

Conditional Survival: A Useful Concept to Provide Information on How Prognosis Evolves over Time ^{CME}

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Abstract

Conditional survival (CS) is defined as the probability of surviving further t years, given that a patient has already survived s years after the diagnosis of a chronic disease. It is the simplest form of a dynamic prediction in which other events in the course of the disease or biomarker values measured up to time s can be incorporated. CS has attracted attention in recent years either in an absolute or relative form where the latter is based on a comparison with an age-adjusted normal population being highly relevant from a public health perspective. In its absolute form, CS constitutes the quantity of major interest in a clinical context. Given a clinical cohort of patients with a particular type of cancer, absolute CS can be estimated by conditional Kaplan–Meier estimates in strata

defined, for example, by age and disease stage or by a conditional version of the Cox and other regression models for time-to-event data. CS can be displayed as a function of the prediction time s in parametric as well as nonparametric fashion. We illustrate the use of absolute CS in a large clinical cohort of patients with multiple myeloma. For investigating CS, it is necessary to ensure almost complete long-term follow-up of the patients enrolled in the clinical cohort and to consider potential age–stage migration as well as changing treatment modalities over time. CS provides valuable and relevant information on how prognosis develops over time. It also serves as a starting point for identifying factors related to long-term survival. *Clin Cancer Res*; 21(7); 1530–6. ©2015 AACR.

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Learning Objectives

Upon completion of this activity, the participant should have a better understanding of the concept as well as basic statistical aspects of conditional survival and how it updates prognosis for patients with cancer who have already survived a number of years.

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Introduction

When determining the prognosis of a patient with a chronic disease, for example, a specific type of cancer, this quantity is

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usually expressed in terms of an overall survival (OS) probability. The survival function $S(t)$ attached to OS denotes the probability that a patient will still be alive t years after diagnosis. Thus, the survival function $S(t)$ provides the relevant information for the patient and the treating physician at $t = 0$, that is, the time of diagnosis. In almost all such clinical situations, additional information on the patient's demographic and tumor characteristics, for example, age, gender, and disease stage, is available at $t = 0$ ("baseline"). These baseline characteristics are then used for a prognostic classification to arrive at a more specific quantification of the patient's prognosis. Thus, for example, the 5-year survival probability, $S(5)$, might be much higher for a patient in an early disease stage as compared with the 5-year survival probability of a patient in an advanced stage of the disease. Such more or less

elaborated classification systems exist for all cancer entities (1) and are routinely used in clinical practice.

OS, however, does not reflect how prognosis changes over time and can, therefore, be considered a "static" prediction. In particular, OS is not very informative for a patient (and his/her treating physician) who has already survived a number of years. Such a patient, still alive after s years, would be much more interested in having information on the conditional probability of surviving further t years, given that she/he already survived s numbers of years. This conditional probability, usually referred to as conditional survival (CS; refs. 2, 3), is given as

$$CS(t|s) = \frac{S(s+t)}{S(s)}$$

by using the standard definition of a conditional probability. Thus, for example, $CS(5|2)$ denotes the conditional probability of surviving $5 + 2 = 7$ years, given that the patient is still alive at $s = 2$ years; with s usually being called the prediction time or, more precisely, the time at which the prediction is made. Of course, CS can also be more specifically determined by using additional information on the patient's baseline characteristics. Clearly, for prediction time $s = 0$, $CS(t|0)$ coincides with the survival function $S(t)$ since $S(0) = 1$.

In principle, CS can be calculated considering usual Kaplan-Meier estimates $\hat{S}(t)$ and is given by

$$\widehat{CS}(t|s) = \frac{\hat{S}(s+t)}{\hat{S}(s)}$$

Thus, for instance, if we want to estimate $CS(5|2)$ we simply divide the Kaplan-Meier estimator at $t = 7$ by the Kaplan-Meier estimator at $t = 2$ resulting in

$$\widehat{CS}(5|2) = \frac{\hat{S}(2+5)}{\hat{S}(2)} = \frac{\hat{S}(7)}{\hat{S}(2)}$$

This leads to the same estimates as an approach in which we compute CS probabilities by restricting ourselves to all patients who are alive at $s = 0, 1, 2, 3, 4, 5$ years, respectively, and not censored before s (we say they are in the "risk set" at s) and calculate the Kaplan-Meier estimator, so-called the conditional Kaplan-Meier estimator, for each of these restricted samples with $s = 0, 1, 2, 3, 4, 5$ years, respectively, as a new time origins.

