

$$\frac{\text{number of incident events}}{\text{number of patient-days}}$$

is calculated. As a rule of thumb, there is a preference for the incidence rate, because its denominator accounts for the patient-time at risk (e.g. [9], Sec. 1.3). Strangely, the connection between these two concepts is rarely demonstrated (a recent exception being [7]). And it does not help much that, as Vandenbroucke and Pearce [17] nicely summarize, for both concepts the terms *mortality* and *morbidity* (depending on the outcome), *rate* or just *incidence* (as in the title of this paper) are being used. Yet another common term for the incidence proportion is *cumulative incidence*; the origins of and the intuitions behind many of these terms have been discussed by Turner and Hanley [16].

Precedent intensive care literature has discussed the statistical analysis of incident ICU events. For studying risk factors for the incidence of nosocomial infections, Irala-Estévez et al. [8] compared logistic regression, which targets the incidence proportion, with Cox regression, which targets incidence rates (and time-dependent generalizations thereof, see the summary section). Irala-Estévez et al. suggested to use Cox regression. In an editorial on this work, Chevret [5] suggested that so-called 'competing risks' may be an issue in Cox analyses and, hence, also for incidence rates. For ICUs (and hospitals), the presence of 'competing risks' (or: 'competing'

events) means that patients do not necessarily acquire an infection on the unit (if the incidence of infection is being studied), but ICU stay may end without prior infection.

For studying ICU mortality, Resche-Rigon et al. [12] stated that alive discharges must be treated as a 'competing risk'. However, Schoenfeld [13] commented that the so-called survival methods—which include incidence rates and Cox regression, potentially also accounting for 'competing risks'—are inappropriate, because simply *delaying* ICU death does not benefit patients who die on the unit. Schoenfeld extended his argument to any ICU outcome and proposed to always consider incidence proportions.

The aim of this paper is to demonstrate the connection between the two concepts of incidence. We show that it is the concept of 'competing risks' that reconciles the two incidence notions. We have chosen to do so using the common epidemiological workhorses incidence rate and incidence proportion. As a consequence, our computations are easily reproducible without dedicated statistical software.

To fix ideas, we exemplarily consider the incidence of ICU mortality. We also assume essentially complete data from a prospective cohort study on an ICU population. Other study designs in the present context are, e.g., discussed by Michel et al. [10]. By 'essentially complete' we mean that follow-up data are available for (essentially) all individuals from ICU admission until end of ICU stay.

For the outcome ICU death, the incidence proportion is typically reported, i.e., the number of ICU deaths divided by the number of patients, because it is considered to reflect 'absolute patient risk'. Below, we will show how to easily calculate the incidence proportion, starting from *both* the incidence rate of ICU mortality *and* the 'competing' incidence rate of alive discharge from the ICU.

The practical consequences will be that

– incidence rates of ICU events do not translate into incidence proportions without consideration of the 'competing' incidence rates,
– 'competing' incidences should always be reported,
– incidence rates explain how incidence proportions come about.

'Competing risks' are omnipresent in outcome studies of ICU events, but we caution readers not to overinterprete the notion of 'competition of risks'—which is why we have always put it into quotation marks. 'Competing risks' is simply a technical term to describe a situation where the incidence of one event such as ICU death may be precluded (for the current admission episode) by the incidence of a different event such as alive discharge.

From incidence rates to incidence proportions via 'competing risks'

Consider the incidence rate of ICU deaths, i.e., number of ICU deaths/number of patient-days. Observation of ICU deaths is subject to 'competing risks', which means that a patient may be discharged alive from ICU and, hence, does not die on the unit. Also introduce the *'competing' incidence rate of alive discharge*,

$$\frac{\text{number of alive discharges}}{\text{number of patient-days}}.$$

The connection between incidence rates and incidence proportions is computationally extremely simple, once we have conceptually acknowledged the existence of an incidence of a 'competing event'. Because ICU cohort data are typically complete in that each patient in the cohort of, say, n patients is followed-up from ICU admission to end of ICU stay (either alive or dead), we have that

$$\text{number of ICU deaths} + \text{number of alive discharges}$$
$$= \text{size of the cohort} = n.$$

