Drug Survival Studies in Dermatology: Principles, Purposes, and Pitfalls

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INTRODUCTION

With rising health-care costs and a growth of pharmaceutical options, health professionals are continuously looking for better and more comprehensive methods to evaluate treatments. In recent years, the term "drug survival" (DS) has made its way through the field of dermatology. This methodological approach, which is based on regular Kaplan–Meier survival analysis, has its roots in rheumatology, where it was first described in 1991 (Wijnands *et al.*, 1991). The method of DS has only relatively recently emerged in dermatology, with most publications limited to biological treatments for psoriasis. In addition, different synonyms have been used to describe DS, such as "drug retention," "drug longevity" or the incorrectly used "drug adherence." For these reasons, not all dermatologists may be familiar with this topic.

Our aim here is to provide an overview of the principles, purposes, and pitfalls of DS analysis to guide physicians in reading and interpreting DS studies.

WHY USE DRUG SURVIVAL?

DS is a comprehensive outcome covering effectiveness, safety, and patients' and doctors' preferences. Identifying drugs with long survival rates as well as ways to prolong DS is therefore important. It is particularly suitable for chronic diseases that require long-term treatment.

WHAT IS DRUG SURVIVAL?

In brief, DS is the time patients remain on a specific drug, investigated using the technique of survival analysis. Survival analysis is a method to analyze longitudinal data for the occurrence of an "event" (Bland and Altman, 1998; Wakkee *et al.*, 2014). It is frequently used in oncology, and in this context, the event typically refers to the death of a patient or to disease progression (Yin *et al.*, 2014). In DS, it refers to the actual discontinuation of a drug. Survival probabilities can be visualized with Kaplan–Meier curves, also widely known from oncology research (Figure 1). Figure 2 provides a translation of these classic curves to DS.

HOW TO PERFORM DRUG SURVIVAL?

If a patient experiences an event (drug discontinuation) at a spe-

WHAT DRUG SURVIVAL ANALYSIS DOES

- Aims to explore the time on drug (drug survival) using the Kaplan–Meier survival technique, which allows for censoring.
- Applies to most chronic diseases in which long drug survival is desired but has been explored mainly in the field of biologics.
- With additional Cox regression analysis, predictors associated with drug survival can be identified.

LIMITATIONS

- Factors that change in time, such as the number of treatment alternatives, may influence drug survival and may be difficult to correct for.
- Identified predictors provide information on a potential association, but do not automatically show a causal link with drug survival.
- Behavior can influence drug survival significantly. However, identifying behavioral factors influencing survival can be the topic of interest of a study as well.

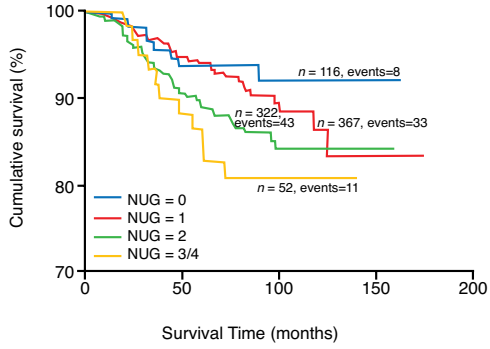

Figure 1. Melanoma-specific survival (log-rank *P* = 0.057). Example of classic Kaplan–Meier survival curve (oncology). Kaplan–Meier survival analysis for cutaneous melanoma overall survival by 0, 1, 2, and 3/4 NUG (number of unfavorable genotypes). The steps (events) in this survival curve refer to the death of a patient (Yin *et al.*, 2014).

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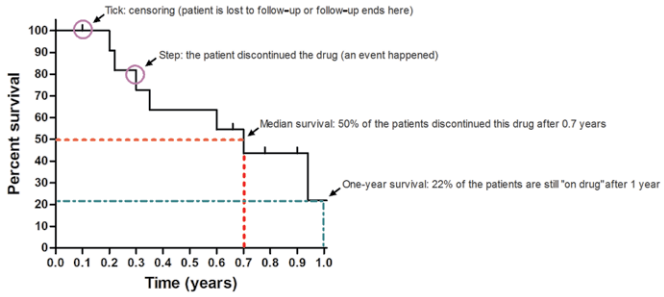

Figure 2. Explanation of Kaplan–Meier drug survival curve. Kaplan–Meier drug survival analysis. Explanation of features of a drug survival curve.