Both approaches by investigating the Kaplan-Meier estimator to estimate CS probabilities $\widehat{CS}(t|s)$ provide identical results.

Independent of the underlying approach used to estimate CS probabilities, CS can additionally be estimated in strata defined by baseline patient and tumor characteristics.

As an alternative to using Kaplan-Meier estimates, we can fit a Cox regression model derived at baseline $s = 0$ to the patient cohort—or another regression model for time-to-event data—by taking important baseline characteristics into account. From the estimates obtained from the Cox regression model, we can then calculate estimates of the survival probabilities $S(t)$ that are necessary to derive estimates of CS according to the equation given above. Or, following the textbook *Dynamic Prediction in Clinical Survival Analysis*, by van Houwelingen and Putter (4), conditional versions of the Cox regression models for the prediction time points $s = 0, 1, 2, 3, 4, 5$ by restricting to all patients who are alive at $s = 0, 1, 2, 3, 4, 5$ years, respectively,

could be investigated to estimate CS probabilities $\widehat{CS}(t|s)$. CS probabilities derived from a Cox regression model will in general produce more stable estimates of CS than will the procedure based on (conditional) Kaplan-Meier estimates in strata (4). In both cases, standard errors that are needed to construct confidence intervals can be calculated in a straightforward manner (5).

In this article, we focus either on conditional Kaplan-Meier estimators or on conditional versions of the Cox regression models for each prediction time point $s = 0, 1, 2, 3, 4, 5$ as new time origins as suggested by van Houwelingen and Putter (4), when estimating CS probabilities $\widehat{CS}(t|s)$.

Data Example

To illustrate the use of CS, we take a clinical cohort of all consecutive patients with multiple myeloma (6, 7) diagnosed in the Department of Hematology, Oncology, and Stem Cell Transplantation at the University Medical Center Freiburg (Germany) from 1997 to 2011 with follow-up until the end of 2011. Table 1 gives a summary on the distribution of gender, age at diagnosis, stage according to Durie and Salmon (D&S; ref. 8), and admission period. These periods are defined by taking different but standardized treatment modalities into account. In the right column of Table 1, we have displayed the results of a Cox regression model in terms of HRs with 95% confidence intervals and P values from the corresponding Wald tests derived at baseline $s = 0$. As expected (9, 10), advanced stage (II and III) leads to a 2-fold increase of the hazard of dying as compared with early stage (I); we used only the D&S prognostic classification system (D&S; ref. 8) and not the International Staging System (11), because the latter was not available for all patients with multiple myeloma in the cohort. The hazard of dying also increases with increasing age at diagnosis whereas gender and admission period do not exhibit an effect on OS (12, 13).

Prognosis at $t = 0$ (baseline) is summarized in Fig. 1A–C. Figure 1A shows the Kaplan-Meier estimator of OS in the whole patient cohort over 25 years. From that we can derive that the 5-year survival probability $S(5)$ is estimated as about 50%. In Fig. 1B and C, we have displayed the Kaplan-Meier estimates of OS according to age at diagnosis and stage, respectively. The estimated 5-year survival probabilities vary substantially, from 25% for patients ages 70 or older to 65% for patients younger than 60 years. Similarly, D&S stage I patients have an estimated

Table 1. Patients' characteristics and results from the Cox model for the clinical cohort of patients with multiple myeloma

	n (%)	HR (95% CI)	P
Gender			
Female	343 (42.0%)	1 (–)	0.89
Male	473 (58.0%)	1.00 (0.83-1.20)	
D&S stage			
I	241 (29.5%)	1 (–)	<0.001
II and III	575 (70.5%)	2.19 (1.76-2.74)	
Age, y			
<60	339 (41.5%)	1 (–)	<0.001
60-70	279 (34.2%)	1.72 (1.37-2.16)	
≥70	198 (24.3%)	3.46 (2.70-4.44)	
Admission			
Before 2001	223 (27.3%)	1 (–)	0.56
2001-2007	285 (34.9%)	1.13 (0.90-1.42)	
After 2007	308 (37.8%)	1.12 (0.83-1.50)	