Hence, calculating the relative magnitude of the incidence rate of ICU death as compared to the sum of both incidence rates, we get

$$\frac{\text{number of ICU deaths}}{\text{number of patient-days}} \bigg/$$
$$\left(\frac{\text{number of ICU deaths}}{\text{number of patient-days}} + \frac{\text{number of alive discharges}}{\text{number of patient-days}} \right)$$
$$= \frac{\text{number of ICU deaths}}{\text{number of patient-days}} \bigg/ \frac{n}{\text{number of patient-days}}$$
$$= \frac{\text{number of ICU deaths}}{n},$$

which is the incidence proportion of ICU death!

The above calculation has the following interpretation: We should think of the incidence rates as *forces* that pull the individual patient towards a certain outcome. In fact, such forces are not necessarily less than 100 % depending on how *patient-time* is measured. The relative magnitude of these forces as compared to the sum of all forces (giving the *any-event force* or *any-event incidence rate*) then yields the incidence proportion (not exceeding 100 %), while the any-event force informs about the length of ICU stay. We now demonstrate these ideas in an ICU data example.

Glossary of statistical terms. The present paper focuses on incidence proportion, incidence rate and 'competing risks'

Incidence proportion	Number of incident events divided by sample size: a relative frequency between 0 and 100 %
Incidence rate	Number of incident events divided by the cumulative at-risk time in the sample: a time-constant incidence 'force' (hazard)
Incidence density	Synonym for *incidence rate*
Incidence	Used both for *incidence proportion* and *incidence rate*
Prevalence	Prevalence of a risk factor (in the data example: pneumonia on admission): number of prevalent patients divided by sample size
Rate	Term ambiguously used both for hazard *rates* and proportions
Patient-days	One common choice for cumulative at-risk time: sum over all patients and all days at risk
'Competing risk'	Event whose incidence precludes occurrence of the event under study, e.g., alive discharge precludes ICU death; omnipresent in ICU data sets; precludes simple inference from rates to proportions
Cause-specific hazard	Like incidence rate in the presence of 'competing risks', but not necessarily time-constant
Logistic regression	Used to study risk factors on transformed (log odds) incidence proportions
Cox regression	Used to study risk factors on hazards
Censoring	Here: observation ends before end of ICU stay; rare in ICU data sets
Left-truncation	Here: study entry after ICU admission, e.g., conditional on positive laboratory test; requires survival methods
Survival methods	Statistical methods for censored and truncated data, e.g., incidence rates, Cox regression, Aalen-Johansen estimator
Aalen–Johansen estimator	on day t for complete data: number of incident events *until* day t divided by sample size; also valid for censored and truncated data

Pneumonia on admission has no effect on, but also increases ICU mortality

Our example data set comes from the SIR 3 cohort study at the Charité university hospital in Berlin, Germany. The aim of the study was to prospectively assess the effect of hospital-acquired infections in intensive care. We exemplarily consider pneumonia diagnosis *on admission to the ICU* and its impact on ICU mortality. Details of the study are reported in [2], a more encompassing risk factor analysis has been given by Wolkewitz et al. [18], and in-depth statistical discussions using the SIR 3 study as an example are in [1] and [19]. In brief, 1876 intensive care patients admitted between February 2000 and July 2001 were included in the study cohort. Overall, 214 (11.4 %) patients died. The data are essentially complete with only 30 (1.6 %) censored observations. Censoring (end of follow-up before of end of ICU stay) was purely due to administrative reasons. For 220 (11.7 %) patients, pneumonia was diagnosed on admission. Of these, 48 (21.8 %) died. Of the 1,656 patients without pneumonia diagnosis on admission, 166 (10.0 %) patients died. Hence, the mortality proportions indicate that pneumonia on admission increases ICU mortality. This impression is substantiated by supplementing the mortality proportions with 95 % confidence intervals (CIs), which are [16.7 %, 28.0 %] with pneumonia diagnosis on admission and [8.6 %, 11.6 %] in the absence of pneumonia on admission.