cific time point in the study period, this leads to a step down in the Kaplan–Meier curve at that time point (Figure 2). If a patient has a shorter follow-up than the time frame of the survival analysis, the patient is "censored" and information is incorporated only *up to the end of follow-up*. Censoring is visualized by a tick mark in the curve (Figure 2). The ability to deal with censoring is an important feature of Kaplan–Meier survival analysis because information about patients with different follow-up periods can be fully incorporated in the model. The proportion of patients still "on drug" can be estimated for specific time intervals. For each time interval, the estimated probability that those who have survived from the beginning of that interval will survive to the end is calculated. This is a conditional probability (Bland and Altman, 1998). A general rule of thumb in survival analysis is that at least 10–20 events must be present in each survival curve for it to be valid. Survival curves of different groups, for instance, the DS of two different drugs, can be compared using the nonparametric log-rank test (Mantel–Cox test).

Three assumptions must be fulfilled when calculating survival rates: (i) at any time point, the patients who are censored have the same (drug) survival prospects as the ones who continue, (ii) survival probabilities are stable throughout the whole period under study, and (iii) the time of event is precisely measured (Bland and Altman, 1998).

With survival analysis we can estimate the impact of explanatory variables on the risk of discontinuation of a drug. Thus, variables that are predictive of long or short DS can be identified. This can be done using multivariable Cox regression analysis (Wakkee *et al*., 2014). Of note, the number of variables that can enter a multivariable Cox regression model is limited to *at most* 10% of the number of observed events. Predictors are usually described with hazard ratios (HRs). HRs describe the chance of an event in one group divided by the chance of an event in the reference group. For instance, if males have an HR of 1.5, it means that they have 1.5 times more chance of shorter drug use than females (reference group). Vice versa, HRs less than 1 correspond to the chance of longer drug use. Moreover, Cox regression analysis can be used to correct for confounding in DS. Adjusted survival curves can be obtained from Cox regression analysis, and can be presented next to the crude Kaplan–Meier survival curves.

WHEN CAN WE USE A DRUG SURVIVAL ANALYSIS?

DS studies have been used and analyzed for various purposes: head-to-head comparisons between drugs were the first to be described in the literature and still form a major purpose

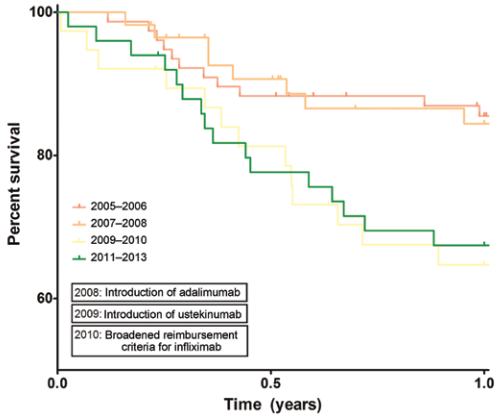

Figure 3. Etanercept one-year drug survival (2005–2013) divided into four time frames. Kaplan–Meier drug survival analysis. Drug survival of etanercept, extracted from the BioCAPTURE registry, a Dutch daily practice biologics registry of psoriasis patients (van den Reek *et al*., 2014), divided for different time periods of initiation of etanercept. Historical occurrences thought to have had an influence on drug survival are described in the boxes.

(Wijnands *et al*., 1991). When different equivalent drugs are prescribed in equivalent patient populations, identifying those with the longest DS rates can be helpful in clinical decision making. Subanalyses split for different reasons of discontinuation can be performed to deepen insight in DS. For instance, if patients frequently stop because of side effects, but also owing to ineffectiveness or disease remission, we should incorporate this important information in our (sub)analyses. If one is interested only in discontinuations due to a particular event, such as discontinuation because of side effects only, all discontinuations for other reasons should be censored.

Second, the distillation of predictors that are associated with the DS of a drug is an important purpose. Useful predictors for clinical practice can be used to select those patients who will benefit most from a certain drug. For instance, if we know that male sex is a strong positive predictor for drug survival of a certain drug, we could retain the drug for males and try to find an alternative drug for females.

Third, studying and comparing DS of different (disease) groups may provide insight into whether we can exchange knowledge between those groups. Comparisons of DS between disease groups have been published (e.g., DS of anti–tumor necrosis factor in three rheumatic diseases) (Heiberg *et al*., 2008). Information from other diseases or specialties using the same drug is frequently adopted without the knowledge of whether this information is actually interchangeable.

Finally, to improve comprehensiveness of DS, our group recently combined DS rates with a quality-of life-measure (DLQI) and named it "happy" drug survival (van den Reek *et al*., 2014). As we put effort in prolonging DS rates, we think it is also important to know whether being on drug is compatible with acceptable quality-of-life rates. Of course, other quality-of-life measures can be used instead of DLQI.