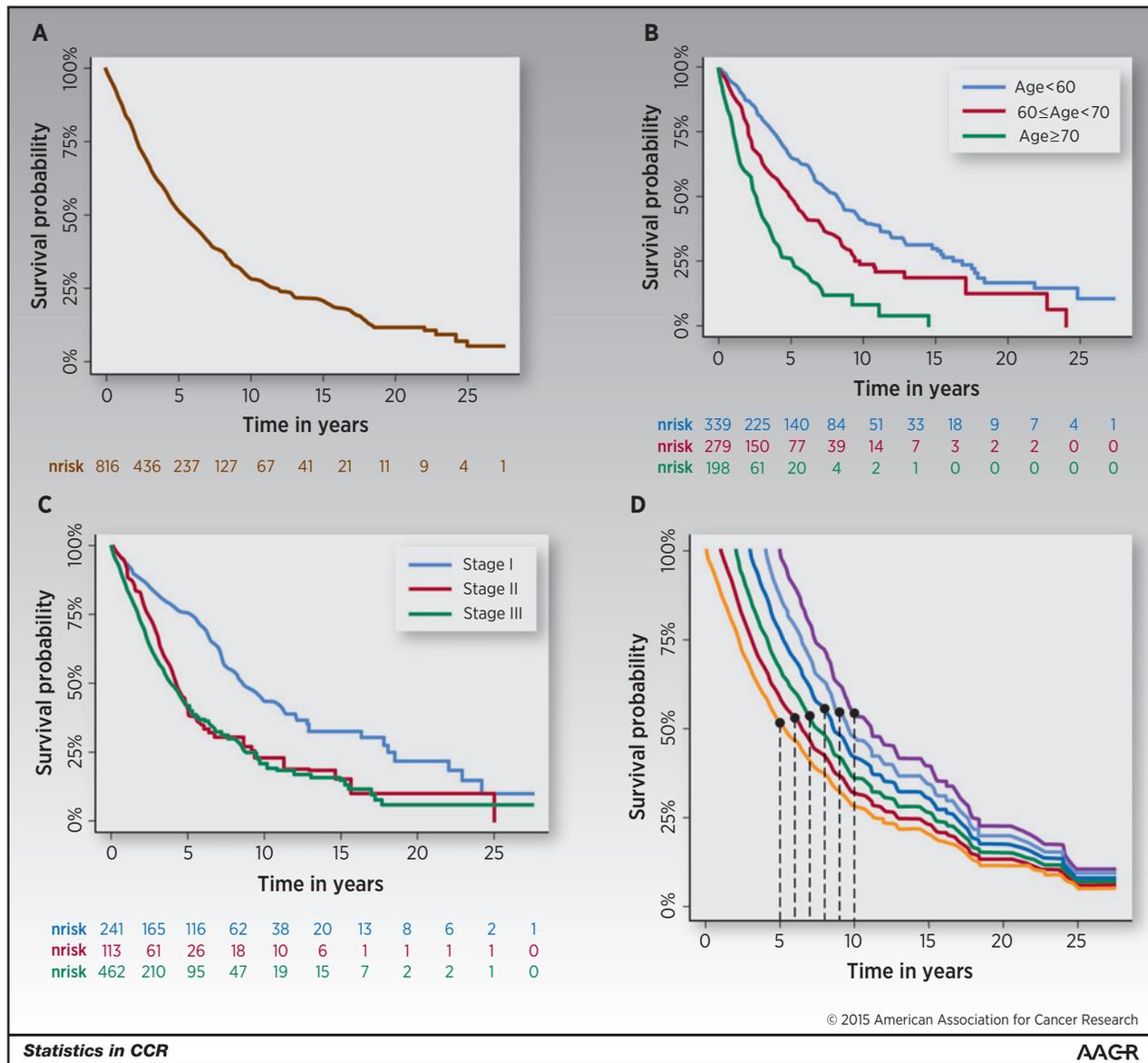


Figure 1. OS of patients with multiple myeloma in the whole clinical cohort (A), by age category (B), and by D&S stage (C). D, conditional survival $CS(t|s)$ in the whole cohort for prediction times $s = 0$ (bottom, orange), $s = 1$ (red), $s = 2$ (green), $s = 3$ (dark blue), $s = 4$ (light blue), and $s = 5$ (top curve, purple).

