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Review

Considerations for analysis of time-to-event outcomes subject to competing risks in veterinary clinical studies☆

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Abstract In veterinary medicine, prospective clinical trials are increasingly utilized to address questions regarding effectiveness of therapies and patient prognosis. A large number of these trials involve time-to-event (TTE) endpoints, which require special methods of analysis to handle data in which not all subjects are observed to have the event of interest. Analyses and interpretation of the results can be further complicated when an endpoint of interest is not observed in some patients because they incur a competing risk, such as death from an unrelated cause. Competing risks have been the source of confusion in many epidemiologic analyses leading to the potential for misinterpretation. In this article, we review

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key considerations for the TTE analysis in the setting of competing risks. We briefly review standard TTE tools, namely Kaplan–Meier survival curves and Cox regression. In the setting of outcomes with competing risks, we provide guidance on the appropriate analysis techniques, such as cumulative incidence curves, to estimate the risk of an event of interest. We also describe a common pitfall of treating competing risks as censoring in Kaplan–Meier survival curve analysis, which can overestimate the event rate of interest. We describe two common regression methods that examine associated risk factors in the presence of competing risks and highlight the different research questions these methods address. This article provides an introductory overview and illustrates concepts with examples from veterinary trials and with example data sets.

Abbreviations

CHF	congestive heart failure
HR	hazard ratio
KM	Kaplan–Meier
SHR	subdistribution hazard ratio
TTE	time to event

Randomized clinical studies provide an important basis for evidence-based practice. As such, the proper design, analysis, and reporting of clinical trials is a subject of increasing interest to consumers of these data, including practitioners, researchers, governmental regulators, and industry. Many clinical cardiovascular studies [1–10] involve time-to-event (TTE) analysis, in which the duration of time from study enrollment to the first occurrence of a clinically meaningful event is studied. This outcome is often referred to as the 'survival' time whether or not the event involves death. TTE or survival analysis generally requires statistical approaches different from those used for other types of outcome data, such as continuous variables (e.g. blood pressure) or dichotomous variables (e.g. the number of patients experiencing disease recurrence within 30 days). Over the course of TTE studies, patients either will have experienced the event, in which case one utilizes the time at which the event occurred, or patients will not have experienced the event, in which case one utilizes the length of time the patient was observed event free. For certain types of TTE analysis, patients not experiencing the event of interest are all treated similarly, regardless of the reason. For instance, in a study of cardiac-related sudden death in dogs with dilated cardiomyopathy [3], patients who were alive at the end of the study, lost to follow-up, or were euthanized or died from non-cardiac causes were all accounted for in a similar fashion; however, these patients differ in an important respect. Patients who are still alive or lost to follow-up still could theoretically experience cardiac-related death at some point in the future, whereas patients dying from another disease cannot. The latter is an example of an intervening event that precludes always observing the event of interest and is termed a *competing risk*. To accurately estimate the probability of the event of interest within a given time period, one must account for the probability of any competing risks.

Competing risks are commonly overlooked, even in highly visible studies. A review [11] of 50 human clinical studies that were published in high-impact medical journals found 35 of 50 (70%) inadequately addressed competing risks. In veterinary medicine, competing risks are rarely, if ever, accounted for. In this article, we review key considerations for TTE analysis in the setting of competing risks. We briefly review standard tools for TTE analysis, namely Kaplan–Meier (KM) survival curves and Cox regression. In the setting of TTE outcomes with competing risks, we provide the reader with guidance on the appropriate analysis techniques, such as cumulative incidence curves, to estimate the risk of an event of interest. We also describe a less familiar regression method that appropriately examines risk factors in the presence of competing risks and highlight how the research question of interest guides the choice of which particular regression method to use. This article provides an introductory overview of these topics and illustrates concepts with examples from veterinary clinical studies and with example data sets. We refer readers interested in further detail to a several excellent references on the topic [12,13].

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