In dermatology, publications on DS have been mainly limited to evaluating biologicals in psoriasis. Recently, a study on fumaric acid esters in psoriasis was published, showing that this methodology can be adapted to other drugs in dermatology (Ismail *et al*., 2014).

Table 1. Seven suggestions for harmonizing drug survival studies

Suggestion	Example
1. Clearly describe population, group characteristics, time frame of analysis, reimbursement criteria, and existence of a drug preference policy	"All Dutch psoriasis patients eligible for biologics using the European reimbursement criteria starting adalimumab between 2011 and 2013 were included. No drug preference policy existed. Patient and treatment characteristics are shown in Table x"
2. Diminish exclusion criteria and, instead, perform subanalyses of interest and/or multivariable regression analysis incorporating intended excluded groups	Do not exclude biologic-naive patients beforehand; instead, present all data and compare two groups (naive versus nonnaive) or analyze influence of naivety
3. Identify possible confounders and discuss their influence	Discuss the possible influence that the introduction of new drugs throughout the study period has on DS
4. Where possible, correct for confounders by means of multivariable regression analysis	If different drugs (etanercept and adalimumab) are compared, correct for existing differences between groups (e.g., biologics naivety or age)
5. Perform sensitivity analyses where needed	Perform analyses with two different cutoff points of ustekinumab (drug with a long half-life): date of last injection versus date of last injection + *t*)
6. Cut off analyses at the moment when a limited amount of patients becomes apparent at a specific time point	If only a few patients remain after 5 years, censor the analysis at an earlier stage
7. Split for reasons of discontinuation if possible	If patients discontinue mainly because of, for example, ineffectiveness and side effects; perform sensitivity analyses for these reasons separately

PITFALLS OF DRUG SURVIVAL ANALYSIS

DS studies have certain limitations that should be considered when performing or reading such studies.

Behavioral factors

DS is influenced by the behavior of physicians and patients. Some doctors or patients will directly stop a drug in case of side effects, whereas others tend to accept more side effects or risks and continue a drug. Also, decreased treatment adherence can indirectly influence drug survival: when nonadherent patients experience decreased effectiveness, doctors probably switch to a different drug because they may not be aware of nonadherence. However, identifying behavioral factors that influence DS can be the topic of interest of a study as well and is not always a "pitfall."

Influence of alternating trends

The number of available alternatives probably influences doctors' decisions (Aletaha, 2009; Heiberg *et al.*, 2008). With a limited number of drugs to switch to, doctors will maximize their efforts to keep patients on a specific drug. We supported

QUESTIONS

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For each question, more than one answer may be correct.

1. What is drug survival?

A. The half-life of a drug.

B. The time patients remain "on drug."

C. The number of patients surviving treatment with a drug.

D. The percentage of responders on a drug.

2. How can different follow-up times of patients be combined in survival analysis?

A. The method of "censoring" can be applied, incorporating all information until the end of follow-up of each individual patient.

B. All patients must have the same follow-up time; otherwise, survival cannot be analyzed.

C. The patient with the shortest follow-up time is leading; that period should be chosen as the maximum duration of the survival analysis.

D. The method of last observation carried forward should be applied; follow-up time of patients with short follow-up can be extended with the information available.

3. What can be used to estimate the required sample size for a reliable survival analysis?

A. Survival studies can only be used for samples with at least 100 patients.

B. The number of events determines the power of survival analyses. A general rule of thumb in survival analysis is that at least 10–20 events must be present in each survival curve.

C. The number of patients determines the power of survival analyses. At least 10–20 patients are needed in each survival curve.

4. If a body weight below 100 kg is a predictor of drug survival with a hazard ratio of 0.5 (95% confidence interval 0.4–0.6), what does this mean?

A. Patients with a body weight <100 kg have a lower chance to stop the drug than patients weighing >100 kg. Thus, <100 kg is predictive for long DS.

B. Patients with a body weight >100 kg have a lower chance to stop the drug than patients weighing <100 kg. Thus >100 kg is predictive for long DS.

C. Patients with a body weight <100 kg have 0.5% chance of discontinuing treatment within the analyzed period.

D. Patients with a body weight >100 kg have 0.5%

chance of discontinuing treatment within the analyzed period.