5-year survival probability of about 75% compared with 40% for D&S stages II and III patients. Figure 1C also shows that D&S stage II and III patients have a very similar prognosis; therefore, we have combined both D&S stages in the Cox regression model.

A first illustration of CS is given in Fig. 1D, in which Kaplan–Meier estimates of CS curves $CS(t|s)$ are displayed for $s = 0, s = 1, \dots$ up to $s = 5$. The lower curve, $CS(t|0)$, coincides with the OS curve shown in Fig. 1A, whereas the upper curve represents $CS(t|5)$ providing the conditional probability of surviving further t years, given that a patient has already survived $s = 5$ years. From the set of curves, we can see, for example, that the estimated 5-year CS probabilities $CS(5|s)$ highlighted by dots are almost identical and equal to 50% for $s = 0, s = 1, \dots$ up to $s = 5$.

CS Displayed as a Function of Prediction Time

Instead of showing a set of survival curves as done in Fig. 1D or presenting some numbers in a table, it is much more informative to display CS as a function of prediction time s . This means that, for example, we would plot $CS(5|s)$, the conditional probability of surviving further 5 years given that a patient has already survived s years. This can in principle be done for every prediction time s , but for practical purposes it is mostly sufficient to do that for $s = 0, s = 1, \dots$ in steps of 1 year (2). In Fig. 2A, we show the estimated 5-year CS using the conditional Kaplan–Meier estimator with the corresponding 95% confidence intervals. The latter are derived from the SEs of the conditional Kaplan–Meier estimates using standard techniques (5).