We now turn to an analysis of the ICU mortality rates. With pneumonia present on admission, the incidence rate for ICU death is

$$\frac{48\,\text{deaths}}{6{,}161\,\text{patient-days}} = 7.79\text{ deaths per 1,000 patient-days}$$

with a 95 % CI of [5.87, 10.34]. The number of patient-days was calculated as the sum over all individual lengths of ICU stay of patients with pneumonia present on admission.

The incidence rate for ICU death without pneumonia on admission is

$$\frac{166\,\text{deaths}}{22{,}337\,\text{patient-days}} = 7.43\text{ deaths per 1,000 patient-days}$$

with a 95 % CI of [6.38, 8.65]. The confidence intervals are based on a log transformation, and can be computed as the incidence rate times $\exp(\pm 1.96/\sqrt{(\text{number of ICU deaths})})$.

We find that the incidence rates for ICU death are comparable with overlapping confidence intervals and an incidence rate ratio of 1.05. These incidence rates alone by no means explain the doubling of mortality *proportions* by pneumonia diagnosis reported earlier. In fact, formally computing

mortality incidence rate of pneumonia patients

$\times$ number of patient-days of patients without

on-admission pneumonia,

yields an expected number of 174.0 ICU deaths, if the patients without pneumonia on admission had the same mortality incidence rate as the patients with pneumonia on admission. However, there were 166 observed ICU deaths in the no-pneumonia group, and the incidence proportions make us expect twice as many deaths in a group of that size.

The point is to also account for the 'competing' incidence rate of alive ICU discharge. With pneumonia present on admission, the incidence rate for ICU discharge is

$$\frac{160 \text{ discharges}}{6{,}161 \text{ patient-days}}$$

$$= 25.97 \text{ discharges per } 1{,}000 \text{ patient-days}$$

with a 95 % CI of $[22.24, 30.32]$. The discharge incidence rate without pneumonia on admission is

$$\frac{1{,}472 \text{ discharges}}{22{,}337 \text{ patient-days}}$$

$$= 65.90 \text{ discharges per } 1{,}000 \text{ patient-days}$$

with a 95 % CI of $[62.62, 69.35]$.

There are two striking aspects of the incidence rates of ICU discharge: Firstly, their magnitude considerably exceeds those of ICU death. This reflects that discharge is much more common than death, even with pneumonia on admission. It also renders the difference between the incidence rates of death even more negligible in comparison.

Secondly, there is a pronounced reducing effect of pneumonia on the incidence rate of discharge with non-overlapping confidence intervals and an incidence rate ratio of 0.39. Because this is, by far, the major incidence rate (and there is essentially no effect of pneumonia on the incidence rate of death), the interpretation is that pneumonia on admission prolongs ICU stay.

This also explains why pneumonia increases the mortality *proportion*: Think of incidence rates as 'forces' (but not as probabilities or proportions). We found that pneumonia patients are exposed to essentially the same mortality force during ICU, as are patients without pneumonia. Because of a prolonged ICU stay, however, pneumonia patients are exposed to the common mortality force for a longer time, which eventually leads to more ICU deaths. We can check this by calculating for the pneumonia patients

$$\frac{48}{6{,}161} \bigg/ \left(\frac{48}{6{,}161} + \frac{160}{6{,}161} \right) = 23.1\,\%,$$

which almost equals the crude mortality proportion of 21.8 % reported earlier. In fact, we would have perfect equality, if the data had not been slightly censored. Alternatively, we could also add a censoring incidence rate in the denominator above to achieve perfect equality, but we leave this subtlety aside.