5. **Which assumptions should be present in survival analysis?**
   - A. (i) At any time point, the patients who are censored have the same survival prospects as the ones who continue, (ii) survival probabilities are stable throughout the whole study, and (iii) the event corresponds with the specified time and is not a raw estimation.
   - B. (i) At any time point, the patients who are censored have the same survival prospects as the ones who continue, (ii) survival probabilities differ throughout the whole study, and (iii) the event does not always correspond with the specified time and is a raw estimation.
   - C. A and B are both incorrect.

this hypothesis with data of our psoriasis cohort by comparing the etanercept DS of different time periods (2005–2013) (Figure 3). We think that important historical occurrences influenced survival, such as the change in reimbursement criteria or the introduction of new drugs. Evolving therapeutic aims could be another explanation for these DS changes (Aletaha and Smolen, 2003). For example, in psoriasis this could be the tendency to pursue higher effectiveness (PASI90 instead of PASI75) or the tendency to incorporate quality-of-life measures in treatment decisions.

The influence of alternating trends is particularly important in head-to-head comparisons between agents that entered the market at different moments in time. For a fair comparison, we propose analyzing data from the moment that all agents were equally available. This advice is in line with the following assumption of survival analysis: "survival probabilities should be the same for subjects recruited at any time point in the study" (Bland and Altman, 1998). However, this advice may restrict the evaluation time and consequently the statistical power of the model because power depends on the number of events in each group. When one prefers to present all available data, sensitivity analyses for restricted analyses should be presented as well to illustrate the impact of violating the above-mentioned assumption.

Predictor identification

The process of predictor identification highly depends on the selection of candidate predictors and selection of study population beforehand. If in one study the selection of predictors that entered the Cox regression model differed from predictors in another study, the results cannot be directly compared.

The selection of candidate predictors should be based on their potential for clinical implementation. In general, baseline characteristics of patients are most informative because only these predictors can help the doctor at the moment of initiating a drug (e.g., age). Predictors are also of interest when they might increase DS. For instance, if high body weight is a predictor of lower DS, the patient could be advised to lose weight or use a higher dose of the drug. It must be noted that predictors only show *association*, not necessarily *causation*; the use of predictors as an intervention therefore should be tested separately. It is important to be aware of the context of a predictor. For instance, if use of concomitant medication was found to be a predictor *but* only nonresponders received concomitant medication in that study, results will be biased. Importantly, no predictors may be selected in a standard Cox model that have not been measured at baseline, or serious biases like these may occur (immortal time bias) (Ho *et al*., 2013). Time-dependent covariates might be part of the solution for this problem (Ho *et al*., 2013).

Time of event

Because the event in a DS analysis depends on the date of discontinuation, problems arise when analyzing drugs with long half-lives. This is especially the case with the new-generation biologics (e.g., ustekinumab). In such cases, different cutoff points can be chosen for the event: date of last administration versus date of last administration plus $t_{½}$. We think that both cutoff points should be analyzed separately to test for robustness because this problem conflicts with the third assumption of survival analysis mentioned above: "the time of event is precisely measured."

CONCLUSION

DS studies have proven to be highly informative in the evaluation of rheumatological, dermatological, and gastroenterological treatments. They have been mainly used for head-to-head comparisons of different biologics, as well as for the identification of predictors related to long DS of a specific drug. The methodology of DS could be adapted to other diseases and drugs in dermatology as well. DS analysis is a relatively simple method requiring, in general, easily attainable information and is most suitable to analyze real-life situations. DS is more comprehensive than classic effectiveness analyses (PASI75). Moreover, in classic effectiveness analyses, disease flares, discontinuations, or dropouts frequently lead to analytical problems.

Because methodological designs and inclusion criteria differ among published DS studies, these studies cannot always simply be compared. Moreover, it must be kept in mind that DS is influenced by behavioral factors and (dynamic) circumstances, such as the availability of therapeutic alternatives; these factors can violate the general assumptions of survival analysis. In our opinion, correction for confounders or sensitivity analyses should be carried out wherever possible.

This paper provides an overview of the methodology, purposes, and limitations of DS specifically addressing the field of dermatology. To make future DS studies more comparable and of high quality, we formulated seven suggestions to harmonize outcomes (Table 1). For indexing and to prevent false interpretations of the concept, we argue that the number of synonyms used should be reduced and we propose the worldwide adoption of the term "drug survival."

CONFLICT OF INTEREST

The authors state no conflict of interest.

CME ACCREDITATION

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SUPPLEMENTARY MATERIAL

A PowerPoint slide presentation appropriate for journal club or other teaching exercises is available at http://dx.doi.org/10.1038/jid.2015.171.

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