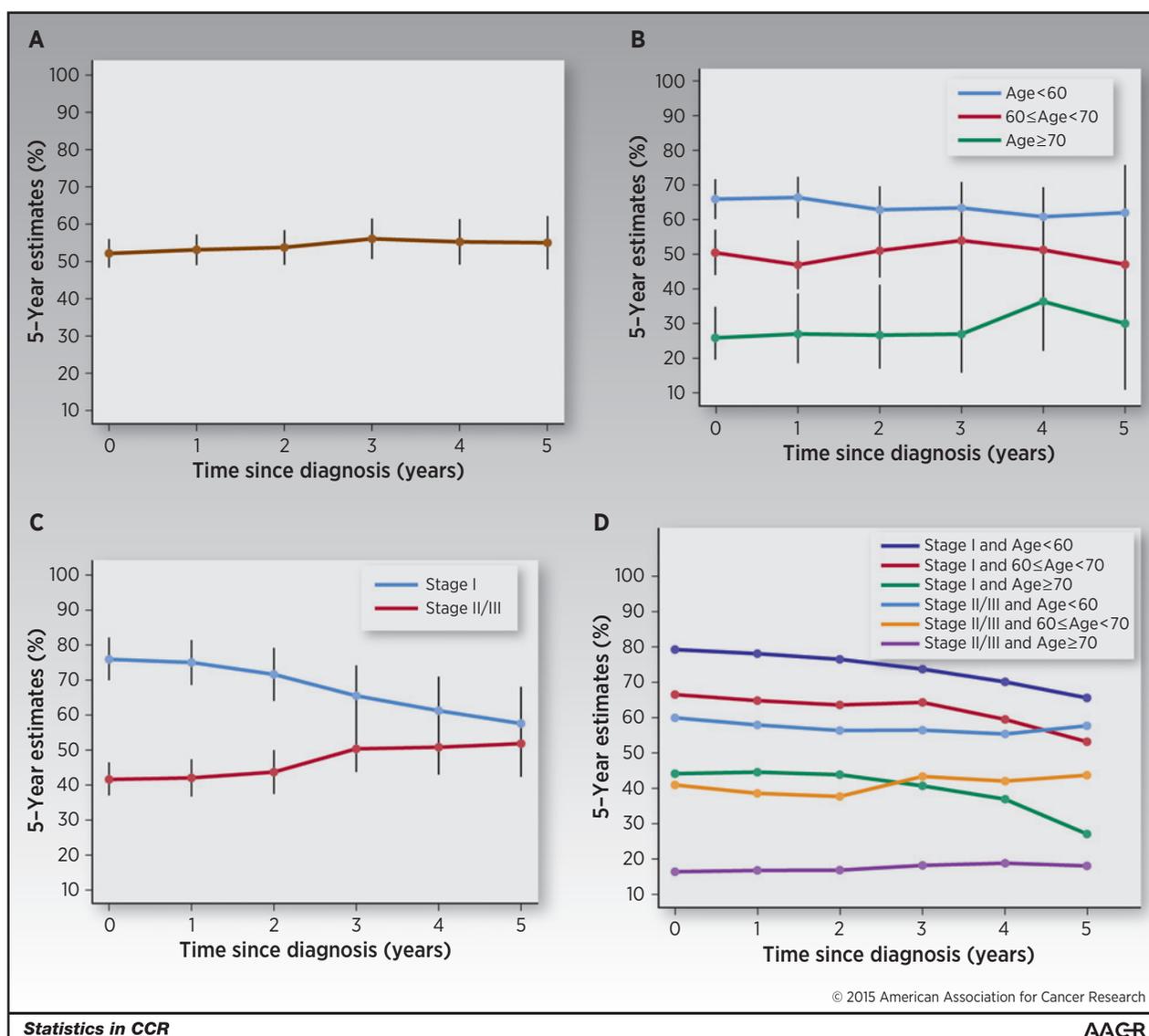


Figure 2.

Five-year conditional survival $CS(5|s)$ as a function of prediction time s in the whole cohort (A), by age category (B), by D&S stage (C), and by age-D&S stage categories (D).

From the presentation in Fig. 2A, it becomes much more evident that 5-year CS is almost constant and about 50% irrespective of prediction time s as can be derived from the set of survival curves displayed in Fig. 1D. We have a similar impression when looking at 5-years CS in the three categories for age at diagnosis (Fig. 2B). Patients younger than 60 years have a constant 5-year CS of about 65% whereas patients ages 70 or older have a much lower, but also constant 5-year CS of about 25%. This constant pattern changes when looking at 5-year CS stratified by D&S stage. Patients with D&S stage I disease have a 5-year CS of about 75% at $s = 0$ (baseline) that decreases to about 60% at $s = 5$. On the other hand, for patients with D&S stage II or III disease, 5-year CS increases from about 40% at $s = 0$ (baseline) to 55% at $s = 5$.

So far, we have used the conditional Kaplan–Meier estimates in the whole patient cohort or in the respective strata defined by age

at diagnosis and D&S stage as displayed in Fig. 1A–C to estimate 5-year CS as a function of prediction time s . For a more detailed stratification, however, the resulting subgroups become too small, to produce sensible estimates. For a stratification by age at diagnosis and D&S stage, we therefore used the alternative method based on the conditional versions of the Cox regression model presented in Table 1, but in a simplified version omitting gender and admission period that both did not show an effect on the hazard of dying. This Cox regression model, which includes age and D&S as covariates, is fitted for each prediction time point $s = 0, 1, 2, 3, 4, 5$, respectively.

Figure 2D shows the estimated 5-year CS for the six age–stage categories confirming the impression that 5-year CS decreases slightly for patients with a favorable age–stage combination at baseline whereas it slightly increases for patients with an unfavorable age–stage combination at baseline. For reasons of clarity,

we did not provide confidence intervals in Fig. 2D, but it has to be taken into account that their width is considerable and increasing with prediction time s ; actually, the largest confidence interval is obtained for the D&S stage I—age older than 70 category as 0.13 to 0.57. Also here, the use of the conditional version of a Cox regression model leads to more stable results in the sense of narrower confidence intervals as compared with the use of Kaplan–Meier estimates in strata.

