Workshop 9 — Appraising a study on prognosis

Frequently, clinicians have to face questions raised by their patients as to the future prospects of their health conditions, including cancers, infectious diseases, and abnormal biomarkers. To answer such questions, we need evidence from well-conducted prognostic studies, which are essentially cohort studies[1] that provide evidence for predicting their probable course and outcomes.

Studies on prognosis generally start by recruiting a representative sample of cases,[2] which are then followed up to document the occurrence of certain defined health outcomes, eg recovery, death, recurrence etc. Factors that affect the occurrence of the health outcome (prognostic factors) are also analysed. Such studies can be based on historical information (historical cohort study) or carried out prospectively (prospective cohort study). The possible biases that might be present in each type of cohort study have been previously discussed in detail.[3]

In this Workshop, the four major questions to be answered when appraising a study on a prognosis are discussed.

BOX. Validity of study results

Validity — selection bias

- Was the source of study subjects described, as well as the inclusion and exclusion criteria, and was a representative sample selected?
- Was the response or participation rate for the sampled subjects reported and reasonably high if certain interventions/treatments were involved as inclusion criteria for defining the cohort?
- Was follow-up complete or loss to follow-up reported?

Validity – measurement/information bias (including misclassification)

- Were objective outcome indicators used? Death from any cause (overall survival) is the most objective outcome. Recurrences (disease-free survival) or symptom-free survival can be subjective and liable to measurement bias. Even cause-specific mortality can be prone to information bias.
- Were outcome assessors blinded to the prognostic factors of individual patients, as well as the hypothesis(es) of the study? This is especially important in prospective studies.
- Were persons involved in retrieving information on prognostic factors from medical records blinded to the outcome statuses of the patients, as well as the hypothesis(es) being explored? This is especially important in historical studies.
- Was the follow-up duration sufficient for observing the relevant health outcomes (eg mortality, recurrence)?

Validity – confounding

- Were all known important prognostic factors taken into consideration when examining the effects of a specific prognostic factor? Moreover, were they adjusted for as necessary in the analysis? Only a real expert for the health condition under consideration can answer these questions well. Notwithstanding this caveat, possible prognostic factors should be examined under the following three headings: personal factors (eg age, smoking, co-morbidity), disease status (eg disease stage, biomarker levels), and treatment(s) received.

(1) How much longer does someone with the specified disease (or condition) and a particular background, expect to live (probable period of survival) or live without a recurrence?

Alternatively, the question can be posed as: **How likely will someone with the specified disease (or condition) and a particular background experience a defined health outcome (eg death/survival/recurrence) in a defined period of time?**

The common prognostic indicators are (i) the median or mean survival time (the former is usually preferred due to non-normal distributions) and (ii) the survival rate (ratio, probability) up to a certain period of time. Information on these indicators may be given for the whole study group, or described separately for different subgroups (often depending on age, gender, disease stage, co-morbidity, etc) and then compared. The detailed information may also be presented graphically in the form of survival curves. Differences between subgroups can be compared using the log-rank test, and the independent effects (influences) of various prognostic factors are usually examined by the Cox's proportional hazards regression with adjustment for other important factors affecting prognosis. The hazard ratio (HR) of a prognostic factor describes the magnitude of its effect on the outcome.

(2) Are the results about the prognostic indicators and prognostic factors basically valid?

As with all types of studies, one should examine whether there was possible selection bias or self-selection bias, whether information regarding exposure (prognostic factor under study), outcomes, and confounding (other known prognostic factors) was objectively acquired. Whether confounding from other factors known to be associated with outcomes were taken into consideration should also be explored. Particularly for the outcome of overall survival, all factors affecting survival in general (eg smoking) should be considered as potential confounders. The specific questions to be answered for ascertaining the validity of results of a study on prognosis are structured under the three major sources of bias (Box).[4]

(3) Are the results reasonably reliable or precise?

The precision of the estimates on the prognostic indicators (survival time, survival rates/probabilities) should be reported to provide clinicians with necessary information to advise their patients. As survival times often do not follow a normal

distribution, reporting ranges (eg interquartile range – 25th to 75th centile) in addition to the median (or mean) should help. One should examine the 95% confidence intervals for the survival rates, as well as the HRs derived from Cox's proportional hazards regression. These can reflect whether the reported point estimates could vary substantially (from a lower to upper boundary), which may in turn affect clinical interpretations and applications.

(4) Can the results be applied to a specific patient or in another setting?

A specific patient similar to those included in the study (eg by virtue of age, gender, nature and stage of disease, co-morbidities, etc) is more likely to benefit from applying the results than someone with very dissimilar background. However, one should only consider applying the results after being satisfied with the validity and reliability/precision of the results. Furthermore, in considering the effect of a certain prognostic factor (eg diet, nutritional supplement), one should examine if the reported effect size (HR) is of clinical importance and not just of statistical significance. Conversely, one should not just stop applying the results simply because the study was conducted in another country or ethnic group. Before evidence from a high-quality study in the local population becomes available, it is only reasonable to adopt the best *available* evidence to guide one's clinical practice.[4]

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