The same calculation for patients without pneumonia gives

$$\frac{166}{22{,}337} \bigg/ \left(\frac{166}{22{,}337} + \frac{1{,}472}{22{,}337} \right) = 10.1\,\%$$

which again almost equals the crude mortality proportion of 10.0 % reported earlier, and would perfectly equal that proportion in the absence of censoring.

In other words: In the present study, pneumonia diagnosis on admission leads to an increased proportion of deaths on ICU, because pneumonia patients had a prolonged ICU stay, during which they were exposed to essentially the same force of mortality. One general practical consequence is that if incidence of some ICU event is reported in terms of incidence rates, 'competing' incidence rates must always be reported.

Figures 1 and 2 illustrate this. In Fig. 1, the thickness of the arrows is proportional to the incidence rates of ICU death and ICU discharge, respectively. The visual impression is that the 'force' of ICU death is the same regardless of pneumonia status on admission, but that the major 'force' of ICU discharge is substantially reduced for the pneumonia patients.

Figure 2 illustrates the consequences on the cumulative probability of ICU deaths until day t since admission, which is estimated based on *all* incidence rates using the formula

$$\frac{\text{number of ICU deaths}}{\text{number of ICU deaths} + \text{number of alive discharges}}$$
$$\times \left(1 - \exp\left(-t \cdot \frac{\text{number of ICU deaths} + \text{number of alive discharges}}{\text{number of patient-days}} \right) \right).$$

The dashed horizontal lines are the incidence rate-based approximations of the crude mortality proportions $48/(48 + 160) = 23.1\,\%$ for the pneumonia patients and $166/(166 + 1472) = 10.1\,\%$ for the patients without pneumonia calculated earlier. The curve for the pneumonia patients reaches 23.1 % after the no pneumonia curve has reached 10.1 %, because pneumonia patients stay longer on ICU.

Summary

Incidence of events during ICU stay is typically quantified as the incidence rate, taking person-time as the denominator, or as the incidence proportion, taking cohort size as the denominator. Occurrence of such events is subject to 'competing risks': an ICU-acquired infection may not be observed due to prior end of ICU stay. Death on ICU may not be observed due to alive discharge from the unit. We recommend to always calculate and report the incidence rates of such 'competing' events. Not considering these 'competing' incidence rates will yield an incomplete and potentially misleading picture.

The sum of *all* incidence rates yields the incidence rate until any event. The incidence rate *of interest* divided by the any-event incidence rate equals the incidence proportion, if (as is realistic in an ICU setting) follow-up data of all patients are complete. Hence, one may calculate the incidence proportions from the incidence rates but not vice versa, because the patient-time at risk cancels out.