Prerequisites for Analyzing CS

From the considerations noted above, it is obvious that we need a sufficiently large dataset for a sensible analysis of CS. In our data example, the clinical cohort consisted of 816 patients diagnosed with multiple myeloma, which may be considered fairly large, but, as we have already seen, subgroups resulting from stratification, for example, by age–stage categories, are much smaller. In the previous section, we have shown that CS should then be derived by a regression model for time-to-event data as the Cox model.

Therefore, a limitation of CS estimated in strata, for example, 5-year CS probabilities for patients ages 70 or older, is that the resulting subgroups become too small to produce sensible estimates for later prediction times. This can in principle be resolved by reducing the conditional probability of surviving further $t = 5$ years of interest $[CS(5|s)]$ to $t = 2$ years of interest $[CS(2|s)]$ given that she/he already survived s years. For instance, patients with cancer diagnosed at older age could benefit from this setting even if the all-cause mortality hazard might be increasing. Because of a potentially increasing all-cause hazard in specific subgroups, such as patients ages 70 and older with D&S stage III, 2- or 5-year CS estimates could indicate a less favorable rather than a favorable future prediction, which still may be informative and gives patients an estimate of their long-term survival. Therefore, CS summaries—albeit useful and informative—need to be appropriately discussed with patients and used with prudent care.

A second prerequisite is that we have to ensure almost complete follow-up. In Fig. 1A–C, we give the number of patients at risk at various time points and see that these numbers dramatically decrease. The reason for this is 2-fold: Patients who died are no longer counted in the risk set as are patients who are censored. Censoring can naturally occur due to the last contact deadline and the resulting termination of follow-up—we call that administrative censoring—but can also occur for other reasons, for example, due to dropout. Clearly, we should minimize the latter, and an inspection of the censoring distribution may be used to check whether we have been successful. Figure 3A displays the Kaplan–Meier estimates of the censoring distribution—sometimes also called the reverse Kaplan–Meier curves (14)—stratified by admission period. Thus, for instance, the blue curve represents the censoring distribution of patients admitted before 2001. Ideally, there should be no censoring for these patients within the first 11 years, and the curve should stay on the 100% level, which it almost always does. Consequently, we have very few dropouts in this clinical cohort, and the censoring distributions reflect more or less the entry distributions of patients in the three admission periods.

When analyzing CS in a clinical cohort, we have to be aware of the fact that this cohort is usually not population based, and potential selection of patients has to be taken into account. Importantly, we must consider change of patient characteristics over time and/or the change of treatment concepts, including intensive or nonintensive therapies. From an inspection of Fig. 3B,

which shows the Kaplan–Meier estimates of OS according to admission period, one could get the impression that patients admitted before 2001 have a better prognosis than patients admitted later. Simultaneously, however, we observe an apparent age–stage migration that is summarized in the bar charts displayed in Fig. 3C and D. From these two figures, we see that patients admitted before 2001 were much younger and in earlier D&S stages as compared with those admitted later. Thus, the results of an unadjusted analysis as presented in Fig. 3B can be totally misleading. Instead, we have to take these patient characteristics properly into account as we have done in the Cox regression model given in Table 1. As we have already seen, admission period does not exhibit an effect after adjusting for age category and D&S stage.

Discussion and Conclusions

We have shown in this article that CS provides further information on the prognosis of patients with cancer, especially how their prognosis evolves over time. Taking the perspective of a patient (and/or her/his treating physician) who already survived a number of years, CS provides the relevant information since prognosis is adjusted for the time the patient already survived. For most tumor entities, it is hoped that CS will increase if a patient survives for a number of years. Zabor and colleagues (3) write "As a rule, CS estimates increase as the number of years survived increases, a relationship that is usually even more striking for patients with advanced-stage disease." This has been shown to hold true for many tumor entities, for example, colon cancer (2), melanoma (3), or lung cancer (5). The shape of CS is directly linked to the shape of the hazard function, which plays a central role for the understanding of mechanisms in survival analysis (15), and is also the basis for investigating the effects of prognostic factors in the Cox regression model. The hazard function, also called the instantaneous death rate (15), is the conditional probability of a patient dying in a short time interval after s , given that the patient is alive at s . Thus, a decreasing hazard rate leads to increasing CS and a constant hazard rate to constant CS, a pattern that we have observed for the patients with multiple myeloma. In our own experience, we have also observed decreasing CS in patients with chronic lymphocytic leukemia that probably reflects the progressive nature of this particular malignant disease.

