The perilousness of proportional hazards models in the competing risks setting

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The simplest means of determining the effect of an exposure on the frequency and timing of two competing events is to contrast the cumulative incidences between the exposed and unexposed groups for each event type. Methods and software are widely available to semi-parametrically model the sub-hazards of the cumulative incidences as proportional and to test whether the constant relative sub-hazards (a_1 and a_2) are different from 1, but a_1 and a_2 are tethered by a strong relationship which is independent of the timing of the competing events; the relationship is fully determined by the overall frequencies of events, and a_1 and a_2 must be on opposite sides of 1. When violations of proportionality occur, separate analyses for the two competing events often yield an inadmissible result in which the estimates of a_1 and a_2 are on the same side of 1, and may even exhibit statistical significance. In turn, reporting results from cause-specific and sub-hazards analyses under proportionality is not conducive to new knowledge because they must be equal under proportionality assumptions. Full characterization of compatibility of concurrent proportionality of cause-specific hazards and sub-hazards will be provided, and will show that strong tethering also occurs among these quantities; and that, of the sub-hazards and cause-specific hazards, at most two of the four can be proportional, but without restriction on which two. The default analytical approach should allow the relative hazards to depend on time because the statistical power to detect lack of proportionality is limited in the case of large numbers of event-free observations. Scenarios where the cause-specific hazards lack specificity will be illustrated. Alternative methods in the presence of strong data include mixtures of parametric models (e.g., generalized gamma) which offer the opportunity to comprehensively characterize the effects of exposure on competing risks without the need to recourse to proportionality assumptions; neither of hazards nor of percentiles. Applications from critical care medicine and from chronic kidney disease epidemiology will be presented.