Fig. 1 Thickness of the *arrows* illustrates incidence rates of ICU death and ICU discharge
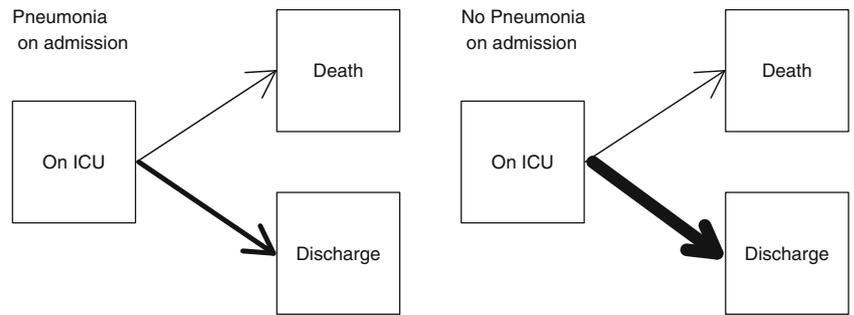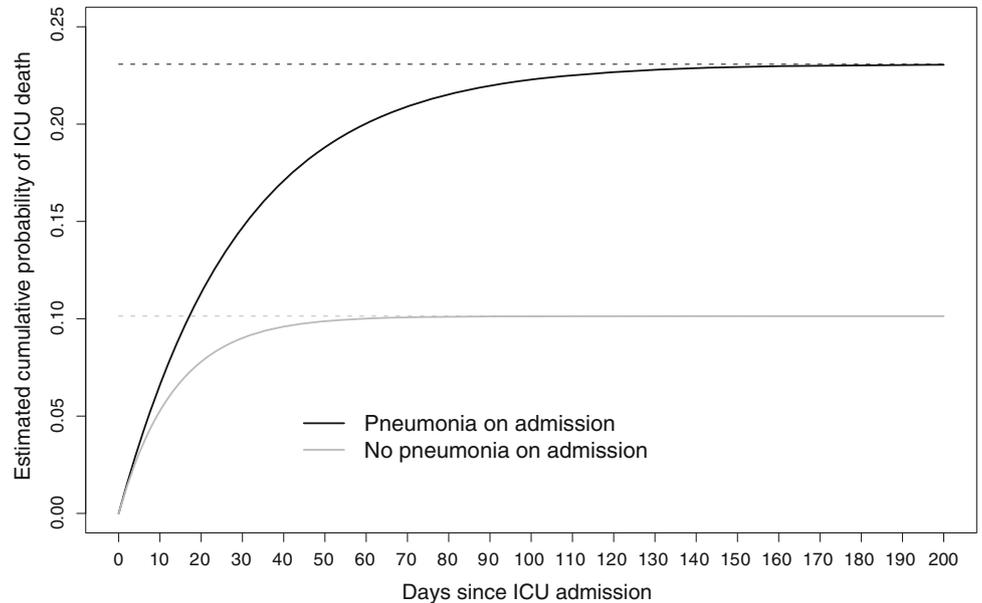

Fig. 2 Cumulative probability of ICU deaths until day t since admission; derived from both incidence rates illustrated in Fig. 1

Both these facts and the data example illustrate that one may use the incidence rates to understand *how* the incidence proportions come about.

If follow-up data are incomplete, the incidence rate will be preferable, because, as noted earlier, it accounts for (observed) patient-time at risk. An ICU-relevant setting where this may happen is when patients enter the cohort not on admission but conditional on some later event, e.g., a positive finding from some laboratory test. Such delayed entry data are called left-truncated and incidence rates account for left-truncation, but incidence proportions do not [3, 15].

However, the use of incidence rates also necessitates a simplification in that they assume the 'force' of an event like death on ICU to be the same for every ICU day. That is, incidence rates assume the underlying event-specific 'force' or hazard to be time-constant. Such an assumption can be checked using a non-parametric ('model-free') generalization of the incidence rate known as the Nelson-Aalen estimator. In fact, the assumption was maintainable in our example (see the Nelson–Aalen estimates in [1]), but may be violated for other ICU data. Furthermore,

general statistical techniques include the Aalen–Johansen estimator as an alternative to incidence proportions, if data are incomplete as described earlier. If data are complete, the Aalen–Johansen estimator at day t for, e.g., ICU death equals the number of ICU deaths until day t divided by the number of patients, i.e., the incidence proportion over the course of time. We also mention the Cox model for comparing time-dependent 'forces' of incident events. A brief tutorial on such methods for the ICU setting is [19], and a practical textbook treatment is [4].

We have exemplarily considered ICU death as an outcome, which is typically reported using incidence proportions. However, our considerations apply to other ICU outcomes as well: Incidence rates do translate into incidence proportions, if the incidence rate of 'competing events' is also accounted for, and this is why it must be reported. We do note, however, that there are ICU outcomes that require models that are more complicated than 'competing risks'. For instance, ventilator-associated pneumonia (VAP) is not only subject to 'competing risks', being a nosocomial infection as discussed above,

but it is also associated with a *time-dependent* exposure [14]. The challenge here is that there are also incidence rates between ventilation statuses 'ventilation off' and 'ventilation on'. Customized statistical techniques have been discussed by [15] and—with special emphasis on VAP—[11]. The use of different denominators for computing VAP incidence has been considered by [6].