We have defined and used CS in a straightforward manner by using the fact that the patient is alive at prediction time s as the conditioning event. Alternatively, one could determine CS, given that the patient is alive and progression/recurrence free at s . This approach is used for example by Zamboni and colleagues (2) when determining CS for patients with colon cancer. In general, by using a patient's "history"—from diagnosis to prediction time s —we can refine CS toward a more specifically determined prognosis. The "history" may contain events in the course of the disease like recurrence or progression (as described above) or longitudinal measurements of one or several biomarkers. This will be especially relevant for disease monitoring based on molecular or other markers obtained by noninvasive or minimally invasive methods, potentially allowing the early detection of treatment response/failure or disease recurrence/progression. A more general approach like this one is called "dynamic prediction" with CS constituting its simplest form. Dynamic predictions can be derived from multistate models and/or joint models for

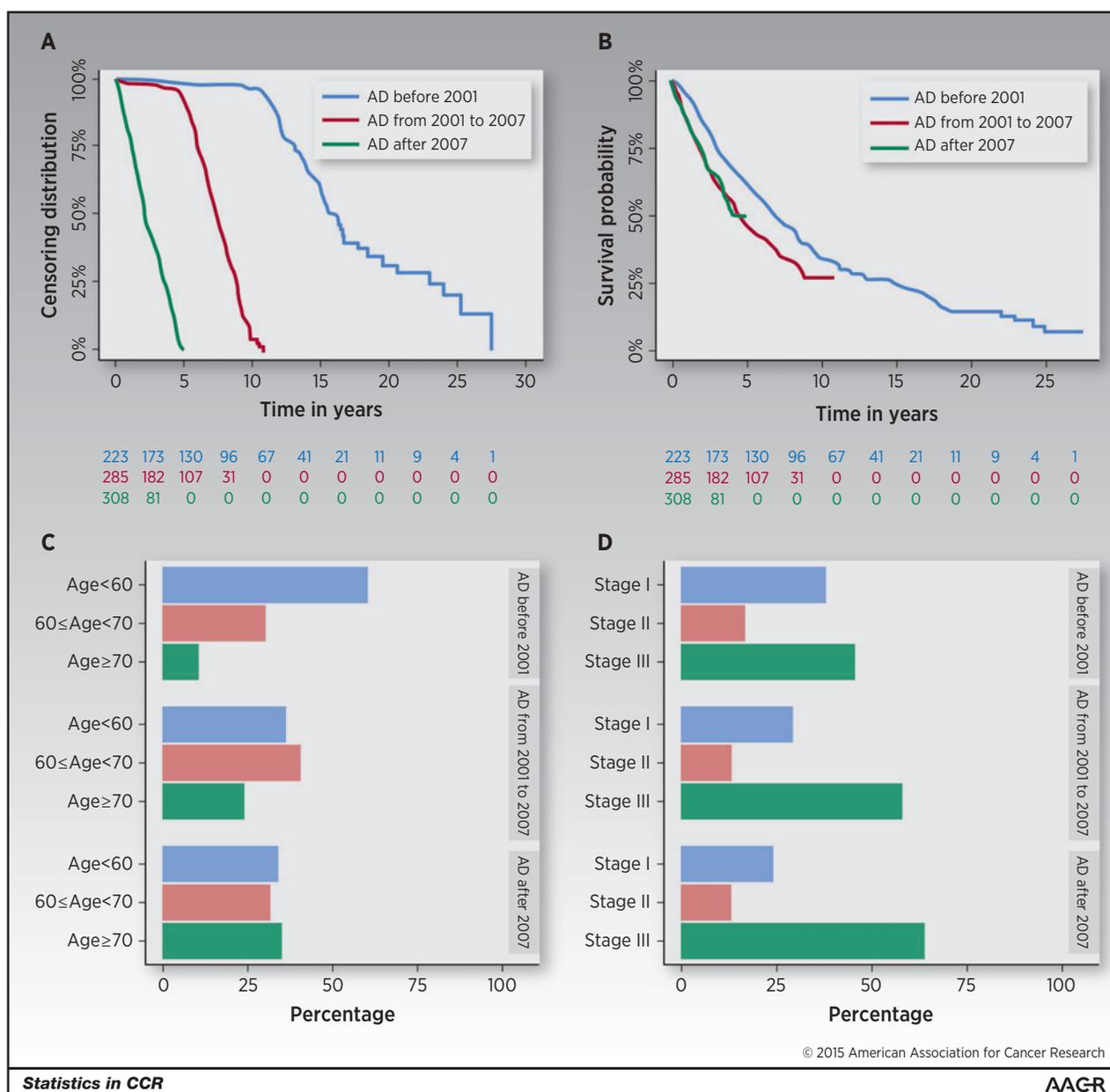


Figure 3. Kaplan-Meier estimates of censoring distribution (A) and of OS (B) according to admission period (AD). C and D, the distribution of age categories and D&S stage by admission period.

longitudinal and time-to-event data (4); statistical methods for development and assessment are available (16), but are beyond this contribution.

Modern statistical methodology (parametric, nonparametric, and regression models) can be used to estimate and analyze CS. In this article, we have only presented two relatively simple approaches: conditional Kaplan-Meier estimates (in the whole patient cohort or in strata defined by baseline characteristics) and CS probabilities derived from conditional versions of Cox regression models. We would like to mention that, as usual in the analysis of survival data, the application of regression models is based on particular assumptions. For the Cox regres-

sion model, this is the proportional hazards assumption, which should be routinely checked. Within the context of CS, however, the refitting of the model at each prediction time point relaxes the proportional hazards assumption and allows the effect of covariates such as D&S stage to vary with time. For this issue and more elaborate approaches, we refer again to van Houwelingen and Putter (4).

We have emphasized that estimation of CS requires large cohorts with (almost) complete long-term follow-up. In the clinical cohort of patients with multiple myeloma, we were able to look at more than 20 years, which is remarkable and, to our knowledge, only achieved in one other study (17). This long