References

1. Beyersmann J, Schumacher M (2008) Time-dependent covariates in the proportional subdistribution hazards model for competing risks. Biostatistics 9:765–776
2. Beyersmann J, Gastmeier P, Grundmann H, Bärwolff S, Geffers C, Behnke M, Rüden H, Schumacher M (2006) Use of multistate models to assess prolongation of intensive care unit stay due to nosocomial infection. Infect Control Hosp Epidemiol 27:493–499
3. Beyersmann J, Wolkewitz M, Allignol A, Grambauer N, Schumacher M (2011) Application of multistate models in hospital epidemiology: advances and challenges. Biom J 53:332–350
4. Beyersmann J, Allignol A, Schumacher M (2012) Competing risks and multistate models with R. Springer, New York
5. Chevret S (2001) Logistic or cox model to identify risk factors of nosocomial infection: still a controversial issue. Intensiv Care Med 27(10):1559–1560
6. Eggimann P, Hugonnet S, Sax H, Touveneau S, Chevrolet JC, Pittet D (2003) Ventilator-associated pneumonia: caveats for benchmarking. Intensiv Care Med 29(11):2086–2089
7. Grambauer N, Schumacher M, Dettenkofer M, Beyersmann J (2010) Incidence densities in a competing events analysis. Am J Epidemiol 172(9):1077–1084

8. Irala-Estévez J, Martínez-Concha D, Díaz-Molina C, Masa-Calles J, del Castillo AS, Navajas RFC (2001) Comparison of different methodological approaches to identify risk factors of nosocomial infection in intensive care units. Intensiv Care Med 27(8):1254–1262
9. Kestenbaum B (2009) Epidemiology and biostatistics: an Introduction to Clinical Research. Springer, New York
10. Michel P, Quenon JL, de Sarasqueta AM, Scemama O (2004) Comparison of three methods for estimating rates of adverse events and rates of preventable adverse events in acute care hospitals. Br Med J 328:199–202
11. Nguile-Makao M, Zahar J, Français A, Tabah A, Garrouste-Orgeas M, Allaouchiche B, Goldgran-Toledano D, Azoulay E, Adrie C, Jamali S et al (2010) Attributable mortality of ventilator-associated pneumonia: respective impact of main characteristics at ICU admission and VAP onset using conditional logistic regression and multi-state models. Intensiv Care Med 36(5):781–789
12. Resche-Rigon M, Azoulay E, Chevret S (2006) Evaluating mortality in intensive care units: contribution of competing risks analyses. Crit Care 10:R5
13. Schoenfeld D (2006) Survival methods, including those using competing risk analysis, are not appropriate for intensive care unit outcome studies. Crit Care 10(1):103

14. Schoenfeld D, Bernard G et al (2002) Statistical evaluation of ventilator-free days as an efficacy measure in clinical trials of treatments for acute respiratory distress syndrome. Crit Care Med 30(8):1772
15. Schumacher M, Allignol A, Beyersmann J, Binder N, Wolkewitz M (2013) Hospital-acquired infections—appropriate statistical treatment is urgently needed! Int J Epidemiol 42(5):1502–1508
16. Turner EL, Hanley JA (2010) Cultural imagery and statistical models of the force of mortality: Addison, gompertz and pearson. J Royal Stat Soc Series A (Stat Soc) 173(3):483–499
17. Vandenbroucke JP, Pearce N (2012) Incidence rates in dynamic populations. Int J Epidemiol 41:1472–1479
18. Wolkewitz M, Vonberg R, Grundmann H, Beyersmann J, Gastmeier P, Bärwolff S, Geffers C, Behnke M, Rüden H, Schumacher M (2008) Risk factors for the development of nosocomial pneumonia and mortality on intensive care units: application of competing risks models. Crit Care 12(2):R44
19. Wolkewitz M, Beyersmann J, Gastmeier P, Schumacher M (2009) Modeling the effect of time-dependent exposure on intensive care unit mortality. Intensiv Care Med 35:826–832. doi:10.1007/s00134-009-1423-6