period causes additional problems, as patients' characteristics as well as treatment modalities may change. Thus, adjustment by means of regression models is absolutely necessary and naïve *ad hoc* analyses can be misleading. It must be acknowledged that a general improvement of prognosis in patients with multiple myeloma as recently described (18–20) is notoriously difficult to investigate within a clinical cohort that is not population based.

CS has occasionally been used in studies reported in *Clinical Cancer Research*. In a recent article, Cucchetti and colleagues (21) investigated CS for cirrhotic patients after hepatic resection for hepatocellular carcinoma. In addition to a figure with OS of the whole patient cohort they presented 5-year CS (with 95% confidence intervals) dependent on various baseline characteristics in a table for $s = 0, s = 1, \dots$ up to $s = 5$ years. If one would plot the given numbers as a function of prediction time one could easily see that CS is in general decreasing in this setting. In an investigation on the prognostic relevance of polymorphisms in the IL4 receptor gene for patients with glioblastoma, Scheurer and colleagues (22) used CS in two ways: For a standard survival analysis they used $CS(t|1)$, i.e., the conditional probability of surviving further t years, given that a patient has already survived the first year. In addition, they presented numbers on $CS(1|s)$ for $s = 0, s = 1, \dots, s = 5$ when comparing the prognosis of patients with

various risk variants. Here as well, a graphical display would have been helpful to make the results regarding CS more accessible.

As a final point, we would like to emphasize that CS is not only a quantity of interest *per se* in clinical cancer research, but can serve as a starting point for further investigations to identify such factors as genetic or other molecular markers (20, 23) related to long-term survival of patients with cancer.

Authors' Contributions

Conception and design: S. Hieke, M. Kleber, M. Engelhardt, M. Schumacher
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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M. Kleber, C. König, M. Engelhardt

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S. Hieke, M. Kleber, C. König, M. Engelhardt, M. Schumacher

Writing, review, and/or revision of the manuscript: S. Hieke, M. Kleber, C. König, M. Engelhardt, M. Schumacher

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M. Kleber, C. König, M. Engelhardt, M. Schumacher

Study supervision: M. Engelhardt, M. Schumacher

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